A Study of INT-747 (6-ECDCA) in Combination with Ursodeoxycholic Acid (URSO®, UDCA) in Patients with Primary Biliary Cirrhosis

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In patients with primary biliary cirrhosis (PBC) taking UDCA, to assess the effects of INT-747 on: Primary: - Alkaline phosphatase (AP) levels - SafetySecondary: - Hepatocellular injury and liver function - Disease-specific and general health...

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

Summary

ID

NL-OMON33908

Source
ToetsingOnline

Brief title
INT 747-202

Condition

- Hepatic and hepatobiliary disorders

Synonym
Primary Billiary Cirrhosis

Research involving
Human

Sponsors and support

Primary sponsor: Intercept Pharmaceuticals

Source(s) of monetary or material Support: Farmaceutische Industrie.

Intervention

Keyword: Combination Therapy, INT-747 (6-ECDCA), Primary Billiary Cirrhosis (PBC), URSO®

Outcome measures

Primary outcome

The primary efficacy endpoint is the effect of INT-747 on serum AP levels at baseline (Day 0) and the end of the study (Day 85).

Secondary outcome

Safety and secondary efficacy endpoints will be evaluated by monitoring the following:

- Adverse experiences
- Clinical laboratory values (including aminotransferase liver enzymes, protein concentrations, and prothrombin time to assess hepatocellular injury and liver function)
- Vital signs
- Disease-specific and general health questionnaires (PBC-40, 5D, and SF-36)
- Symptoms (pruritus VAS questionnaire)
- Liver inflammation and fibrosis biomarkers
- Plasma drug and metabolite concentrations

Study description

Background summary

PBC is a chronic liver disease characterized by inflammation of the liver, progressive destruction of the hepatic bile ducts, liver fibrosis, increased

blood levels of bile salts and bile accumulation in the liver. When the disease progresses, liver transplantation might be required and/or the patient may die. The only registered therapy specifically for PBC is Ursodeoxycholacic ((UDCA/URSO®). In a subset of the patients treated with URSO®, liver enzymes normalise over time. URSO® however does not appear to be effective on the bile secretion or as an antifibrotic agent. In pre-clinical studies INT-747, does seem to have an effect on the bile secretion and to have antifibrotic efficacy. Because URSO® is standard therapy for the treatment of PBC and in case it can be demontrated that INT-747 is safe and effective in this condition, a combination of these two treatment options might be prescribed in the future. This study assesses the effect of co-administration of the two therapies in patients with PBC in who liverfunctiontests did not normalise on URSO®.
See also protocol pages 13 - 16.

Study objective

In patients with primary biliary cirrhosis (PBC) taking UDCA, to assess the effects of INT-747 on:

Primary:
- Alkaline phosphatase (AP) levels
- Safety

Secondary:
- Hepatocellular injury and liver function
- Disease-specific and general health symptoms
- Biomarkers of hepatic inflammation and fibrosis
- Plasma trough concentrations of INT-747 and its major, known metabolites

Study design

Multi-center, randomized, double-blind, placebo-controlled, multi-dose, parallel-group study.

Intervention

One daily dose in combination of Ursodeoxycholicacid:
Group 1: 10 mg INT-747
Group 2: 25 mg INT-747
Group 3: 50 mg mg INT-747
Group 4: Placebo

Study burden and risks

Physical Exam: screening + day 85
ECG: screening + day 85

PBC-40 QOL and 5D questionnaires: screening, baseline, day 29, day 57 and day 85
5D questionnaire: day 15
SF-36 QOL questionnaires: baseline and day 85
Pruritis VAS questionnaires: baseline, day 15, day 29, day 57 and day 85
Vital signs: on all visits except day 99 (follow-up)
Transient Elastography, Fibroscan: day 0 and day 85
Bloodsample collection for laboratory parameters: all visits (for specific analysis per visit, see "schedule of study procedures" on page 27 and appendix B of the protocol). On day 0 and 85 the patient should be fasted for at least 8 hours prior to blood sample collection.

Risks:
Bloodsample collection: there is a chance of pain or brusing and infection when taking a blood sample.
All assessments will be performed by qualified physicians, nurses and study personel.

PBC is a chronic liver disease that eventually could result in liver cirrhosis for which a liver transplantation might be required or which could result in the patient's death. The only registered treatment for PBC is ursodoxycholicacid (UDCA). The co-administration of INT-747 could possibly increase the effectiveness of the treatment of PBC. Phase I study results indicate that INT-747 doses used in this protocol are generally well tollerated. There are no invasive interventions besides the blood sample collections.

Risk Fibroscan: non-invasive method via ultrasound.

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

•Male or female age 18 to 70 years.
•Stable dose of ursodeoxycholic acid (URSO®, UDCA) for at least 6 months prior to screening.
• Female patients must be postmenopausal, surgically sterile, or if premenopausal, prepared to use 1 effective method of contraception with all sexual partners during the study and for 14 days after the end of dosing. Effective methods of contraception are considered to be: o Barrier method, i.e., (a) condom (male or female) or (b) diaphragm with spermicide; or o Hormonal (e.g., contraceptive pill, patch); or o Intrauterine device (IUD); or o Vasectomy (partner).
• Male patients must be prepared to use 1 effective method of contraception with all sexual partners during the study unless they have had a prior vasectomy.
• Proven or likely PBC, as demonstrated by the patient presenting with at least 2 of the following 3 diagnostic factors:
o History of increased AP levels for at least 6 months prior to Day 0
o Positive AMA titer (>1:40 titer on immunofluorescence or M2 positive by ELISA) or PBC-specific antinuclear antibodies (antinuclear dot and nuclear rim positive)
o Liver biopsy consistent with PBC
• Screening AP level between 1.5 and 10 × ULN.
• Willing and able to give written informed consent

Exclusion criteria

• Administration of the following drugs at any time during the 3 months prior to screening for the study: colchicine, methotrexate, azathioprine, or systemic corticosteroids.
• Screening conjugated (direct) bilirubin >2 × ULN.
• Screening ALT or AST >5 × ULN.
• Screening serum creatinine >1.5 mg/dL (133 micromol/L).

• History or presence of hepatic decompensation (e.g., variceal bleeds, encephalopathy, or poorly controlled ascites).
• History or presence of other concomitant liver diseases including hepatitis due to hepatitis B or C virus (HCV, HBV) infection, primary sclerosing cholangitis (PSC), alcoholic liver disease, definite autoimmune liver disease or biopsy proven nonalcoholic steatohepatitis (NASH).
• Known history of human immunodeficiency virus (HIV) infection.
• History or presence of any other disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs including bile salt metabolism in the large intestine (e.g., inflammatory bowel disease).
• Other clinically significant medical conditions, including renal insufficiency.
• Other medical conditions that are not well controlled or for which medication needs are anticipated to change during the study. Concomitant medications must be stable for 14 days prior to the first dose of study medication, and should be expected to remain stable during the course of the study.
• History of alcohol abuse (defined as consumption of more than 210 mL of alcohol per week; or the equivalent of 14 4-ounce glasses of wine, or 14 12-ounce cans/bottles of beer or wine coolers) or other substance abuse within the prior 1 year.
• Participation in another investigational drug, biologic, or medical device study within 30 days prior to Day 0.
• History of noncompliance with medical regimens, or patients who are considered to be potentially unreliable.
• Blood or plasma donation within 30 days prior to dosing.
• Mental instability or incompetence, such that the validity of informed consent or compliance with the study is uncertain.
• If female: pregnant, lactating, or positive serum or urine pregnancy test.

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:	Recruitment stopped
Start date (anticipated):	27-04-2009
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	6a-ethylchenodeoxycholic acid
Generic name:	-
Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo

Ethics review

Approved WMO Date:	12-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2007-001425-10-NL
ClinicalTrials.gov	NCT00550862
CCMO	NL24341.078.08