A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, MULTIPLE CENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF NGM282 ADMINISTERED FOR 12 WEEKS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS (PSC)

Published: 17-12-2015
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Primary Objective: • Evaluate the treatment effect of NGM282 as measured by the mean change in alkaline phosphatase (ALP) from Baseline to Week 12 in patients with PSC.Secondary Objectives:• Assess the safety and tolerability of NGM282 in patients...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bile duct disorders
Study type	Interventional

Summary

ID

NL-OMON43892

Source
ToetsingOnline

Brief title
NGM 15-0106

Condition

- Bile duct disorders

Synonym
bile-duct disorder, inflammation and fibrosis of the bile-ducts

Research involving
Human

Sponsors and support

Primary sponsor: NGM Biopharmaceuticals, Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: NGM282, primary sclerosing cholangitis

Outcome measures

Primary outcome

The primary efficacy endpoint for this study will be the mean change in ALP in

patients with confirmed PSC after 12 weeks of treatment.

Secondary outcome

The following secondary endpoints will be investigated:

Efficacy and PD

• Percent change from Baseline at Week 12 in ALP

• Changes and percent changes from Baseline at Week 12 in

o ALT, AST, bilirubin (total, direct), and GGT

o C4 and serum bile acids

• Bile mediated absorption as measured by fat soluble vitamins and fecal fat

content

• Changes in pruritus and fatigue, as measured by the weekly mean of the daily

Numeric Rating Scale scores

• Incidence and severity of IBD associated intestinal symptoms

• Incidence and severity of acute cholangitis

Changes in cholestatic symptoms, safety, and tolerability

• Safety and tolerability of NGM282 in subjects with PSC with 12 weeks of

treatment though the prevalence of AEs, LISSA results, changes in clinical

safety laboratory assessments, changes in vital signs, changes in ECGs, changes

in physical examination, and the prevalence of concomitant medications

• The absolute and percentage changes from Baseline at Week 12 of total

cholesterol, HDL cholesterol, and LDL cholesterol

Pharmacokinetics

• The exposure of 1 mg and 3 mg of NGM282 in subjects with PSC after 12 weeks

of treatment

Exploratory pharmacodynamics

• Assess the changes from Baseline to Week 12 of the following:

o Calprotectin

o Fecal microbiome composition

Study description

Background summary

This is a multiple center evaluation of NGM282 in a randomized, double blind, placebo controlled, parallel group study when administered for 12 weeks as a daily subcutaneous (SC) injection in patients with PSC. Approximately 60 patients will be randomized across approximately 40-45 sites worldwide.

Study objective

Primary Objective:
• Evaluate the treatment effect of NGM282 as measured by the mean change in alkaline phosphatase (ALP) from Baseline to Week 12 in patients with PSC.

Secondary Objectives:
• Assess the safety and tolerability of NGM282 in patients with PSC with 12 weeks of treatment.
• Evaluate the percentage change from Baseline at Week 12 in ALP.
• Evaluate the absolute and percentage changes from Baseline at Week 12 of the following:
o Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total, direct), and gamma glutamyl transpeptidase (GGT)
o Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides
o 7 alpha hydroxy 4 cholesten 3 one (C4) and serum bile acids
o Bile mediated absorption as measured by fat soluble vitamins and fecal fat content
• Evaluate changes in pruritus and fatigue
• Compare NM282 versus placebo with respect to the incidence and severity of:
o Inflammatory bowel disease (IBD) associated intestinal symptoms during the study period.
o Acute cholangitis during the study period.
• Evaluate the exposure of 1 mg and 3 mg of NGM282 in patients with PSC.
• Compare the dose related changes in safety, tolerability, and pharmacodynamic (PD) parameters.

Exploratory Objectives:
• Assess the changes from Baseline to Week 12 of the following:
o Calprotectin
o Fecal microbiome composition
o Exploratory fibrosis markers

Study design

This is a multiple center evaluation of NGM282 in a randomized, double blind, placebo controlled, parallel group study when administered for 12 weeks as a daily subcutaneous (SC) injection in patients with PSC. Approximately 60 patients will be randomized across approximately 40-45 sites worldwide. Patients to be studied will have confirmed PSC as defined by an elevated ALP and either cholangiography or liver histology consistent with PSC. The presence of IBD is allowed as well as treatment with stable doses of biologic, immunosuppressant, or systemic corticosteroid therapy. Ursodeoxycholic acid (UDCA) therapy is allowed at stable doses for at least 3 months and < 27 mg/kg/day. Patients with decompensated cirrhosis, cholangiocarcinoma (diagnosed or suspected), acute cholangitis, or recently placed bile duct stents will be excluded from this study. All patients with concomitant IBD will be required to have had a colonoscopy within 12 months of Screening with no evidence of dysplasia. Patients will undergo a magnetic resonance cholangiopancreatography (MRCP) at Screening.
Patients will sign the Informed Consent Form (ICF) at or prior to the Screening Visit, and will undergo screening assessments to verify eligibility for the study (up to 6 weeks).

On Day 1, subjects will be randomized into one of the three treatment arms (NGM282 1 mg, NGM282 3 mg, or placebo) in a 1:1:1 ratio. Subjects will be stratified at randomization, according to concurrent UDCA or no UDCA, to ensure an even distribution across the three groups. Study drug self administration instructions and training will be provided to the subjects and a weekly study drug kit will be dispensed. Treatment assignment will be blinded to the sites, subjects, Sponsor, and Medical Monitor throughout the study period.
The first dose (Day 1) and doses at Weeks 1, 2, 4, 8, and 12 will be self administered in the clinic, with all other doses through Week 12 self administered at home. Self administration should occur at approximately the same time in the morning for every dose in both the clinic and at home.
Subjects will return to the clinic on Weeks 1, 2, 4, and 8 for on treatment assessments and to receive weekly study drug kits. Week 12 will be the End of Treatment (EOT) clinic visit. Subjects will return to the clinic at Week 16 for an End of Study (EOS) follow up visit.

Intervention

All subjects will be treated with NGM282 or placebo for 12 weeks, and will be monitored after completing their final dose of NGM282 or placebo (4 weeks). The total duration of individual participation will be approximately 22 weeks.

Study burden and risks

Burden and risks:

Please refer to Section 5 in Investigator's Brochure for side effects of the IMP.

Possible risks associated with study-related procedures

• Blood Collection: Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding at the site of collection.

• ECG: As a result of the patches that are placed on your skin when performing the ECG, there is the possibility of rash or minor irritation of the skin at the location of patch application.

• MRCP: Magnetic resonance cholangiopancreatography uses a strong magnetic field, which is not harmful in itself, but implanted medical devices that contain metal may malfunction or cause problems during the exam. If you have any implanted devices please inform the study doctor before the procedure.

There may also be side effects and discomforts that are not yet known.

Benefit:
NGM282 represents a potentially important therapeutic option for the treatment of other bile acid disorders such as PSC through pharmacologic FGF19 signaling to reduce the synthesis of toxic bile acids.

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

Patients who meet the following criteria may be included in the study:
1. Males and females between 18 and 75 years of age inclusive who are able to comprehend instructions and follow the study procedures, and are willing to sign an Informed Consent Form (ICF).;2. Confirmed diagnosis of PSC based any two of the following three criteria:
a. Historical evidence of an elevated ALP > ULN from any laboratory

b. Liver biopsy consistent with PSC
Patients with small-duct PSC on liver biopsy must also have a concurrent diagnosis of IBD
c. Abnormal cholangiography consistent with PSC as measured by MRCP, ERCP, or percutaneous transhepatic cholangiography;3. Subjects must have certain additional laboratory parameters in specified ranges at Screening, as follows:
a. ALP > 1.5 × ULN
b. Total bilirubin <= 2.5 mg/dL
c. ALT and AST < 5 × ULN
d. Serum creatinine < 2 mg/dL or creatinine clearance > 60 mL/min by Cockroft-Gault calculation
e. Platelets < 100 K/uL
f. International Normalized Ratio (INR) <= 1.3 (in the absence of warfarin or other anticoagulant therapy)
g. Carbohydrate antigen 19-9 (CA19-9) <= 130 U/mL
Patients with a CA 19-9 > 130 U/mL may be enrolled if they have two results a minimum of 4 weeks but not greater than 1 year apart and not more than 50 U/mL difference between the two results;4. Patients taking UDCA will be allowed to enroll if meeting the following criteria:
a. Total daily dose of < 27 mg/kg/day
b. Minimum of 12 weeks of treatment
c. No significant dosage changes during 8 weeks prior to Screening
d. Minimum of 12 weeks washout period prior to Screening if UDCA is stopped;5. Patients with concomitant IBD are allowed to enroll upon meeting the following criteria:
a. A colonoscopy within 12 months of Screening with no evidence of dysplasia
b. No episode of an IBD flare or IBD flare-related bloody diarrhea or evidence of a flare within 6 months of Screening and through Day 1
c. Stable doses of biologic treatments, immunosuppressive, or systemic corticosteroids (< 10 mg/day) for > 12 weeks months prior to Screening and through Day 1
Vedolizumab is an excluded biologic treatment;6. Female patients are eligible for the study if they meet the following criteria:
a. Are not pregnant or nursing
b. Of non-childbearing potential defined as women who have had a
hysterectomy, bilateral oophorectomy, medically documented ovarian failure,
or are documented postmenopausal (follicle-stimulating hormone
> 40 mIU/mL);OR;Of childbearing potential defined as including women < 55 years of age with
2 years of amenorrhea and both the following criteria:
i. Both a negative serum pregnancy test at Screening and urine pregnancy test prior to Randomization
ii. Correct and consistent use of one of the following methods of birth control in addition to a male partner using a condom from Screening to 30 days after the last dose of study drug:
1. hormone-containing contraceptive
2. intrauterine device with a failure rate < 1% per year
3. cervical cap or diaphragm with spermicidal agent
4. tubal sterilization
5. vasectomy in male partner;7. Male subjects must agree to consistently and correctly use a condom in combination with one of the above methods of birth control from date of consent to 30 days after the last dose of study drug.;8. Subjects must be able to comply with the SC

self-administration instructions for study drug and be able to complete the study schedule of procedures.

Exclusion criteria

Any of the following will exclude potential subjects from the study:;1. Clinically significant acute or chronic liver disease of an etiology other than PSC.
a. Patients with stable treated overlapping PSC and autoimmune hepatitis (AIH) will be allowed to enroll into the study.
i. Stable treated overlapping PSC/AIH is defined as on a consistent regimen of immunosuppressive therapy for a minimum of 12 weeks and no evidence of a hepatic flare during that time period.;2. Secondary or IgG4-related sclerosing cholangitis;3. Presence of a dominant stricture of clinical concern on MRCP at Screening.
a. Patients with dominant stricture can be enrolled if the investigator feels there is no evidence on MRI or cholangiography indicative of cholangiocarcinoma or that the stricture will not result in significant fluctuations in ALP during Screening or Study period
b. Patients with a dominant stricture must have a bilirubin of <= 2.5 mg/dL for at least 6 months prior to Screening.;4. Placement of a bile-duct stent or percutaneous bile-duct drain within 3 months of Screening
a. Patients who have undergone a balloon dilation procedure of a stricture will be allowed to enroll into the study after a minimum of 4 weeks post-procedure.;5. History, evidence, or high suspicion of cholangiocarcinoma or other hepatobiliary malignancy based on imaging, screening laboratory values, and/or clinical symptoms;6. Acute cholangitis within 12 weeks of Screening and through Day 1.
a. Chronic preventive antibiotics for cholangitis will be allowed in the study.
b. Intermittent courses of antibiotics for the presumptive treatment of cholangitis are allowed if outside the 12-week window prior to Screening.;7. Evidence of decompensated cirrhosis (Child-Pugh B or C) based on histology, relevant medical
complications, or laboratory parameters.
a. Patients with compensated cirrhosis will be allowed to enroll into the study.
b. Patients with pre-sinusoidal esophageal varices with no history or evidence of bleeding may be enrolled as long as there is no other evidence of hepatic decompensation.;8. Prior liver transplantation;9. Any contraindication or inability to obtain a screening MRCP or colonoscopy (only in patients with concomitant IBD, if historical colonoscopy within the 12-month window is not available);10. Screening electrocardiogram (ECG) with clinically significant abnormalities as
determined by the Investigator;11. Positive for HBsAg, HCV-RNA, or anti-HIV;12. History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to Screening); subjects under evaluation for malignancy are not eligible. ;13. Clinically-relevant drug or alcohol abuse within 12 months of screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication.;14. Use of any prohibited concomitant medications as described in Section 5.7 within 4 weeks of Day 1 visit;15. Patients with severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized

antibodies;16. Participation in a study of another investigational agent within 4 weeks or five half-lives of the investigational drug (whichever is longer) prior to Screening;17. History of clinically significant unstable or untreated illness or any other major medical disorder that may interfere with subject treatment, assessment, or compliance with the protocol;18. Any acute or chronic condition or other disease that, in the opinion of the Investigator, would limit the patient*s ability to complete and/or participate in this clinical study;19. Presence of any other conditions (e.g., geographic or social), actual or projected, that the investigator feels would restrict or limit the patient*s participation for the duration of the study;20. Employment by NGM, participating contract research organization (CRO), or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study) or are immediate family of an NGM employee, participating CRO, or study-site employee (hence, conflict of interest issues). Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
The Investigator has discretion to repeat assessments/procedures if he/she believes there is a good chance the results were spurious and do not accurately represent the subject*s true values. Repeat assessments/procedures must be conducted within the 6-week Screening Period, prior to randomization, and a subject may only be rescreened for these labs a single time.

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:	Recruitment stopped
Start date (anticipated):	16-06-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NGM282
Generic name:	rec-h-FGF19

Ethics review

Approved WMO Date:	17-12-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-003392-30-NL
CCMO	NL55396.018.15