Randomised, double-blind, placebo-controlled and parallel group trial to investigate the effects of two doses (up-titration to a fixed dose regimen) of oral BI 685509 on portal hypertension after 24 weeks treatment in patients with clinically significant portal hypertension (CSPH) in compensated cirrhosis

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

Summary

ID

NL-OMON54020

Source
ToetsingOnline

Brief title
A study to investigate the effect of BI 685509 in people with CSPH.

Condition

- Hepatic and hepatobiliary disorders
- 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: cirrhosis, CSPH, HVPG

Outcome measures

Primary outcome

The primary endpoint is the percentage change in HVPG from baseline (measured

in mmHg) after 24 weeks of treatment.

Secondary outcome

- Percentage change in HVPG from baseline (measured in mmHg) after 8 weeks of

treatment

- Response defined as > 10% reduction from baseline HVPG (measured in mmHg)

after 8

weeks of treatment

- Response defined as > 10% reduction from baseline HVPG (measured in mmHg)

after 24

weeks of treatment

- Occurrence of one or more decompensation events (i.e. ascites, VH, and / or

overt HE)

during the 24 week treatment period

- Occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on

Investigator

judgement, during the first 8 weeks of the treatment period

- Occurrence of CTCAE grade 3 (or higher) hypotension or syncope based on

Investigator

judgement, during the 24 week treatment period

- Occurrence of discontinuation due to hypotension or syncope during the first

8 weeks of

the treatment period

- Occurrence of discontinuation due to hypotension or syncope during the 24

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 compare two doses of BI 685509 (2 mg and 3 mg BID) with placebo, on top of standard of care, in patients with CSPH in compensated alcohol-related cirrhosis. The primary objective is to estimate the mean difference between treatment groups with placebo in percentage change in HVPG from baseline measured after 24 weeks. Safety and tolerability will also be investigated.

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 4 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 randomised 24 week double-blind treatment period. Randomisation to one of three treatment groups (i.e. one of the two doses of BI 685509 or placebo) will occur at Visit 2 in a 1:1:1 ratio. Following randomisation patients will begin the intake of trial medication and will enter a dose-titration period. Following the dose-titration period, and if the dose is tolerated, patients will remain on their maximum planned maintenance dose for the remainder of the treatment period until they reach the End of Treatment (EoT) visit and 24 weeks of treatment. After the 24 week randomised treatment period all patients will enter a 4 week follow-up period without trial medication.

See protocol section 3.1

Intervention

24 weeks of treatment consisting of a 2 weeks dose up-titration period and a 22 weeks maintenance period.
- 50 patients on BI 685509 2 mg (Group 1)
- 50 patients on BI 685509 3 mg (Group 2)
- 50 patients on placebo (Group 3)

Inake of tablets twice a day (2 tablets per dose so 4 tablets per day).

See protocol section 4.1

Study burden and risks

Burden:
Participants will have to visit the hospital 14 times in a maximum period of 34 weeks. During the hospital visits, the following assessments are performed (total number during the entire study):
- Physical examination: 3x (and if deemed necessary based on investigator judgement)
- Blood pressure and heart rate measurement: 12x (3 times during visits 2-5)
- Measuring height, weight, and waist and hip circumference: 12x
- ECG: 12x (3 times during visits 2-5)
- Blood collection: 11x
- Pregnancy test (if applicable): 9x
- Gastroscopy: 1x
- HVPG (Hepatic Venous Pressure Gradient) measurement: 3x
- Echo: 5x
- Fibroscan (from liver and spleen): 5x
- Blood collection for biobanking (optional): 3x
- Patient Reported Outcomes (EQ-5D-5L, SF-36v2, CLDQ): 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: 7x
- 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: 7x
- 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 28 weeks period.
- Study medication intake (twice a day for 24 weeks).

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

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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 alcohol-related cirrhosis. Diagnosis 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).
6. Abstinence from significant alcohol misuse / abuse for a minimum of 2 months

prior to screening (Visit 1a), and the ability to abstain from alcohol throughout the trial (both evaluated based on Investigator judgement).
7. Willing and able to undergo HVPG measurements per protocol (based on Investigator judgement)
8. 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.
9. 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.
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.
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, 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 apparent HE).
2. History of other forms of chronic liver disease (e.g. non-alcoholic steatohepatitis [NASH], Hepatitis B virus [HBV], untreated HCV, autoimmune liver disease, primary biliary cholangitis, primary sclerosing cholangitis, Wilson*s disease, haemachromatosis, alpha-1 antitrypsin [A1At] deficiency).
3. Has received curative anti-viral therapy with direct-acting anti-virals within the last 2 years for HCV, or, if such a treatment was > 2 years ago and there is no sustained virological response (SVR) at screening, or, must take curative anti-viral therapy with direct-acting anti-virals throughout the trial.
4. ARLD without adequate treatment (e.g. lifestyle modification) or with ongoing pathological drinking behaviour (misuse / abuse based on Investigator judgement).
5. 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.
6. SBP < 100 mmHg and DBP < 70 mmHg at screening (Visit 1a).
7. Model of End-stage Liver Disease (MELD) score of > 15 at screening (Visit 1a), calculated by the central laboratory.
8. Hepatic impairment defined as a Child-Turcotte-Pugh score >= B8 at screening (Visit 1a), calculated by the site, using central laboratory results.
9. ALT or AST > 5 times upper limit of normal (ULN) at screening (Visit 1a), measured by the central laboratory.
10. eGFR (CKD-EPI formula) < 20 mL/min/1.73 m2 at screening (Visit 1a),

measured by the central laboratory.
11. Alpha-fetoprotein > 50 ng/mL (> 50 µg/L) at screening (Visit 1a), measured by the central laboratory.
12. An active infection with SARS-CoV-2 (or who is known to have a positive test from screening [Visit 1a] until randomisation [Visit 2]).
13. Prior orthotopic liver transplantation.
14. Prior or planned TIPS or other porto-systemic bypass procedure.
15. Known portal vein thrombosis.
16. History of clinically relevant orthostatic hypotension, fainting spells or blackouts due to hypotension or of unknown origin (based on Investigator judgement).
17. 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.
18. QTcF-interval > 450 ms in men or > 470 ms in women at screening, a family history of long QT syndrome, or concomitant use of therapies with a known risk of Torsade de Pointes at screening or planned initiation of such therapies during the trial.
19. Major surgery (based on Investigator judgement) performed within 3 months prior to randomisation (Visit 2) or planned during the trial, e.g. hip replacement.
20. 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.).
21. 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.
22. 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.
23. Previous randomisation in this trial, previous exposure to BI 685509, or an allergy/ contraindication to BI 685509 and matching placebo / or any of their 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 whilst in the trial.

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:	Pending
Start date (anticipated):	07-03-2022
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	BI 685509
Generic name:	nvt

Ethics review

Approved WMO Date:	04-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2023
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:	03-04-2023
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:	23-11-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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Approved WMO Date:	28-03-2024
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	EUCTR2021-001285-38-NL
ClinicalTrials.gov	NCT05161481
CCMO	NL78570.018.21