A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis (NASH)

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

Summary

ID

NL-OMON45452

Source
ToetsingOnline

Brief title
Stellar 4

Condition

- Hepatic and hepatobiliary disorders

Synonym
Inflammation of the liver, Nonalcoholic Steatohepatitis (NASH)

Research involving

Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences Inc

Intervention

Keyword: Digestive System Diseases, Fatty Liver, Non-alcoholic Fatty Liver Disease

Outcome measures

Primary outcome

The primary efficacy endpoint at Week 48 includes the proportion of subjects who achieve a >= 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH (defined as a >= 1-point increase in hepatocellular ballooning or lobular inflammation).

The clinical efficacy endpoint at Week 240 is event-free survival (EFS). EFS will be assessed by time to the first clinical event including liver decompensation events, liver transplantation, or all-cause mortality.

Secondary outcome

Secondary Endpoints:

• Proportion of subjects who have a >= 1-stage improvement in fibrosis without worsening of NASH at Week 240;

• Proportion of subjects who have a >= 1-stage improvement in fibrosis at Week 48 and Week 240;

• Proportion of subjects who have NASH resolution at Week 48 and Week 240

The safety of SEL in subjects with cirrhosis due to NASH will be assessed

during the study through the reporting of AEs, clinical laboratory tests, vital sign assessments and concomitant medication usage.

An external Data Monitoring Committee (DMC) that consists of three hepatologists and a PhD statistician will review the progress of the study.

They will convene after 50 subjects have completed the Week 4 visit and approximately every 6 months thereafter to monitor the study for safety events.

Study description

Background summary

see protocol page 19 "1.1 background"

Study objective

The primary objective of this study is:
• To evaluate whether selonsertib (SEL, previously known as GS 4997) can cause fibrosis regression and reduce associated complications in subjects with cirrhosis due to NASH.
The secondary objective of this study is:
• To assess the safety and tolerability of SEL in subjects with NASH and cirrhosis

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of SEL in subjects with compensated cirrhosis due to NASH.
Subjects meeting the study*s entry criteria will be randomly assigned in a 2:2:1 ratio.

Randomization will be stratified by the presence or absence of diabetes mellitus (as determined by medical history or based on Screening lab values if previously undiagnosed [i.e. hemoglobin A1c (HbA1c) >= 6.5% or fasting plasma glucose >= 126 milligram/deciliter [mg/dL]) and by Enhanced Liver Fibrosis (ELF*) score >= 11.27 or < 11.27 during Screening.

Subjects who experience a hepatic clinical event prior to completing the Week 240 Visit of the Randomized Phase will be offered the option to rollover into

an Open Label (OL) Phase of the study. Each of these clinical events (except all-cause mortality and liver transplantation) will require confirmation by a Hepatic Events Adjudication Committee. All deaths will be reviewed by this committee to determine if liver-related.
Once the clinical event (except all-cause mortality and liver transplantation) is confirmed by the Hepatic Events Adjudication Committee, the subject will no longer participate in the Randomized Phase and will be offered the option to receive SEL 18 mg in the OL Phase for a total treatment duration of 240 weeks inclusive of the Randomized Phase. Rollover into the OL Phase of the study must occur within 60 days of confirmation of the event. Subjects starting the OL Phase of the study will complete the same study procedures as during the Randomized Phase of the study, starting with the Day 1 visit with the exception of liver biopsy, and intensive PK substudy. Hepatic clinical events will only be adjudicated during the Randomized Phase of the study.
Cardiovascular events including cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for cardiac failure, and coronary revascularization will be adjudicated by an independent Cardiovascular Events Adjudication Committee. Subjects experiencing a cardiovascular event will continue in the Randomized Phase and not rollover into the OL Phase. Cardiovascular events will be adjudicated during the Randomized Phase and the OL Phase of the study.

Intervention

• Treatment Group A: one SEL 6 mg tablet + one PTM SEL 18 mg tablet administered orally once daily
• Treatment Group B: one PTM SEL 6 mg tablet + one SEL 18 mg tablet administered orally once daily
• Treatment Group C: one PTM SEL 6 mg tablet + one PTM SEL 18 mg tablet administered orally once daily

Study burden and risks

Selonsertib (SEL, formerly GS-4997) has been studied in 13 Phase 1 and 2 clinical studies involving approximately 800 subjects including patients and healthy volunteers. In 3 Phase 2 studies of 557 patientssubjects (72 with non-alcoholic steatohepatitis [NASH], 151 with pulmonary artery hypertension [PAH], and 334 with diabetic kidney disease [DKD]) who were treated for up to 48 weeks with SEL, most side effects reported were mild. The most common side effects occurring in greater than 10% of SEL treated patients in any of the 3 Phase 2 studies were:
• Headache
• Diarrhea
• Nausea
• Sinusitis (inflammation of the sinuses)
• Nasopharyngitis and upper respiratory tract infection (common cold)

• Cough
• Dizziness
• Fatigue (feeling tired)

Abnormal liver tests have been observed with SEL.

In animal studies, SEL has been associated with embryofetal toxicity (malformations in fetuses and spontaneous abortions).

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

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Willing and able to give informed consent prior to any study specific procedures being performed
2) Liver biopsy consistent with NASH (defined as the presence of at least grade 1 steatosis, hepatocellular ballooning, and lobular inflammation according to the NAFLD Activity Score [NAS]) and cirrhosis (F4 fibrosis) according to the NASH CRN classification, in the opinion of the central reader
a) A historical liver biopsy within 12 months of the Screening visit may be accepted as the Screening biopsy if the sample is deemed acceptable for interpretation by the central reader
b) If the subject is deemed ineligible for this study, the liver biopsy, if performed according to protocol specifications and is within 6 months of the Screening visit, may be used to determine eligibility for study GS-US-384-1943
3) Subject has the following laboratory parameters at the Screening visit, as determined by the central laboratory:
a) ALT <= 8 x ULN
b) CLcr >= 30 mL/min, as calculated by the Cockcroft-Gault equation
c) HbA1c <= 9.5% (or serum fructosamine <= 381 µmol if HbA1c is unable to be resulted)
d) INR <= 1.4, unless due to therapeutic anti-coagulation
e) Platelet count >= 100,000/µL
4) Body Mass Index (BMI) >= 18 kg/m2 at Screening
5) Males and non-pregnant, non-lactating females between 18 70 years of age; inclusive based on the date of the Screening visit
6) Females of childbearing potential (as defined in Appendix 3) must have a negative pregnancy test at Screening and Day 1
7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.

Exclusion criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study.
1) Prior history of decompensated liver disease, including clinical ascites, HE, or variceal bleeding
2) CP score > 7, as determined at Screening, unless due to therapeutic anti-coagulation
3) MELD score > 12, as determined at Screening, unless due to therapeutic anti-coagulation
4) Chronic HBV infection (HBsAg positive)
5) Chronic HCV infection (HCV Ab and HCV RNA positive). Subjects cured of HCV infection less than 5 years prior to the Screening visit are not eligible
6) Other causes of liver disease including, but not limited to, alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders (e.g., primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis), drug-induced hepatotoxicity, Wilson disease, iron overload, and alpha-1-antitryspin deficiency, based on medical history and/or centralized review of liver histology
7) History of liver transplantation
8) Current or history of HCC
9) Any weight reduction surgery in the 2 years prior to Screening or planned during the study

(weight reduction surgery is disallowed during the study), and malabsorptive weight loss surgery (e.g., Roux-en-Y or distal gastric bypass) at any time prior to Screening
10) Weight loss > 10% within 6 months of Screening
11) HIV infection (HIV Ab and HIV ribonucleic acid [HIV RNA] positive)
12) Current alcohol consumption greater than 21 oz/week for males or 14 oz/week for females (1oz/30mL of alcohol is present in 1 12oz/360mL beer, 1 4oz/120mL glass of wine, and a 1 oz/30 mL measure of 40 proof alcohol)
13) Positive urine drug screen for amphetamines, cocaine or opiates (i.e. heroin, morphine) at Screening. Subjects on stable methadone or buprenorphine maintenance treatment for at least 6 months prior to Screening may be included in the study. Subjects with a positive urine drug screen due to prescription opioid based medication are eligible if the prescription and diagnosis are reviewed and approved by the investigator
14) Unstable cardiovascular disease as defined by any of the following:
a) Unstable angina, myocardial infarction, coronary artery bypass graft surgery or coronary angioplasty within 6 months prior to Screening
b) Transient ischemic attack or cerebrovascular accident within 6 months prior to Screening
c) Symptomatic obstructive valvular heart disease or hypertrophic cardiomyopathy
d) Symptomatic congestive heart failure
e) Uncontrolled or recurrent ventricular tachycardia or other arrhythmia requiring an automatic implantable cardioverter defibrillator (AICD). Stable, controlled atrial fibrillation is allowed.
15) Use of any prohibited concomitant medication as described in Section 5.4. Subjects on Vitamin E must be on a stable dose for at least 6 months prior to the diagnostic liver biopsy and subjects on antidiabetic medications must be on a stable dose for at least 3 months prior to diagnostic liver biopsy
16) History of a malignancy within 5 years of Screening with the following exceptions:
a) Adequately treated carcinoma in situ of the cervix
b) Adequately treated basal or squamous cell cancer or other localized non-melanoma skin cancer
17) Unable to safely undergo a liver biopsy
18) Participation in another investigational study of a drug or device within 30 days or within 5 half-lives of the prior investigational agent (whichever is longer) prior to Screening
19) Concurrent participation in another therapeutic clinical study
20) Known hypersensitivity to SEL, the metabolites, or formulation excipient
21) Any laboratory abnormality or condition that, in the investigator*s opinion, could adversely affect the safety of the subject or impair the assessment of study results
22) Presence of any condition that could, in the opinion of the investigator, compromise the subject*s ability to participate in the study, including a history of substance abuse or a psychiatric condition requiring hospitalization or emergency room visit within 2 years of Screening
23) Unavailable for follow-up assessment or concern for subject*s compliance with the protocol procedures

Study design

Design

Study phase:	3
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):	16-07-2017
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nap
Generic name:	Selonsertib

Ethics review

Approved WMO Date:	22-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	11-10-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2016-004148-13-NL
ClinicalTrials.gov	NCT03053063
CCMO	NL61100.042.17