A Phase 2 Dose Ranging, Randomized, Double Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Primary Biliary Cholangitis (PBC) with or without an Inadequate Response to Ursodeoxycholic Acid (UDCA)

Published: 09-07-2018
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Primary Objective:* To evaluate the effect of EDP-305 on alkaline phosphatase (ALP) levels.Secondary Objective:* To evaluate the safety and tolerability of EDP-305* To evaluate the effect of EDP-305 on bilirubin levels* To evaluate the effects of...

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

Summary

ID

NL-OMON48564

Source
ToetsingOnline

Brief title
INTREPID

Condition

- Hepatic and hepatobiliary disorders

Synonym
Primary Biliary Cholangitis

Research involving
Human

Sponsors and support

Primary sponsor: Enanta Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Industry sponsored by the sponsor;Enanta Pharmaceuticals;Inc.

Intervention

Keyword: EDP-305, Primary Biliary Cholangitis (PBC)

Outcome measures

Primary outcome

* Proportion of subjects with at least 20% reduction in ALP from pretreatment

value or normalization of ALP at Week 12

Secondary outcome

Secondary Endpoints:

* Frequency of adverse events (AEs), serious AEs, and AEs leading to

discontinuation through Week 12

* Bilirubin (Total, Conjugated, Unconjugated) decline from Baseline at

Week 12

* Change from Baseline in Alanine aminotransferase (ALT) and Aspartate

aminotransferase (AST), Gamma-Glutamyl transferase (GGT) at Week 12

* Change from Baseline of noninvasive liver fibrosis markers (Enhanced Liver

Fibrosis [ELF] panel, PRO C3, AST to Platelet Ratio Index [APRI] and fibrosis-4

[FIB-4]) at Week 12

* Change from Baseline in fibrinogen, CRP, IL6, IL1*, TNF-*, TNF-* , alpha2

macroglobulin and haptoglobin levels at Week 12

* Change from Baseline in Triglycerides (TG), Total Cholesterol (TC), High

Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol

(LDL-C) at Week 12

* Change from Baseline in 5D-itch scale and Visual Analog Score (VAS) at Week

12

* Change from Baseline in PBC-40 Quality of Life (QoL) at Week 12

* Pharmacokinetic parameters of EDP-305 (and metabolites): Cmax, Tmax, and

AUClast.

* Pharmacodynamic parameters of EDP-305: FGF19, C4 and Bile Acid (BA) at

Week 12

Study description

Background summary

PBC is a chronic and progressive liver disease that affects thousands of people worldwide. During decades, there has been only one approved treatment for this condition, namely ursodeoxycholic acid (UDCA). However, it has been demonstrated that up to 40% of patients don*t have a good response to UDCA and may experience a faster progression of the disease and consequently liver related complications. Most recently another treatment which still requires close monitoring, namely Obeticholic acid, has been approved for patients with PBC without adequate response or intolerance to UDCA. In consequence, there is still need for better therapies for patients with an inadequate response or intolerance to UDCA especially those with more advanced liver disease. Results from experimental and clinical studies suggest that EDP-305 has the potential to satisfy this unmet need, and therefore, EDP-305 is now being tested in this clinical study.

Study objective

Primary Objective:
* To evaluate the effect of EDP-305 on alkaline phosphatase (ALP) levels.

Secondary Objective:
* To evaluate the safety and tolerability of EDP-305
* To evaluate the effect of EDP-305 on bilirubin levels
* To evaluate the effects of EDP-305 on other markers of liver function
* To evaluate the effects of EDP-305 on non-invasive markers of liver fibrosis
* To evaluate the effects of EDP-305 on inflammatory markers
* To evaluate the effects of EDP-305 on lipids
* To evaluate the effects of EDP-305 on pruritus
* To evaluate the effects of EDP-305 on Quality of Life (QoL)
* To evaluate the pharmacokinetics (PK) of EDP-305 and metabolites in plasma
* To evaluate the pharmacodynamics (PD) of EDP-305

Study design

Study Design:
This is a multicenter, double blind, placebo controlled, dose ranging Phase 2 study assessing the safety and efficacy of two doses of orally administered EDP-305. The total maximum length of time for participation for each subject enrolled in the study will be approximately 20 weeks. The study will consist of a Screening Period, Treatment Period and a Follow-up Period.

Screening Period:
After reviewing and signing the Informed Consent Form (ICF), subjects will be screened and must meet all criteria for entry into the study. The Screening Visit must occur between Days -28 and -1 (up to 4 weeks). All Screening assessments must occur within the -28 to -1 window.

Treatment Period:
Subjects who have met all study criteria will report to the site on the morning of Day 1. Subjects must have fasted for at least 8 hours prior to dosing. Subjects will be randomized in a 3:3:1 manner to receive one of two doses of EDP-305 or placebo QD. Procedures performed are specified in the Schedule of Assessments. Predose assessments will be conducted (including laboratory sample collection) before the subject receives the first dose of study drug in the clinic. Following dosing, PK and biomarker samples will be collected. Prior to leaving the clinic on Day 1, study drug will be dispensed to the subjects and the subjects will be given instructions for taking study drug at home. Subjects will take study drug once daily for a total of 12 weeks returning to the clinic for efficacy and safety assessments on Day 3 and Weeks 2, 4, 8 and 12. On study days when there is a clinic visit, subjects will be administered their daily dose in the clinic. Additional PK and PD samples will be collected over a period of 8 hours on Day 1 and Week 12 (Day 84/End of Treatment, [EOT]) from subjects at a subset of sites that have the technical capability to collect and process intensive (longer duration) PK and PD samples (PK/PD Sub-study).

Safety Follow-up and Early Termination Visit:
The safety follow-up visit (or End of Study [EOS] visit) will occur 4 weeks after the last dose of study drug for all subjects, including those who discontinue treatment early (ie, prior to completing 12 weeks of dosing). Final study assessments will be completed at that visit.

Subjects who discontinue treatment early should return to the clinic as soon as possible following the last dose of study drug for an EOT visit. They should then return for the EOS visit 4 weeks following last dose of study drug.

Intervention

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Study burden and risks

Please refer to section E9.

Contacts

Public
Enanta Pharmaceuticals, Inc.

Arsenal St. 500
MA - Watertown 02472
US
Scientific
Enanta Pharmaceuticals, Inc.

Arsenal St. 500
MA - Watertown 02472
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Each subject must meet all of the following criteria to be enrolled into this study:
1. An informed consent document must be signed and dated by the subject
2. Male and female subjects of any ethnic origin between the ages of 18 and 75 years, inclusive
3. Male or female with a diagnosis of PBC by at least two of the following criteria:
* History of ALP above ULN for at least 6 months
* Positive Anti-Mitochondrial Antibodies (AMA) titers (>1/40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA] or positive PBC-specific antinuclear antibodies [PBC-ANAb])
* Documented liver biopsy result consistent with PBC (with no cirrhosis)
4. For subjects with no documented liver biopsy performed within 2 years, subjects must undergo a transient elastography (Fibroscan) showing liver stiffness <14.0 kPA
5. Must be on a stable dose of UDCA 12-20 mg/kg/day for at least 6 months prior to Screening or intolerant of UDCA in the opinion of the Investigator (no UDCA for at least 12 weeks prior to Screening)
6. Alkaline Phosphatase (ALP) *1.67 × ULN and/or total bilirubin >ULN but <2 × ULN (<2.4 mg/dL)
7. Subjects must have Screening laboratory values for Hepatitis B surface antigen (HBsAg), anti-HCV antibodies and HCV RNA negative, and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies (Ab) as seronegative. NOTE: Subjects previously infected by chronic hepatitis C and treated with direct acting antivirals (DAAs) with sustained virologic response (SVR) for at least 3 years will be allowed.
8. Female subjects of childbearing potential must agree to use two effective methods of contraception from the date of Screening until 90 days after the last dose of EDP-305. Effective methods of contraception are defined as:
* a condom for the male partner and at least one of the following for the female participant:
o Intrauterine device
o Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive Note: The above does not apply to female subjects of non-childbearing potential (ie, physiologically incapable of becoming pregnant) defined as:
- has had a complete hysterectomy greater than or equal to 3 months prior to dosing or
- has had a bilateral oophorectomy (ovariectomy) or
- has had a bilateral tubal ligation or fallopian tube inserts or
- is postmenopausal (a demonstration of a total cessation of menses for *1 year with an FSH level of >35 mIU/mL).
9. All male participants who have not had a vasectomy must use effective contraception from Day -1 to 90 days after their last dose of study drug. Effective contraception is defined as a

condom and spermicide for the male, or condom and at least one of the following for a female partner:
* Intrauterine device
* Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive
* Be of non-childbearing potential
10. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug
11. Screening body mass index (BMI) of *18 kg/m2
12. Subject must be willing and able to adhere to the assessments, visit schedule, prohibitions and restrictions, as described in this protocol

Exclusion criteria

Subjects who meet any of the following criteria will be excluded from this study:
1. Laboratory Screening Results:
* AST >5 × ULN
* ALT >5 × ULN
* Patients with Gilbert*s syndrome will not be allowed due to interpretability of bilirubin levels
* Total white blood cells (WBC) <3000 cells/mm3
* Absolute neutrophil count (ANC) <1500 cells/mm3
* Platelet count <140,000/mm3
* Prothrombin time (international normalized ratio, INR) >1.2
* Serum creatinine >2 mg/dL or clearance creatinine <60 mL/min (based on Cockroft- Gault Method)
2. Suspected to have relevant nonalcoholic fatty liver disease (NAFLD) as based on the judgment of the Investigator at Screening
3. Known history of alpha-1-Antitrypsin deficiency
4. Use of immunosuppressants known to have an effect on the liver of patients with PBC (eg, colchicine, methotrexate, or azathioprine) in the 3 months preceding Screening.
5. Current use of fibrates, including fenofibrates. NOTE: Subjects who discontinued fibrates for at least 3 months before Screening can participate
6. Use of an experimental treatment for PBC within the past 6 months
7. Prior use and/or concomitant treatment with OCA
8. Use of experimental or unapproved drugs within 1 year of Screening
9. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Principal Investigator (PI)
10. Pregnant or nursing females
11. Recipients of liver or other organ transplantation or anticipated need for orthotropic organ transplantation in one year as determined by a Model for End-Stage Liver Disease (MELD) Score *15
12. Co-existing liver or biliary diseases, such as primary sclerosing cholangitis, choledocholithiasis, acute or chronic hepatitis, autoimmune hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), acute infection of bile duct system or gall bladder, history of gastrointestinal bleeding (secondary to portal hypertension), cirrhosis, cholangiocarcinoma diagnosed or suspected liver cancers

13. Cirrhosis with or without complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma
14. Hepatorenal syndrome (type I or II) or Screening serum creatinine >2 mg/dL (178 *mol/L)
15. Prior variceal hemorrhage, uncontrolled encephalopathy, Child-Pugh Class A, B and C, esophageal varices, or refractory ascites within the previous 6 months of Screening (defined as date informed consent signed)
16. Patients with a history of severe pruritus requiring current or prior systemic treatment (e.g., with BAS or rifampicin)
17. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease)
18. Any condition possibly affecting drug absorption (eg, gastrectomy <3 years prior to Screening). NOTE: Subjects who have undergone gastric surgeries known to not affect drug absorption such as gastric band or gastric sleeve will be allowed if they are stable for at least 1 year prior to Screening.
19. History of regular alcohol consumption exceeding 14 drinks/week for females and 21 drinks/week for males within 6 months of Screening. One drink is defined as 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor)
20. Participation in a clinical trial within 30 days prior to study drug administration
21. Clinically significant electrocardiogram (ECG) abnormalities or QTcF greater than 450 ms for males and 470 ms for females at either Screening or Baseline, or any prior history of QT abnormality
22. Use of CYP3A4 and P-gp inducers and inhibitors within 14 days prior to the first dose of study medication and throughout study duration
23. Clinically significant history of drug sensitivity or allergy, as determined by the PI
24. Subject has received an investigational agent or investigational vaccine within 30 days, or a biological product within 3 months or 5 elimination half-lives (whichever is longer) prior to the planned intake of study drug
25. Use of a new statin regimen from Screening and throughout study duration.
NOTE: Subjects on a stable dose of statins for at least 3 months prior to Screening are allowed. No dose modification during the study will be allowed.
26. Use of immunosuppressants (eg, systemic corticosteroids) for more than 2 consecutive weeks in duration within 1 year prior to Screening.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	14-05-2019
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	EDP-305
Generic name:	n.a.

Ethics review

Approved WMO

Date:	09-07-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	29-11-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2017-003528-62-NL
ClinicalTrials.gov	NCT03394924
CCMO	NL65779.058.18

Study results

Date completed:	16-01-2020
Results posted:	14-01-2021

First publication
22-10-2020