A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multiple-dose Phase 2 Study to Evaluate the Efficacy and Safety of BMS-986263 in Adults with Compensated Cirrhosis from Nonalcoholic Steatohepatitis (NASH)

Published: 12-08-2022
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Primary objectiveTo evaluate the efficacy of BMS-986263 compared with placebo to improve liver fibrosis in participants with compensated cirrhosis due to NASHSecondary objectives1. To further assess the efficacy of BMS-986263 compared with placebo...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON53971

Source
ToetsingOnline

Brief title
IM025-017

Condition

- Hepatic and hepatobiliary disorders

Synonym
Nonalcoholic Steatohepatitis

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Compensated cirrhosis, Liver Disease, NASH, nonalcoholic steatohepatitis

Outcome measures

Primary outcome

To evaluate the efficacy of BMS-986263 compared with placebo to improve liver fibrosis in participants with compensated cirrhosis due to NASH, by:

Proportion of participants who achieve >= 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), as determined by liver biopsy after 12 weeks of treatment.

Secondary outcome

To further assess the efficacy of BMS-986263 compared with placebo to improve liver fibrosis, as determined by liver biopsy, in participants with compensated cirrhosis due to NASH, by:

* Proportion of participants with >= 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score), with no worsening of NASH after 12 weeks of treatment (worsening defined as an increase of the NAS by >= 1 point)

* Proportion of participants with >= 2 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) after 12 weeks of treatment Proportion of

* Proportion of participants with >= 1 stage improvement in liver fibrosis (modified Ishak score) after 12 weeks of treatment

* Proportion of participants with >= 2 stage improvement in liver fibrosis

(modified Ishak score) after 12 weeks of treatment

* Change from baseline in CPA after 12 weeks of treatment

To assess the safety and tolerability of BMS-986263 in participants with

compensated cirrhosis due to NASH, by:

* Incidences of SAEs, AEs, clinical laboratory values, vital signs, physical

examination findings, and ECGs

* Change from baseline in BMD, as measured by DXA scan, at Follow-up Week 24

To assess the PK of BMS-986263 in participants with compensated cirrhosis due

to NASH

* Plasma concentrations of siRNA, DPD, HEDC, and S104 (components of BMS-986263

for injection)

Study description

Background summary

Study IM025017 aims to demonstrate the antifibrotic efficacy of BMS-986263, using
a liver fibrosis histological endpoint, and the safety and tolerability of BMS-986263, as assessed
by adverse events (AEs), serious adverse events (SAEs), laboratory results (including assessment
of potential drug-induced liver injury), vital signs, physical examinations, electrocardiograms
(ECGs), retinoid toxicity monitoring, infusion-related reaction monitoring, and bone mineral
density (BMD) monitoring, in participants with nonalcoholic steatohepatitis (NASH) and

compensated cirrhosis.
Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver
disease in the world today. NASH, which is the more advanced form of NAFLD, is defined as the
presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning), with or
without fibrosis. NASH is associated with increased mortality rates due to cardiovascular-, liver-,
and cancer-related deaths. Currently, there are no approved drugs for the treatment of NASH. With
the increasing prevalence of obesity and obesity-related diseases, NASH could soon become the
leading indication for liver transplantation and the leading cause of hepatocellular carcinoma
(HCC) globally.
NASH patients with cirrhosis have a particularly high unmet medical need for effective therapies.
Among NASH patients, the stage of fibrosis is the strongest predictor of disease-specific mortality,
and patients with cirrhosis are at the greatest risk for disease-related morbidity and mortality.
Patients with cirrhosis are particularly at increased risk for poor clinical outcomes, including
hepatic decompensation events and the need for liver transplant. It is reasonable to assume that an
improvement in fibrosis would be predictive of clinical benefit, and a reduction of fibrosis in
patients with compensated cirrhosis, if substantial, could lead to improvements in liver function
and long-term clinical outcomes.

Study objective

Primary objective
To evaluate the efficacy of BMS-986263 compared with placebo to improve liver fibrosis in participants with compensated cirrhosis due to NASH

Secondary objectives
1. To further assess the efficacy of BMS-986263 compared with placebo to improve liver fibrosis, as determined by liver biopsy, in participants with compensated cirrhosis due to NASH
2.To assess the safety and tolerability of BMS-986263 in participants with compensated cirrhosis due to NASH
3. To assess the PK of BMS-986263 in participants with compensated cirrhosis due to NASH

Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose Phase 2 study to evaluate the efficacy, safety, and tolerability of BMS-986263 in adults with compensated cirrhosis due to NASH. The primary study endpoint is the proportion of participants who achieve >= 1 stage improvement in liver fibrosis (NASH CRN Fibrosis Score) on biopsy after 12 weeks of treatment.
The study includes:
* A screening period of up to 8 weeks
* A 12-week, double-blind treatment period, during which participants will receive 1 of the following 3 treatments by intravenous (IV) infusion: 45 mg BMS-986263 once every week (QW), 90 mg BMS-986263 QW, or placebo QW
* A follow-up period of 24 weeks, during which participants will not receive investigational treatment

Participants meeting eligibility criteria during the screening period will enter the treatment period and be randomized to receive 45 mg BMS-986263 QW, 90 mg BMS-986263 QW, or placebo QW by IV infusion in a double-blind manner for 12 weeks. Participants will be stratified at Randomization by the presence of definite steatohepatitis on biopsy (yes versus no). At least 80% of participants will be required to have definite steatohepatitis on the biopsy used to confirm eligibility. Participants will receive study treatment via IV administration for a total of 12 weeks. Liver biopsy will be performed at Week 12.

This study will utilize an external Data Monitoring Committee for the duration of the study to assess safety data, and an external Independent Pathology Review Committee to assess liver biopsies for eligibility and efficacy.

Intervention

Patients who have completed screening procedures (up to 56 days duration) and met inclusion/exclusion criteria will be randomized on Day 1 of the treatment period.
Patients will be randomized in a 1:1:1 ratio using interactive response technology (IRT) to one of three treatments by intravenous (IV) infusion:
1. 45 mg BMS-986263 once every week
2. 90 mg BMS-986263 once every week
3. Placebo

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements, blood tests for safety and efficacy assessment, pregnancy testing (for females

of child bearing potential), and monitoring for adverse events and serious adverse events. Patients will be asked to complete questionnaires (CLDQ-NASH, EQ-5D-5L, PGI-S-F and PGI-S-NS). Some visits require: CT/MRI scans, MRE scans, ECGs, DXA scans and fibroscans. If there is no archival liver biopsy tissue available or the sample was taken too long ago (>=12 months) patients will be required to have a biopsy in order to participate. A liver biopsy is also required at the end of the treatment period. Patients will be monitored for 12 weeks after treatment completion. The frequency of visits and number of procedures carried out during this trial would be typically considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimize any risks or discomfort to the patient.
BMS will conduct rigorous safety monitoring to ensure patients safety by regularly & systematically reviewing safety data; the reported safety events will be closely followed-up.
Study medication and procedures related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

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 and female participants, ages >= 21 years to <= 75 years of age, inclusive, at the time of screening;
*Liver biopsy performed within 12 months prior to the screening visit or performed during the screening period. A liver biopsy performed prior to informed consent form, if utilized for eligibility, must be available for central pathology reading prior to Randomization.
i) Liver biopsy consistent with NASH Clinical Research Network (CRN) Fibrosis
Score Stage 4, as assessed by central pathology reading.
ii) Liver biopsy must either be consistent with steatohepatitis, as assessed by central
pathology reading, OR, for liver biopsies without definite steatohepatitis, there should
be some evidence of steatosis and/or ballooning and the following definition of NASH
cirrhosis must be fulfilled:
(1) Absence of other causes of liver disease AND either of the following:
(a) At least 2 of the 3 following criteria:
(i) History of body mass index [BMI] >= 30 kg/m2
(ii) History of type 2 diabetes mellitus
(iii) History of hypertension AND/OR history of dyslipidemia
OR
(b) Previous histologic readings of steatohepatitis (for biopsies > 12 months prior to screening visit) AND either history of BMI >= 30 kg/m2 OR history
of type 2 diabetes mellitus.

NOTE: At least 80% of participants will be required to have definite steatohepatitis on
the biopsy used to confirm eligibility.

Exclusion criteria

*Other active causes of liver disease (eg, alcoholic liver disease, hepatitis B

virus infection, chronic hepatitis C virus infection, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced hepatotoxicity, Wilson disease, homozygous α-1-antitrypsin deficiency, iron overload [with blood iron saturation > 50%], or hemochromatosis)
* Past or current evidence of hepatic decompensation (eg, ascites, variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis)
* Liver transplantation (past or planned)
* Child-Pugh Score > 6 at screening. Participants with a Child-Pugh Score > 6 with elevated total bilirubin and who have Gilbert Syndrome and direct bilirubin <= the upper limit of normal (ULN) may be included after discussion with the Medical Monitor
* Model for End-stage Liver Disease (MELD) score > 14 at screening. Participants with a MELD Score > 14 with elevated total bilirubin and who have Gilbert Syndrome and direct bilirubin <= the ULN may be included after discussion with the Medical Monitor
* Evidence of HCC at screening based on (i) serum alpha-fetoprotein (AFP) > 20 ng/mL
(> 16.5 IU/mL) or (ii) Liver Reporting & Data System 3, 4, or 5 as determined by historical computed tomography (CT)/magnetic resonance imaging (MRI) within 3 months prior to screening or from multiphasic CT/MRI of liver during screening
* The participant*s laboratory test results at screening include any of the following:
* Albumin < 2.8 g/dL
* INR > 2.2
* Alanine aminotransferase value >= 5× the ULN
* Aspartate aminotransferase value >= 5× the ULN
* Total bilirubin > 3.0 mg/dL, unless participant has a diagnosis of Gilbert Syndrome and direct bilirubin <= ULN
* Platelet count < 85,000/µL
* Hemoglobin A1c >= 9.0%
* Serum vitamin A (retinol) > ULN
* Inability to safely undergo a liver biopsy in the opinion of the investigator.

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:	Will not start
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BMS-986263
Generic name:	BMS-986263

Ethics review

Approved WMO Date:	12-08-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-02-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-05-2023
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2019-003932-22-NL
ClinicalTrials.gov	NCT04267393
CCMO	NL81984.000.22

Study results

Results posted: 20-08-2024

Summary results
Trial never started

First publication
01-01-1900