A Two Part Phase IIa/b Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Dose-ranging Study to Assess Efficacy, Safety, and Tolerability of the Combination of Zibotentan and Dapagliflozin, and Dapagliflozin Monotherapy Versus Placebo in Participants with Cirrhosis with Features of Portal Hypertension

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This study has been transitioned to CTIS with ID 2023-505405-17-00 check the CTIS register for the current data. The main objective of this Phase IIa/b study is to demonstrate the effectof zibotentan on HVPG, and that dapagliflozin can mitigate...

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

Summary

ID

NL-OMON51672

Source
ToetsingOnline

Brief title
ZEAL

Condition

- Hepatic and hepatobiliary disorders
- Vascular hypertensive disorders

Synonym
end-stage liver disease, hypertension of the portal vein of the liver

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca

Intervention

Keyword: cirrhosis with portal hypertension, combination of zibotentan and dapagliflozin, Phase IIa/b trial

Outcome measures

Primary outcome

PART A:

Obj: To evaluate the change from baseline in HVPG on zibotentan and

dapagliflozin in combination versus placebo.

endpoint: Absolute change in HVPG from baseline to Week 6.

PART B:

Obj: To evaluate the proportion of participants achieving at least 20% decrease

in HVPG or a reduction to or below 12mmHg in HVPG on zibotentan and

dapagliflozin in combination and dapagliflozin monotherapy versus placebo.

endpoint: HVPG response, where a responder is defined as at least 20% decrease or a reduction to or below 12 mmHgin HVPG from baseline to Week6.

Secondary outcome

PART A:

obj: To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination versus placebo.

endpoint: Percent change in HVPG from baseline to Week6.

obj: To evaluate the proportion of participants achieving HVPG < 10 mmHg or a reduction in HVPG of >= 1.5 mmHg on zibotentan and dapagliflozin versus placebo.

endpoint: HVPG response, where a responder is defined as HVPG <10 mmHg or a reduction in HVPG of >= 1.5 mmHg from baseline to Week 6.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on change in body weight.

endpoint:

•Evaluation of change in body weight (kg) overtime course of studya.

•Percentage and absolute change from baseline inbody weight at Week6.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on accumulated additional loop-diuretic equivalents use.

endpoint: Percentage and absolute change in accumulated dosage of loop-diuretic equivalentscuse from baseline to Week 6.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination versus placeboon body water volumes and body fat mass.

endpoint:

•Change in total body water, extracellular water,and intracellular water volumes from baseline toWeek6.

•Change in total body fat mass from baseline toWeek6.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination versus placebo on changes in office-based systolic and diastolic blood pressure.

endpoint: Change in systolic and diastolic blood pressure from baseline to Week6.

PART B:

obj: To evaluate the change from baseline in HVPG on zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo.
endpoint: Percentage and absolute change in HVPG from baseline to Week6.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on change in body weight.
endpoint: •Evaluation of change in body weight (kg) overtime course of studya.•Percentage and absolute change from baseline inbody weight at Week6 and Week16b.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on accumulated additional loop-diuretic equivalents use.
endpointL Percentage and absolute change in accumulated dosage of loop-diuretic equivalentscuse from baseline to Week6 and Week16.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination and dapagliflozin monotherapy versus placebo on body water volumes and body fat mass.

endpoint: •Change in total body water, extracellular waterand intracellular

water volumes from baseline toWeek6 and Week16.•Change in total body fat mass

from baseline toWeek6 and Week16.

obj: To evaluate the effect of zibotentan and dapagliflozin in combination and

dapagliflozin monotherapy versus placebo on changes in office-based systolic

and diastolic blood pressure.

endpoint: Change in systolic and diastolic blood pressure from baseline to

Week6 and Week16.

Study description

Background summary

Patients with cirrhosis with features of portal hypertension have limited treatment options and
significant risk of decompensation and death with limited pharmacological treatment options.

2.2.1 Cirrhosis with Features of Portal Hypertension
Cirrhosis is the end-stage result of chronic liver injury/disease and is characterised by
advanced fibrosis and, ultimately, hepatic failure. Cirrhosis may be compensated in which no
clinical complications that affect outcome (i.e., variceal haemorrhage, ascites, hepatic
encephalopathy, hepatocellular cancer) have occurred, or decompensated, in which patients
have had at least one clinical complication. In decompensated patients, the liver is unable to
perform vital metabolic, synthetic and storage functions (Tsochatzis et al, 2014). The
aetiology of cirrhosis varies with viral hepatitis (hepatitis B and C), alcoholic liver disease,

and non-alcoholic steatohepatitis (NASH) being the leading causes of cirrhosis globally, with
less common causes including autoimmune hepatitis, primary sclerosing cholangitis, primary
biliary cholangitis, haemochromatosis, and Wilson*s disease (Romanelli et al, 2016). Cirrhosis
is a serious condition which leads to significant morbidity, resource intensive complications,
hepatocellular carcinoma, and, in the absence of liver transplantation, death. The Global
Burden of Disease study in 2017 reported over 1.32 million cirrhosis-related deaths globally,
which was approximately 2.4% of all deaths worldwide
(GBD 2017 Cirrhosis Collaborators, 2020).
Portal hypertension is a major complication of chronic liver disease. The primary cause of
portal hypertension in cirrhosis is an increase in intrahepatic vascular resistance due to
structural changes associated with fibrosis and increased vascular tone in the hepatic
microcirculation (Iwakiri, 2014). As portal hypertension develops, the formation of collateral
vessels and arterial vasodilation progress, which results in increased blood flow to the portal
circulation (Iwakiri, 2014). Eventually, a hyperdynamic circulatory syndrome develops,
leading to oesophageal varices and/or ascites (Poordad, 2015).

2.2.2 Current Treatment Options for Patients with Cirrhosis with Features of Portal Hypertension
Standard treatment for patients with chronic liver disease centres upon treatment of the
underlying cause of liver disease, e.g., abstinence from alcohol, anti-viral agents for viral
hepatitis, and treatment of underlying metabolic disease in NASH. Although HCV can now be
eradicated, given the continued emergence of fatty liver diseases, disease modifying therapies
are in general expected to have marginal impact on the outcome in patients with cirrhosis with
portal hypertension (Gunarathne et al, 2020). Accordingly, there is an enormous unmet need
for new treatments in patients with cirrhosis with features of portal hypertension. Current
guidelines support the use of non-selective beta blockers, diuretics and vasoactive drugs
(Gunarathne et al, 2020). In patients developing variceal haemorrhage,

intervention with TIPS
may be used to reduce portal hypertension (García-Pagán et al, 2020).

Study objective

This study has been transitioned to CTIS with ID 2023-505405-17-00 check the CTIS register for the current data.

The main objective of this Phase IIa/b study is to demonstrate the effect of zibotentan on HVPG, and that dapagliflozin can mitigate fluid retention safety concerns
regarding its use in this population.

Study design

This is a two part Phase IIa/b multicentre, randomised, double-blind, placebo-controlled, parallel group dose-ranging study to assess the efficacy, safety, and tolerability of the combination of zibotentan and dapagliflozin, and dapagliflozin monotherapy versus placebo in participants with cirrhosis with features of portal hypertension.

Part A will assess the efficacy, safety, and tolerabilityof the combination of 2.5 mg zibotentan and 10 mg dapagliflozin versus placebo in participants with Child-Pugh A cirrhosis with features of portal hypertension and with no history of decompensation events. If the safety profile is determined to be acceptable at the conclusion of Part A, Part B will investigate efficacy, safety, and tolerability of 1, 2.5, or 5 mg zibotentan combined with 10 mg dapagliflozin and of 10 mg dapagliflozin monotherapy versus placebo in participants with cirrhosis with features of portal hypertension. Part B will include a broader range of Child-Pugh A and Child-Pugh B cirrhosis participants, including those with more severe disease, a history of decompensation events, or current ascites.

The study will be conducted in approximately 30 study centres in North America and Europe.

Part A will include the following periods:
*Screening Period: up to 6weeks; to confirm participant eligibility and collect baselinedata (Visits 1 and 2). Before randomisation, baseline HVPG recording (Visit 2) must beof good enough quality as judged by central reader of HVPG, to randomise theparticipant.

*Treatment Period: 6 weeks; at Visit 3 (Day1), participants will be randomised and willtake the first dose of the study intervention. At each study visit during the treatmentperiod (except at days of HVPG assessment and VCTE/Fibroscan assessment),participants will take the once daily dose at the

study centre.

*Follow-up Period: 2 weeks; participants will return to the study centre for follow-upassessments approximately 2 weeks after their last dose of study intervention.

Disclosure Statement: This is a parallel group, 2-arm study that is blinded to the participants, investigators, and sponsor.

Part B will include the following periods:
*Screening Period: up to 6weeks; to confirm participant eligibility and collect baselinedata (Visits 1 and 2). Before randomisation, baseline HVPG recording (Visit2) must be of good enough quality as judged by central reader of HVPG, to randomise the participant.
*Treatment Period: 16 weeks; at Visit 3 (Day1), participants will be randomised and willtake the first dose of the study intervention. At each study visit during the treatmentperiod (except at days of HVPG assessment and VCTE/Fibroscan assessment, if visitprocedures are separated on different days), participants will take the once daily dose atthe study centre.
*Follow-up Period: 2 weeks; participants will return to the study centre for follow-upassessments approximately 2 weeks after their last dose of study intervention.

Disclosure Statement: This is a parallel group, 5-arm study that is blinded to the participants, investigators, and sponsor.

Intervention

Part A: Participants who meet the eligibility criteria and agree to participate will be randomised to one of the following 2 treatment groups (15participants per group).

*Treatment Group 1: placebo matching zibotentan capsule + placebo matchingdapagliflozin tablet.
*Treatment Group 2: zibotentan capsule 2.5 mg + dapagliflozin tablet 10mg

The study intervention will be a once daily dose of the assigned study intervention (oralcapsules and tablets) for 6weeks, in addition to their standard of care therapy. Total study duration for participants in Part A will be approximately 14weeks (including the screening and follow- up period).

Part B: Participants who meet the eligibility criteria and agree to participate will be randomised to one of the following 5treatment groups (22participants per group).

*Treatment Group 1: placebo matching zibotentan capsule + placebo

matchingdapagliflozin tablet.
*Treatment Group 2: placebo matching zibotentan capsule + dapagliflozin tablet 10 mg.
*Treatment Group 3: zibotentan capsule 1 mg + dapagliflozin tablet 10mg.
*Treatment Group 4: zibotentan capsule 2.5 mg + dapagliflozin tablet 10mg.
*Treatment Group 5: zibotentan capsule 5 mg + dapagliflozin tablet 10 mg.

Study burden and risks

Dapagliflozin administration is generally safe and well tolerated. The potential and identified risks of dapagliflozin treatment have been well characterised through the dapagliflozin clinical development program and from post marketing data. In clinical studies, commonly reported AEs include UTIs, genital infections, polyuria, and hypoglycaemia when combined with insulin or a sulfonylurea. In addition, diabetic ketoacidosis was commonly seen in T1DM patients treated with dapagliflozin but was rare in clinical trials with T2DM patients.

The adverse clinical effects of zibotentan observed in healthy volunteers and oncology populations were largely due to its pharmacologically-mediated effects on ET receptor antagonism resulting in vasodilation: headache, hypotension, nasal congestion, peripheral oedema, conjunctival reddening, dizziness, flushing, minor decreases in systemic vascular resistance, minor increases in cardiac output, and effects due to haemodilution which leads to a reduction in the concentration of the cellular elements of blood: reduction in Hb, anaemia.
Reduction in Hb tends to develop within a month of commencing the drug and in most patients is mild (CTC Grade 1/2), non-progressive and tends to reverse on stopping drug.
However, some patients in oncology studies have developed clinical anaemia. The adverse clinical effect of heart failure has been observed, being more commonly reported in Castration-resistant Prostate Cancer (CRPC) patients receiving zibotentan than in those receiving placebo. The frequency of reports in patients receiving zibotentan has been less than 10% and most cases have responded to standard heart failure treatment.

More detailed information about the known and expected benefits and potential

risks of
zibotentan and dapagliflozin may be found in the respective Investigator*s Brochures
(Zibotentan Investigator*s Brochure and Dapagliflozin Investigator*s Brochure).

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

Participant must be aged 18 years and <= 80 years of age at the time of signing theinformed consent.

Part A participants who have the following:
(a) Clinical and/or histological diagnosis of cirrhosis with either (i) features of portalhypertension or (ii) liver stiffness >= 21 kPa.

(b) MELD score < 15.
(c) Child-Pugh score <= 6.
(d) No clinically evident ascites
(e) No evidence of worsening of hepatic function (eg, no clinically significant change insigns, symptoms, or laboratory parameters of hepatic disease status) within the lastmonth prior to dosing, as determined by the investigator or usual practitioner.
(f) HVPG recording of good enough quality as judged by a central reader.

Part B participants who have the following:
(a) Clinical and/or histological diagnosis of cirrhosis with features of portalhypertension.
(b) MELD score < 15.
(c) Child-Pugh score < 10.
(d) No ascites or ascites up to grade 2 without change in diuretic treatment within the lastmonth prior to first dose and no paracentesis within the last month or plannedparacentesis in the next 4 months at screening.
(e) No evidence of worsening of hepatic function (eg, no clinically significant change insigns, symptoms, or laboratory parameters of hepatic disease status) within the lastmonth prior to dosing, as determined by the investigator or usual practitioner.
(f) HVPG recording of good enough quality as judged by a central reader.

Exclusion criteria

Study principal exclusion criteria:
a) Any evidence of a clinically significant disease which in the investigator's opinion makes it undesirable for the participant to participate in the study.
b) Liver cirrhosis caused by chronic cholestatic liver disease
c) ALT or AST >= 150 U/L and/or total bilirubin >= 3 × ULN
d) Acute liver injury caused by drug toxicity or by an infection.
e) Any history of hepatocellular carcinoma.
f) Liver transplant or expected liver transplantation within 6 months of screening.
g) History of TIPS or a planned TIPS within 6 months from enrolment into the study.
h) Active treatment for HCV within the last 1 year or HBV antiviral therapy for less than 1 year.
i) Participants with T1DM.

Medical Conditions (Part A only)
a) INR > 1.5.
b) Serum/plasma levels of albumin <= 35 g/L.
c) Platelet count < 75 × 109/L.
d) History of ascites

e) History of hepatic hydrothorax
f) History of portopulmonary syndrome
g) History of hepatic encephalopathy
h) History of variceal haemorrhage
i) History of acute kidney injury
j) History of heart failure, including high output heart failure (eg, due to hyperthyroidism or Paget's disease)

Medical Conditions (Part B only)
a) INR > 1.7.
b) Serum/plasma levels of albumin <= 28 g/L.
c) Platelet count < 50 × /109L.
d) Acute kidney injury within 3 months of screening.
e) History of encephalopathy of West Haven grade 2 or higher.
f) History of variceal haemorrhage within 6 months prior to screening.
g) NYHA functional heart failure class III or IV or with unstable heart failure requiring hospitalisation for optimisation of heart failure treatment and who are not yet stable on heart failure therapy within 6 months prior to screening.
h) Heart failure due to cardiomyopathies that would primarily require specific other treatment: eg, cardiomyopathy due to pericardial disease, amyloidosis or other infiltrative diseases, cardiomyopathy related to congenital heart disease, primary hypertrophic cardiomyopathy, cardiomyopathy related to toxic or infective conditions (ie, chemotherapy, infective myocarditis, septic cardiomyopathy).
i) High output heart failure (eg, due to hyperthyroidism or Paget's disease).
j) Heart failure due to primary cardiac valvular disease/dysfunction, severe functional mitral or tricuspid valve insufficiency, or planned cardiac valve repair/replacement.

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:	Recruiting
Start date (anticipated):	03-04-2023
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Forxiga
Generic name:	dapagliflozine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	zibotentan
Generic name:	NA

Ethics review

Approved WMO Date:	01-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2023
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
EU-CTR	CTIS2023-505405-17-00
EudraCT	EUCTR2021-006577-30-NL
ClinicalTrials.gov	NCT05516498
CCMO	NL82798.056.22