Randomised, open-label and parallel group trial to investigate the effects of oral BI 685509 alone or in combination with empagliflozin on portal hypertension after 8 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis.

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The trial will investigate the safety and tolerability of BI 685509 in patients with CSPH in compensated cirrhosis due to HBV, HCV and NASH with or without T2DM and the combination of BI 685509 and empagliflozin in patients with CSPH in compensated...

Ethical review	Approved WMO
Status	Pending
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON53952

Source
ToetsingOnline

Brief title
Investigate BI685509 with/without empagliflozin in patients with CSPH.

Condition

- Vascular hypertensive disorders

Synonym
Clinical significant portal hypertension (CSPH), high blood pressure in portal vein

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim BV

Intervention

Keyword: Compensated cirrhosis, CSPH, HVPG

Outcome measures

Primary outcome

The primary endpoint is the percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of treatment.

Secondary outcome

- occurrence of a response, which is defined as > 10% reduction from baseline HVPG (measured in mmHg) after 8 weeks of treatment

- occurrence of one or more decompensation events (i.e. ascites, VH, and / or overt HE) during the 8-week treatment period

- occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on Investigator judgement, during the 8-week treatment period

- occurrence of discontinuation due to hypotension or syncope during the 8-week treatment period

Study description

Background summary

Portal hypertension (PH) is the initial and main consequence of cirrhosis and is responsible for the majority of its complications. The only currently approved clinical approaches to prevent PH-related decompensating events in patients with compensated cirrhosis are endoscopic variceal ligations or off-label use of non-selective betablockers (NSBBs) or carvedilol for the prophylaxis of a first variceal bleeding. However, not all patients with PH achieve a haemodynamic response with these current treatment options. NSBBs and carvedilol are currently used to prevent complications of cirrhosis and improve survival in patients, but these benefits only occur in less than half of patients treated, and mostly in those who achieve a substantial decrease in portal pressure. An unmet need remains for a substantial number of patients who cannot tolerate treatment with NSBBs or carvedilol due to decreased systemic blood pressure (BP) and heart rate (HR), and who have a higher risk for further progression into decompensation.

Therefore, there is an existing unmet medical need to reduce portal pressure and improve liver perfusion in this population of patients with PH and especially clinically significant portal hypertension (CSPH) and compensated cirrhosis. CSPH is associated with an increased risk of developing varices, overt clinical decompensation (ascites, VH, and HE), postsurgical decompensation, and hepatocellular carcinoma.

Study objective

The trial will investigate the safety and tolerability of BI 685509 in patients with CSPH in compensated cirrhosis due to HBV, HCV and NASH with or without T2DM and the combination of BI 685509 and empagliflozin in patients with CSPH in compensated cirrhosis due to NASH with T2DM, on top of standard of care respectively. The primary objective is to estimate the percentage change in HVPG from baseline measured after 8 weeks.

Study design

Patients will be enrolled in the trial and screened for eligibility once they have signed the informed consent. The screening period consists of up to 3 visits (Visits 1a, b and c) and will last a maximum of 6 weeks. Patients will be able to progress from one visit to the next when eligibility of the previous visit is confirmed. Patients who remain eligible and who successfully complete this period will proceed to the 8-week open label, active treatment period.

In total, 80 patients will enter the trial with 20 patients in the HBV arm (treatment group 1: 3mg BID BI 685509 alone), 20 patients in the HCV arm (treatment group 2: 3mg BID BI 685509 alone) and 40 patients in the NASH arms (treatment group 3 and 4). NASH patients without diagnosis of T2DM can only enter treatment group 3 (3mg BID BI 685509 alone) at Visit 2. NASH patients

with diagnosis of T2DM will be randomized at visit 2 in a 1:1 ratio into either treatment group 3 (3mg BID BI 685509 alone) or treatment group 4 (3mg BID BI 685509 + 10mg QD empagliflozin).

Following enrollment and randomization at visit 2, patients will begin the intake of trial medication(s) and will enter a dose-titration period of BI 685509. Following the dose-titration period, and if the dose is tolerated, patients will remain on the highest dose of BI 685509 for the remainder of the treatment period until they reach the End of Treatment (EoT) visit and 8 weeks of treatment. Patients in the treatment group 4 will receive a fixed dose of 10mg QD empagliflozin in addition to BI 685509 starting at visit 2. After the 8 week treatment period all patients will enter a 4 week follow-up period without trial medication.

See protocol section 3.1

Intervention

8 weeks of treatment consisting of a 2 weeks dose up-titration period and a 6 weeks maintenance period.

20 patients in the HBV arm: treatment group 1 with 3mg BID BI 685509
20 patients in the HCV arm: treatment group 2 with 3mg BID BI 685509
20 patients in the NASH patient arm with or without diagnosis of T2DM: treatment group 3 with 3mg BID BI 685509
20 patients in the NASH patient arm with diagnosis of T2DM: treatment group 4 with 3mg BID BI 685509 + 10mg QD empagliflozin

See protocol section 4.1

Study burden and risks

Burden:
Participants will have to visit the hospital 10 times in a maximum period of 18 weeks. During the hospital visits, the following assessments are performed (total number during the entire study):
- Physical examination: 2x (and if deemed necessary based on investigator judgement)
- Blood pressure and heart rate measurement: 8x (3 times during visits 2-5)
- Measuring height, weight, and waist and hip circumference: 8x
- ECG: 8x (3 times during visits 2-5)
- Blood collection: 7x
- Pregnancy test (if applicable): 5x
- Gastroscopy: 1x (if necessary)
- HVPG (Hepatic Venous Pressure Gradient) measurement: 2x
- Echo: 4x

- Fibroscan (from liver and spleen): 4x
- Blood collection for biobanking (optional): 2x
- Participants must visit the hospital fasted on the days that an HVPG measurement, gastroscopy, Fibroscan, ultrasound, some blood samples (safety testing, PK, biomarker or biobanking) needs to be performed: 6x
- Patients need to complete a reminder card by entering time of study medication intake 3 days prior to the visits where PK samples are collected: 5x
- Women should not become pregnant or breast-feed during the study
- participants are provided with a device to measure their blood pressure and heart rate at home every day during a 12-week period.
- Study medication intake (twice a day Bi 685509 for 8 weeks for patients with HVB, HVC and NASH with or without diabetes type 2; NASH patients with diabetes type 2 who are randomized in the empagliflozin arm will take Bi 685509 twice a day + empagliflozin once a day).

Risks:
Patients may experience side effects.
There are also risks associated with blood draws, HVPG measurements and gastroscopy. See protocol section 1.4.2.

Contacts

Public
Boehringer Ingelheim

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Scientific
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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. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
2. Male or female who is >= 18 (or who is of legal age in countries where that is greater than 18) and <= 75 years old at screening (Visit 1a)
3. Clinical signs of CSPH as described by either one of the points below. Each trial patient must have a gastroscopy during the screening period (Visit 1b) or within 6 months prior to screening (Visit 1b).
• documented endoscopic proof of oesophageal varices and / or gastric varices at screening (Visit 1b) or within 6 months prior to screening (Visit 1b)
• documented endoscopic-treated oesophageal varices as preventative treatment
4. CSPH defined as baseline HVPG >= 10 mmHg (measured at Visit 1c), based on a local interpretation of the pressure tracing
5. Diagnosis of compensated cirrhosis due to HCV, HBV, or NASH with or without T2DM. Diagnosis of cirrhosis must be based on histology (historical data is acceptable) or on clinical evidence of cirrhosis (e.g. platelet count < 150 x 109/L [150 x 103/µL], nodular liver surface on imaging or splenomegaly etc.)
Diagnosis of NASH based on either
• Current or historic histological diagnosis of NASH OR steatosis
OR
• Clinical diagnosis of NASH based on historic or current imaging diagnosis of fatty liver (Fibroscan, US, MRI, CT) AND at least 2 current or historic comorbidities of the metabolic syndrome (overweight/obesity, T2DM, hypertension, hyperlipidemia)
6. Willing and able to undergo HVPG measurements per protocol (based on Investigator judgement)
7. If receiving statins must be on a stable dose for at least 3 months prior to screening (Visit 1b), with no planned dose change throughout the trial
8. If receiving treatment with NSBBs or carvedilol must be on a stable dose for at least 1 month prior to screening (Visit 1b), with no planned dose change throughout the trial
9. If receiving pioglitazone, GLP1-agonists, or vitamin E must be on a stable dose for at least 3 months prior to screening (Visit 1b), with no planned dose change throughout the trial
10. WOCBP must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly from the randomisation visit (Visit 2) until 7 days after the last treatment in this trial. The patient must agree

to periodic pregnancy testing during participation in the trial.
11. Men able to father a child and who have a female sexual partner of CBP, must use a condom with or without spermicide, or adopt complete sexual abstinence, or be vasectomised (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), from the randomisation visit (Visit 2) until 7 days after the last treatment in this trial.

Exclusion criteria

1. Previous clinically significant decompensation events (e.g. ascites [more than perihepatic ascites], VH and / or overt / apparent HE)
2. History of other forms of chronic liver disease (e.g. alcohol-related liver disease (ARLD), autoimmune liver disease, primary biliary sclerosis, primary sclerosing cholangitis, Wilson*s disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency)
3. Patients without adequate treatment for HBV, HCV or NASH as per local guidance (e.g. antiviral therapy for chronic HBV or HCV infection or lifestyle modification in NASH)
• if received curative anti-viral therapy for HCV, no sustained virological response (SVR) or SVR sustained for less than 2 years prior to screening or if HCV RNA detectable
• If receiving anti-viral therapy for HBV, less than 6 months on a stable dose prior to screening, with planned dose change during the trial or HBV DNA detectable
• Weight change >= 5% within 6 months prior screening
4. Must take, or wishes to continue the intake of, restricted concomitant therapy or any concomitant therapy considered likely (based on Investigator judgement) to interfere with the safe conduct of the trial
5. SBP < 100 mmHg and DBP < 70 mmHg at screening (Visit 1a)
6. Model of End-stage Liver Disease (MELD) score of > 15 at screening (Visit 1a),
calculated by the central laboratory
7. Hepatic impairment defined as a Child-Turcotte-Pugh score >= B8 at screening (Visit 1a),
calculated by the site, using central laboratory results
8. ALT or AST > 5 times upper limit of normal (ULN) at screening (Visit 1a), measured by
the central laboratory
9. eGFR (CKD-EPI formula) < 20 mL/min/1.73 m2 at screening (Visit 1a), measured by the
central laboratory
10. Alpha-fetoprotein > 50 ng/mL (> 50 µg/L) at screening (Visit 1a), measured by the
central laboratory
11. An active infection with SARS-CoV-2 (or who is known to have a positive

test from
screening [Visit 1a] until randomisation [Visit 2])
12. Prior orthotopic liver transplantation
13. Prior or planned TIPS or other porto-systemic bypass procedure
14. Known portal vein thrombosis
15. History of clinically relevant orthostatic hypotension, fainting spells or blackouts due to
hypotension or of unknown origin (based on Investigator judgement)
16. QTcF-interval >450 ms in men or >470 ms in women at screening (Visit 1a), a family
history of long QT syndrome, or concomitant use of therapies with a known risk of
Torsade de Pointes or planned initiation of such therapies during the trial
17. Type 1 diabetes mellitus, or history of other autoimmune causes of diabetes mellitus (e.g.
LADA)
18. Patients at increased risk of ketoacidosis in the opinion of the investigator.
19. Contraindication to any of the trial assessments (e.g. poor patient co-operation for
gastroscopy, cardiac pacemakers for FibroScan® [if contraindicated based on local market
approval] etc.)
20. Major surgery (major according to the investigator*s assessment) performed within 12
weeks prior to randomisation (Visit 2) or planned during the trial, e.g. hip replacement.
21. Any documented active or suspected malignancy or history of malignancy within 5 years
prior to screening (Visit 1a), except appropriately treated basal cell carcinoma of the skin
or in situ carcinoma of uterine cervix
22. History of (in the 6 months prior to randomisation [Visit 2]), or ongoing, chronic drug
abuse, or not expected to comply with the protocol requirements for any other reason that,
based on Investigator judgement, makes the patient an unreliable trial recruit or unlikely
to complete the trial as scheduled
23. Previous randomisation in this trial, previous exposure to BI 685509, or an allergy /
contraindication to BI 685509 and / or any of the excipients
24. Currently enrolled in another investigational device or drug trial, or less than 30 days or 5
half-lives (whichever is longer) prior to randomisation (Visit 2) since ending another
investigational device or drug trial, or receiving other investigational

treatment(s)
25. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
26. Any other medical condition that, based on Investigator judgement, poses a safety risk
for the patient or may interfere with the objectives of the trial

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2022
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BI 685509
Generic name:	NVT
Product type:	Medicine
Brand name:	Jardiance
Generic name:	Empagliflozine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-03-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	27-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.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	EUCTR2021-005171-40-NL
ClinicalTrials.gov	NCT05282121
CCMO	NL80492.018.22