TITLE PAGE

Protocol Title	Evaluation of Efficacy, Safety and Tolerability of NGM282 (Aldafermin) in a Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study in Subjects with Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis (ALPINE 4)
Name of Investigational Product	Aldafermin (NGM282)
Protocol Number	282-CC-207
Sponsor Name/Contact	NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: +1 (650) 243-5555 Fax: +1 (650) 583-1646
Sponsor Study Name/Contact	[redacted] Vice President, Clinical Operations NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080, USA
Sponsor Medical Monitor Name/Contact	[redacted] Senior Vice President, Chief Medical Officer NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080, USA
IND / EudraCT Number	124675 / 2019-002341-38
Current Version – Date	Version 6.0 – 11 November 2021
Previous Version - Date	Version 1.0 – 29 August 2019 Version 2.0 – 28 October 2019 Version 3.0 – 29 January 2020 Version 4.0 – 24 September 2020 Version 5.0 – 16 March 2021

SPONSOR PROTOCOL APPROVAL AND SIGNATURE PAGE

Protocol Title	Evaluation of Efficacy, Safety and Tolerability of NGM282 (Aldafermin) in a Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study in Subjects with Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis (ALPINE 4)
Protocol Number	282-CC-207
Name of Investigational Product	Aldafermin (NGM282)
Date of Issue/Version #	11 November 2021, Version 6.0

I have read and approve the protocol specified above and agree on its content.
I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practices and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

NGM Biopharmaceuticals, Inc.,
Representative:

[redacted]

[redacted]

INVESTIGATOR PROTOCOL APPROVAL AND SIGNATURE PAGE

Protocol Title	Evaluation of Efficacy, Safety and Tolerability of NGM282 (Aldafermin) in a Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study in Subjects with Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis (ALPINE 4)
Protocol Number	282-CC-207
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INVESTIGATOR STATEMENT

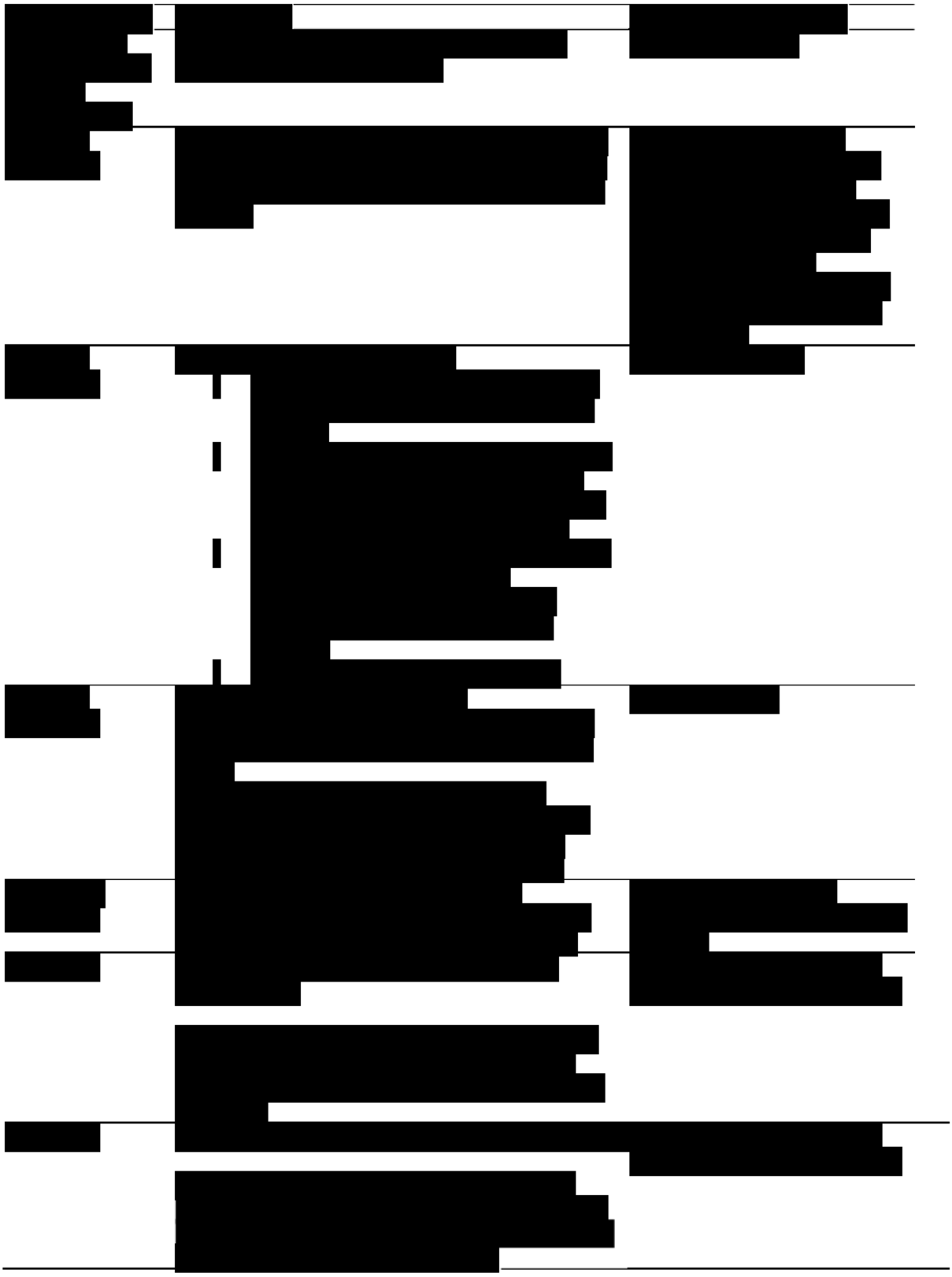
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by NGM Biopharmaceuticals, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date (DD MMM YYYY)	Site Number

PROTOCOL CHANGE HISTORY

Version 6.0, 11 November 2021



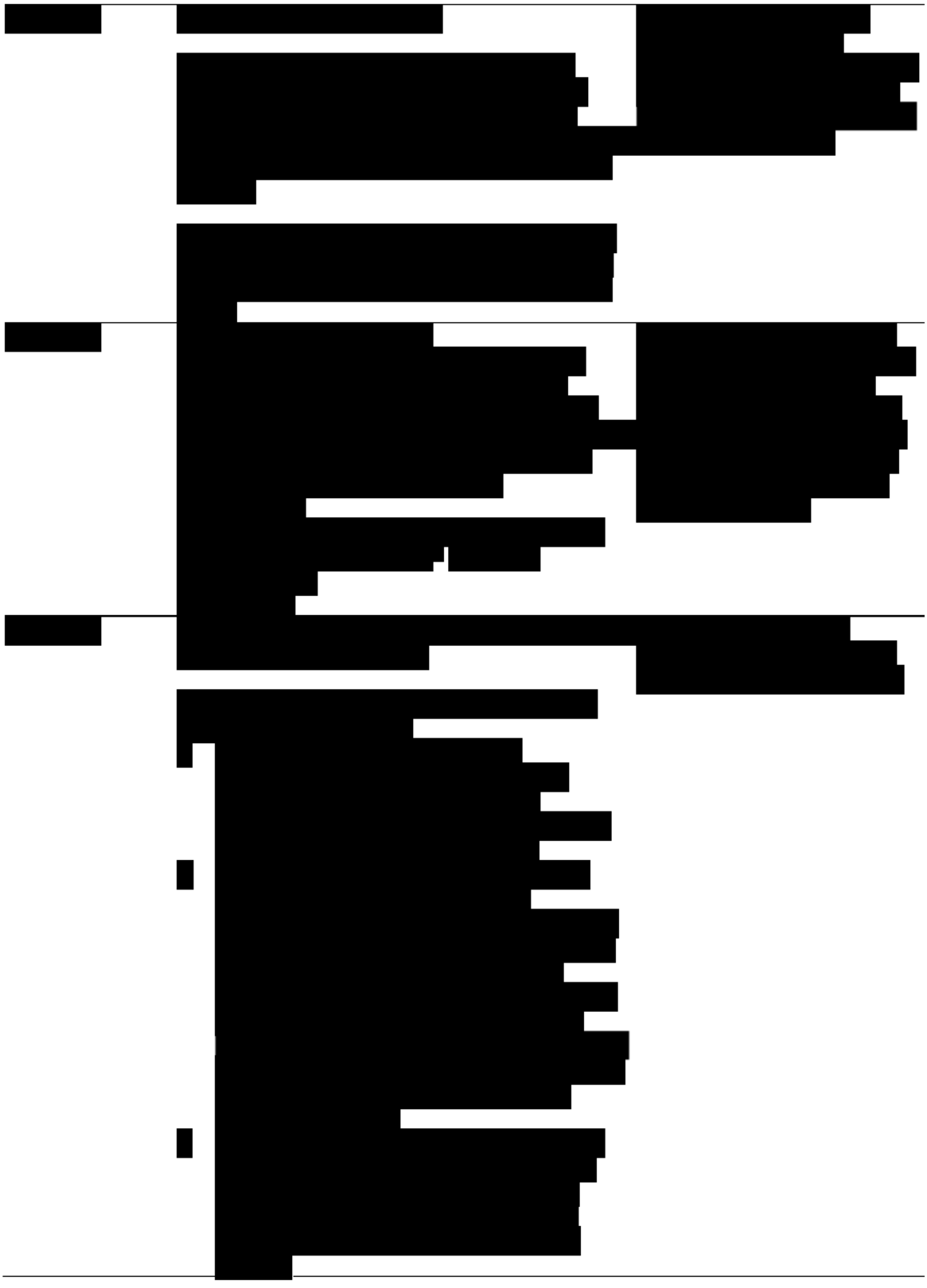


TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition/Explanation
AAV	Adeno-associated virus
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AFP	Alpha fetoprotein
[redacted]	[redacted]
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASCVD	Atherosclerotic Cardiovascular Disease
ASK1	Apoptosis signal-regulating kinase 1
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration–time curve
BA	Bile acid
BLM	Baseline measurements
BMI	Body mass index
$C_{4h\ post\text{-}dose}$	Concentration at 4 hours post-dose
C4	7-alpha-hydroxy-4-cholesten-3-one
CBC	Complete blood count (hematology clinical laboratory evaluations)
CCR2 / CCR5	C-C chemokine receptor type 2 / C-C chemokine receptor type 5
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CI	Confidence interval
CK	Creatine kinase
CL/F	Clearance divided by the bioavailable fraction
CLDQ-NASH	Chronic Liver Disease Questionnaire for NASH
C_{max}	Maximum drug concentration
CMH	Cochran-Mantel-Haenszel
CPA	Collagen proportional area
CRA	Clinical Research Associate
CRF	Case Report Form
CRN	Clinical Research Network
cT1	Corrected T1
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CV	Cardiovascular
CYP7A1	Cholesterol 7α hydroxylase
D	Day
DBC	Double blind cohort
DILI	Drug-Induced Liver Injury
EC	Ethics Committee
ECG	Electrocardiogram
EGD	Esophagogastroduodenoscopy, aka upper endoscopy
ELF	Enhanced liver fibrosis
EOS	End of Study
EOT	End of Treatment
ER	Emergency room
F4	Fibrosis stage 4 cirrhosis
FDA	Food and Drug Administration
FGF19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal

Abbreviation	Definition/Explanation
GLP	Good Laboratory Practice
GLP1	Glucagon-like peptide-1
GRE	Gradient recalled echo
HbA1C	Hemoglobin A1C
HBsAg	Hepatitis B virus surface antigen
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein-cholesterol
HIV	Human immunodeficiency virus
h	Hour(s)
HOMA-IR	Homeostasis model assessment–estimated insulin resistance
[redacted]	[redacted]
HVPG	Hepatic venous pressure gradient measurement
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
ISR	Injection-site reaction
ITT	Intent-to-treat
[redacted]	[redacted]
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LFC	Liver fat content
LI-RADS	Liver Imaging and Reporting Data System
LISSA	Local injection-site symptom assessment
LLT	Lowest Level Term (MedDRA)
MAD	Multiple ascending dose
MAR	Missing at random
MCP-Mod	Multiple Comparison Procedure – Modelling
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end-stage liver disease
MI	Multiple imputation
mITT	Modified intent to treat
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging–proton density fat fraction
n	Number
NAb	Neutralizing antibody
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
NGM	NGM Biopharmaceuticals, Inc.
NIH	National Institutes of Health
No.	Number
NOAEL	No-observed-adverse-effect level
NPO	Nothing by mouth
NRS	Numeric Rating Scale
NZW	New Zealand White
OCA	Obeticholic acid
PBC	Primary biliary cholangitis
PD	Pharmacodynamics; pharmacodynamic
PDFF	Proton density fat fraction
PEth	Phosphatidylethanol

Abbreviation	Definition/Explanation
PI	Principal investigator
PIIINP	Propeptide of type III procollagen
PK	Pharmacokinetics; pharmacokinetic
PNPLA3	Patatin-like phospholipase domain-containing protein 3
PP	Per protocol
Pro-C3	Novel serum marker deriving exclusively from collagen III synthesis and deposition
PSC	Primary sclerosing cholangitis
PT	Preferred term
REML	Restricted maximum likelihood
RUQ	Right upper-quadrant
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBC	Single blind cohort
SC	Subcutaneous
SD	Standard deviation
SHG	Second Harmonic Generation
SHP	Small heterodimer partner
SNP	Single nucleotide polymorphism
SOC	System organ class OR Standard of care
SOP	Standard Operating Procedure
$t_{1/2}$	Apparent terminal elimination half-life
T2D	Type 2 Diabetes
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TIMP-1	Tissue inhibitor of metalloproteinase 1
TNF	Tissue necrosis factor
T_{max}	Time to maximum concentration
UA	Urinalysis
ULN	Upper limit of the normal range

1. SYNOPSIS

Synopsis	Study 282-CC-207
Protocol Title:	Evaluation of Efficacy, Safety and Tolerability of NGM282 (Aldafermin) in a Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study in Subjects with Compensated Cirrhosis Due to Nonalcoholic Steatohepatitis (ALPINE 4)
Protocol Number:	282-CC-207
Phase:	2b
Investigational Product:	NGM282 International nonproprietary name (INN): aldafermin
Primary Objective and Endpoints	The primary objective of this study is to evaluate the efficacy and safety of aldafermin compared to placebo. 1. The primary efficacy endpoint is the change in Enhanced Liver Fibrosis (ELF) score from baseline to Week 48 with aldafermin or matched placebo. 2. The primary safety endpoint is frequency, severity, and timing of adverse events (AEs) and serious adverse events (SAEs).
Secondary Objectives and Endpoints	The secondary objectives of this study are to evaluate the efficacy of aldafermin and the effect of aldafermin on pharmacokinetics and on biomarkers of target engagement, fibrogenesis, and imaging. The following will be measured: 1. Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAFLD Activity Score [NAS] for ballooning, inflammation, or steatohepatitis), after 48 weeks of treatment with aldafermin or matched placebo, in subjects who had a minimum 1 point in each category (hepatocellular ballooning, steatohepatitis, and lobular inflammation) of NAS at baseline as determined by the central pathologist evaluation. 2. Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) after 48 weeks of treatment with aldafermin or matched placebo. 3. Changes from baseline in fibrosis as measured by Collagen Proportionate Area (CPA) and/or Second Harmonic Generation (SHG) methodologies at Week 48. 4. Aldafermin concentrations pre-dose at all treatment visits and 4-hours post-dose at Day 1, Week 24, and Week 48 in all subjects.

Synopsis	Study 282-CC-207
	In a subset of subjects participating in an optional PK study, full PK profiles up to 24 hours will be assessed at Day 1 and steady state at end of treatment (EOT, Week 48). 5. Changes from baseline over time in C4 and serum bile acids and compared to placebo. 6. Changes from baseline over time in Pro-C3 compared to placebo. 7. Changes from baseline over time in alanine transaminase (ALT) and aspartate transaminase (AST) and compared to placebo in subjects with elevated transaminases at baseline. 8. Changes from baseline over time in liver stiffness measure (LSM by FibroScan®) and compared to placebo.
Exploratory Endpoints	[redacted]

Synopsis	Study 282-CC-207

Synopsis	Study 282-CC-207
	[redacted]
Inclusion Criteria:	Subjects must meet the following criteria for study entry: 1. Males and females between 18 and 75 years of age, inclusive, who are able to comprehend and willing to sign an Informed Consent Form (ICF). 2. Liver biopsy consistent with a diagnosis of NASH cirrhosis according to NASH CRN criteria and per the central pathologist evaluation. a. A historical biopsy is acceptable if tissue slides are available from within 12 months prior to Screening and are acceptable for the central pathologist evaluation. b. Liver biopsies must be consistent with cirrhosis according to the NASH CRN classification (NASH CRN fibrosis score of 4), as assessed by the central reader (see also Inclusion Criterion 4). c. NASH must be the etiology of cirrhosis (i.e., no other causes of cirrhosis; see also Inclusion Criterion 4) d. A limited number of subjects (capped at 10% of planned enrollment) with clinical diagnosis of NASH cirrhosis may be enrolled despite a NASH CRN fibrosis score of 3. Clinical diagnosis of NASH cirrhosis must meet at least one of the following: • Agile 4 score ≥0.57 (Younossi 2020, Boursier 2021) • Platelet count ≤140,000/mm^3 and Liver Stiffness Measure (LSM) by FibroScan® ≥13.6 kPA (Eddowes 2019) • FIB-4 ≥3.25 *3. Criterion deleted per protocol Version 5.0.* 4. Subjects must have Definitive NASH cirrhosis as defined in Noureddin 2020 as follows: a. Current biopsy shows cirrhosis with steatohepatitis. There is no evidence for a competing etiology.

Synopsis	Study 282-CC-207

b. Previous biopsy showed steatohepatitis, but now with cirrhosis either by clinical history or current features, imaging, noninvasive tests, or biopsy. If there is a current biopsy, it does not show evidence of steatosis or steatohepatitis, as these histological findings may have disappeared (burn-out). There is no evidence for a competing etiology. There is at least 1 coexisting or history of metabolic comorbidity to corroborate a diagnosis of NAFLD.

c. Current biopsy shows cirrhosis with steatosis. There is no evidence for competing etiology. There are at least 2 coexisting or history of metabolic comorbidities, including obesity and/or T2DM to corroborate a diagnosis of NAFLD.

Have AFP ≤20 ng/mL at Screening.

Negative for hepatic lesions/nodules indicating HCC risk:

a. MRI is the preferred imaging modality. There must be no nodules with a Liver Imaging and Reporting Data System (LI-RADS) score of ≥2 by central radiologist evaluation.

b. If MRI is not available or not possible to be performed, a multi-phasic CT scan may be used to assess HCC risk. There must be no nodules with a LI-RADS score ≥2 by central radiologist evaluation.

c. If MRI and CT are not available or not possible to be performed for screening a potential subject, then ultrasonography of the liver may be performed:

i. If no hepatic lesions or nodules (local radiologist evaluation) and AFP ≤20 ng/mL, the potential subject may be considered further for enrollment.

ii. For any findings of hepatic lesions or nodules (local radiologist evaluation) that are not clearly benign cysts and have not been shown clearly benign by prior CT or MRI, follow-up MRI must be performed and meet criteria (no nodules with LI-RADS score of ≥2 evaluated centrally) in order for the potential subject to be considered further for enrollment.

7. Subjects with T2D or insulin resistance are permitted as long as diabetic medications are reasonably "stable" within 3 months prior to Screening, as outlined in Section 6.4.

8. Other concomitant medications/therapies used for the treatment of coexisting conditions are acceptable (Section 6.4), if on a stable

Synopsis	Study 282-CC-207

regimen for at least 3 months prior to the Screening, except for non-statin lipid lowering agents, which can be used until Day 1 of Screening.

9. Statin use is acceptable based on the following criteria, as assessed by the investigator at Screening:

    a. **Statin-naïve** is defined as no administration of statins within 3 months prior to Screening
    b. **Statin-Experienced** is defined as currently receiving ≤50% of the maximal approved dose of statin therapy

        i. Requires a reasonably stable statin dose at least 3 months prior to Screening.

    Note: The following are the acceptable daily doses of approved statin therapies, and other lipid lowering agents. Also listed under Section 6.4:

        i. Atorvastatin: ≤40 mg/day
        ii. Fluvastatin: ≤40 mg/day
        iii. Lovastatin: ≤40 mg/day (for both immediate and extended release)
        iv. Pitavastatin: ≤2 mg/day
        v. Pravastatin: ≤40 mg/day
        vi. Simvastatin: ≤40 mg/day
        vii. Rosuvastatin: ≤20 mg/day

10. The following additional laboratory parameters must be met at Screening

    a. Total bilirubin ≤1.3 mg/dL

        i. if Gilbert's Syndrome, with direct bilirubin within ULN.

    b. HbA1c ≤9.5%
    c. Platelet count ≥120,000/mm^3

    Subjects who meet the Baveno VI criteria with a platelet count >110,000/mm^3 and <120,000/mm^3 may be enrolled if they meet the expanded Baveno VI criteria (Note: No more than 30% of the remaining population will be enrolled using the Baveno VI criteria).

Synopsis	Study 282-CC-207

d. Creatinine clearance ≥60 mL/min as calculated by Cockcroft-Gault equation

e. Serum alanine amino transferase (ALT) levels ≤5 x ULN

f. Serum aspartate amino transferase (AST) levels ≤5 x ULN

g. Alkaline phosphatase ≤1.5 x ULN

h. Serum albumin ≥3.5 g/dL

i. International normalized ratio (INR) ≤1.7.

Note: A 10% laboratory variability is allowed on platelets and bilirubin values. Platelet variability does not apply to Baveno VI.

11. Female subjects must be either of a) non-childbearing potential, defined as women who have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, documented postmenopausal, or a follicle stimulating hormone ≥40 mIU/mL, OR b) if of childbearing potential, defined as including women <55 years of age with ≤2 years of amenorrhea (absence of menstruation and not due to any reversible medical cause or any current medication use), then have a negative serum pregnancy test at Screening and urine pregnancy test at the Day 1 visit prior to first dose of study drug, and must be non-lactating and non-breastfeeding. Note: Females who do not meet this criterion can be included if they meet Inclusion Criterion 12.

12. Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must agree to consistent and adequate birth control from Screening to End of Study (Week 54):

- Recommended forms of contraception for males: condom, vasectomy, and sexual abstinence
  - i. Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the female subject of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.
  - ii. Condom use is not considered as a highly effective form of contraception alone and may be used effectively with a second method of contraception.
  - iii. Sexual abstinence is considered a highly effective method only if defined as abstaining from heterosexual intercourse during the entire period of risk associated with

Synopsis	Study 282-CC-207
	the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. • Recommended forms of contraception for females: hormone containing contraceptive medication, Intrauterine device with failure rate <1% per year, cervical cap or diaphragm with spermicidal agent, bilateral tubal occlusion (tubal sterilization), sexual abstinence i. Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation ii. Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation iii. Cervical cap or diaphragm with spermicidal agent is not considered as a highly effective form of contraception alone and may be used effectively with a second method of contraception Sexual abstinence is considered a highly effective method only if defined as abstaining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. 13. Able and willing to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.
Exclusion Criteria:	The following will exclude subjects from the study: 1. Other causes of liver disease that are primary, secondary, or otherwise causes of cirrhosis or which may confound the intended patient population according to the investigator, including but not limited to alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders, primary biliary cirrhosis, drug-induced hepatotoxicity, Wilson's disease, hemochromatosis, and alpha-1-anti-trypsin deficiency based on medical history and/or centralized read of liver histology.

Synopsis	Study 282-CC-207
	2. Evidence of drug induced steatohepatitis secondary to amiodarone, corticosteroids, estrogens, methotrexate, tetracycline, or other medications known to cause hepatic steatosis. 3. History of hepatic decompensation, including variceal bleeding, ascites, or hepatic encephalopathy. 4. Prior or pending liver transplantation. 5. Child Pugh class B and C status. 6. Model of end stage liver disease (MELD) score >12. 7. Evidence of worsening liver disease (defined below) between screening visits (i.e., Day -56 and Day -42) including measures of AST, ALT, alkaline phosphatase (ALP) or total bilirubin (TBL): a. For subjects with TBL, AST, ALT, or ALP baseline levels >ULN, the second assessment should not exceed an increase of 35% over the first assessment. Note: An unscheduled visit may be necessary to confirm eligibility if the difference exceeds the allowable percent difference. If performed, unscheduled visit results will be compared to the average of Day -56 and Day -42 results to determine eligibility. If liver function tests are repeated to verify eligibility criteria have been met, there must be a minimum of 14 days (2 weeks) between the Day -42 visit and any unscheduled visit. 8. History of porto-systemic shunt procedure 9. No evidence of gastroesophageal varices as documented by one of the following assessments: a. A historical and locally evaluated EGD obtained within 365 days of screening or b. A locally evaluated EGD conducted during the screening period *If no EGD is available, the latest EGD assessment guidelines during a global pandemic† for patients with compensated cirrhosis (i.e., the expanded Baveno VI criteria, Petta 2018) as follows can be used as a replacement for the EGD to determine eligibility:

Synopsis	Study 282-CC-207

c. Platelet count >110,000/mm^3, and a FibroScan® <30 kPa on a M probe or <25 kPa on a XL probe

Note: No more than 30% of the remaining population will be enrolled with the expanded Baveno VI criteria

†*EGD waived in patients with compensated cirrhosis during a global pandemic per AASLD/ASGE guidelines.*

10. Clinically significant cardiovascular or cerebrovascular event or new diagnosis within 6 months of Screening, including but not limited to congestive heart failure, myocardial infarction, acute coronary syndrome, revascularization, stroke (hemorrhagic or ischemic), transient ischemic attack (TIA), or implanted defibrillator or pacemaker (for uncomplicated elective, non-biventricular pacemaker procedure, 3 months post procedure will be allowed).

11. Gastric bypass or bariatric surgery in the past 5 years or planned procedure during the study period.

12. 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.

13. Documented significant weight change (± 5%) <3 months prior to Screening.

14. Screening ECG with clinically significant abnormalities that in the investigator's opinion, require evaluation and possible treatment.

15. Positive for HBsAg, antiHIV Ab, or antiHCV Ab plus HCV-RNA. Subjects who are antiHCV Ab- positive but HCV-RNA negative (secondary to treatment or viral clearance) are eligible with at least a 1-year period since documented sustained viral response at Week 12 post-treatment.

16. 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* or breast ductular carcinoma *in situ* is allowed if appropriately treated within 2 years prior to Screening); subjects under evaluation for suspected malignancy are not eligible. History of hepatocellular carcinoma at any point regardless of treatment or treatment success will be excluded.

Synopsis	Study 282-CC-207

17. A positive drug screen (e.g., morphine, heroin, cocaine) will exclude subjects unless it can be clearly explained by a prescribed medication. The diagnosis and prescription must be approved by the investigator and the Medical Monitor.

18. Significant alcohol intake as measured by a phosphatidylethanol (PEth) level ≥200 ng/mL AND significant alcohol use, as determined by the Alcohol Use Disorders Identification Test (AUDIT-C) alcohol consumption questionnaire (Appendix 3).

19. *Criterion deleted per protocol Version 3.0.*

20. Consumption of ≥21 units of alcohol per week in males and ≥14 units of alcohol per week in females for two years prior to screening, where a "unit" of alcohol is equivalent to a 12-ounce beer, 4-ounce glass of wine, or 1-ounce shot of hard liquor.

21. Use of any prohibited concomitant medications as described in Section 6.4 within 3 months prior to screening;

    a. Weight loss medications.

    b. Any medication that is contraindicated according to the rosuvastatin package insert (Appendix 5) or if subject has a known hypersensitivity to rosuvastatin product components (Section 6.1.3).

    c. Hepatotoxic medications (Appendix 6); allopurinol allowed.

    d. Anabolic steroids.

22. History of statin intolerance, as defined by presence of significant side effects while on statins and/or inability to take or use statins for treatment.

23. Prior participation in a clinical trial of aldafermin unless previously enrolled into a placebo arm of the trial.

24. History of severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies.

25. Participation in a study of another investigational agent within 28 days or five half-lives of the drug (whichever is longer) prior to Screening.

Synopsis	Study 282-CC-207
	26. Any acute or chronic condition that, in the opinion of the investigator, would limit the subject's ability to participate, complete, and/or would confound data interpretation in this clinical study.
Study Design/ Methodology:	This study is a double-blind, randomized, placebo-controlled, multi-center study of aldafermin in subjects with histologically confirmed compensated cirrhosis due to NASH. The study consists of a screening period, a double-blind treatment period of 48 weeks, and a safety follow-up period of 6-10 weeks. Subjects will be treated with either aldafermin or matched placebo given as a subcutaneous injection daily for 48 weeks. Eligible subjects will have histologically confirmed cirrhosis (NASH CRN fibrosis Stage 4, with a limited number of subjects with fibrosis Stage 3 with a clinical diagnosis of cirrhosis) due to NASH. Historical biopsy may be used for inclusion into the study. Otherwise, a liver biopsy must be obtained for eligibility assessment. Liver biopsy results of either historical or screening biopsy must be confirmed by a central pathologist reading. At Screening, all subjects will undergo evaluation for risk of HCC. A gadolinium-enhanced MRI or multi-phasic CT scan showing no evidence of nodules with a Liver Imaging and Reporting Data System (LI-RADS) score of ≥2 on central read will be required at Screening to rule out HCC risk. For potential subjects unable to obtain an MRI or CT scan, ultrasound that is negative for hepatic lesions/nodules (local read) at Screening may be used. In all cases, AFP must be ≤20 ng/mL. Subjects with suspicious lesions/nodules at ultrasound followed by observation of nodules that are LI-RADS ≥2 by central read of gadolinium-enhanced MRI or multi-phasic CT scan at Screening will be excluded from enrollment and will be referred for further evaluation for HCC per the standard of care (SOC). Subjects will also be excluded if EGD documented any signs of esophageal or gastric varices. Up to approximately 150 eligible subjects will be randomized into 1 of 4 treatment groups in a 3:2:2:3 ratio to receive either subcutaneous placebo, 0.3 mg aldafermin, 1 mg aldafermin, or 3 mg aldafermin, respectively. Under protocol Version 5.0 and subsequent versions, eligible subjects will no longer be randomized into the 0.3 mg aldafermin treatment group. Instead, subjects will be randomized into 1 of 3 treatment groups in a 4:3:4 ratio to receive either subcutaneous placebo, 1 mg aldafermin, or 3 mg aldafermin, respectively. Subjects randomized to the 0.3 mg aldafermin treatment group prior to protocol Version 5.0 will continue to receive the same dose until treatment completion. No more than 30% of the remaining population will be

Synopsis	Study 282-CC-207
	enrolled with the expanded Baveno VI criteria. Randomization will be stratified by clinical diagnosis of T2D versus no T2D to ensure planned allocation ratio of treatment groups within each stratum. Study drug self-administration instructions and training will be provided to the subjects and study drug kits will be dispensed. In the clinic, subjects will self-administer the first dose of aldafermin/placebo (Day 1) and doses at Weeks 2, 6, 12, 18, 24, 30, 36, 42, and 48 study visits. Subjects will self-administer all other doses through Week 48 at home. Self-administration should occur at a similar time for every dose in both the clinic and at home. Subjects will return to the clinic on Weeks 2, 6, 12, 18, 24, 30, 36, 42, and 48 for on treatment assessments. Subject cholesterol levels will be followed during the course of the study, and treatment with over-encapsulated rosuvastatin/matched placebo will start at Week 2 according to a lipid management algorithm (Appendix 4). LDL-C levels and related safety data will be evaluated at Weeks 2, 6, 12, 18, 24, 30, 36, and 42 in all subjects by an independent third-party Medical Monitor who will determine the need for initiation/titration of rosuvastatin according to the protocol. Rosuvastatin will be used to manage cholesterol levels according to the established lipid management algorithm described in Appendix 4. Rosuvastatin and matched placebo are over-encapsulated to maintain the treatment blind. Initiation and ongoing dose adjustments of rosuvastatin/matched placebo will be managed through the [redacted] by a third-party Medical Monitor who is unblinded to subject lipid levels but blinded to the treatment assignment (aldafermin or matched placebo). The sponsor and study sites will be blinded to subject lipid levels, rosuvastatin/placebo allocation, and the specific rosuvastatin dosing decisions. A kit containing rosuvastatin or matched placebo bottles will be assigned based on assessment by the unblinded Medical Monitor, at each study visit from Week 2 through Week 42 (statin-naïve) or Week 48 (statin-experienced), according to the lipid management algorithm and will be delivered to subjects via a courier service vendor (Section 6.1.3.1) or to the study site for subjects to collect, depending on subject preference. Reference Appendix 4 for specific dosing algorithm for statin-naïve and statin experienced subjects. Over-encapsulated rosuvastatin will be initiated at Week 2, starting at 5 mg QD in statin-naïve subjects whose ASCVD 10-year risk score is

Synopsis	Study 282-CC-207
	≥7.5% (US) or ≥ moderate level risk (European), Appendix 4. In subjects who are statin-naïve with diabetes or a history of myocardial infarction or stroke, or other ASCVD risk-enhancing diagnoses, rosuvastatin will be initiated at 5 mg at Week 2 if LDL-C is not already at the goal of ≤70 mg/dL (1.8 mmol/L). Though there is incremental cardiovascular benefit to additional LDL-C lowering (Sabatine 2018), other reports, including the meta-analysis by Ma, et al. suggest an association between low LDL-C levels and hemorrhagic stroke (Ma 2019), and overall, controversy remains regarding the long-term safety of medications that can help achieve low LDL-C levels such as PCSK9 inhibitors (Pasta 2020, Bandyopadhyay 2018). Thus, for safety considerations, statin-naïve subjects with risk-enhancing diagnoses who are already at an LDL-C treatment goal of ≤70 mg/dL (1.8 mmol/L) will be initiated on over-encapsulated rosuvastatin placebo. At subsequent clinic visits, lipid levels will be evaluated and treatment with over-encapsulated rosuvastatin may be initiated or placebo may be continued. Subjects who are statin-experienced (i.e., on statin concomitant medication), will be switched to an equivalent intensity rosuvastatin dose at Week 2. For self-identified Asians, 10 mg is considered a high intensity dose, and 5 mg is considered a moderate intensity dose. Matched placebo will be given to statin-naive study subjects who do not meet initiation criteria at Week 2 or subsequent visits. LDL-C values will be further evaluated at study visit Week 6, 12, 18, 24, 30, 36, and 42, in order to identify subjects who require rosuvastatin initiation or dose-escalation. Specific LDL goal or treatment success criteria are described in detail in Section 8.3.17. Subjects who do not meet rosuvastatin increase criteria will continue on their prior assigned dose of over-encapsulated rosuvastatin/ matched placebo. Subjects on the maximum dose of rosuvastatin 40 mg whose LDL-C levels are still not at goal will continue on the study with rosuvastatin 40 mg unless the subject experiences a cardiovascular-related SAE (e.g., myocardial infarction, CVA). Subjects experiencing a CV-related SAE on rosuvastatin 40 mg will discontinue both aldafermin and rosuvastatin for the remainder of the trial, and cardiovascular care will continue per the subject's regular physician and as per local standard of care practices. Subjects who experience rosuvastatin-related intolerance (by evaluation of muscular symptoms and creatine kinase (CK) levels) will be evaluated by follow-up laboratory testing after the over-encapsulated rosuvastatin/placebo has been held. Depending on the CK levels and clinical status, subjects may be allowed to restart over-encapsulated rosuvastatin/placebo at a reduced dose. Algorithm details are found in Section 7.1.1, part ii.

Synopsis	Study 282-CC-207
	All subjects will be assessed at Weeks 49 and 54 to confirm their LDL-C levels have either decreased to near baseline, at which point no additional follow-up is needed. Subjects who do not meet LDL-C decrease criteria at Week 54 will have an additional 4-week follow-up visit at Week 58 to confirm that their LDL-C level returned to near baseline. Subjects may remain on statin through Week 58. As part of safety monitoring, subjects will undergo ultrasound and alpha fetoprotein (AFP) testing at Weeks 24 and 48 to screen for HCC. Subjects with new lesions ≥10 mm with AFP >20 ng/mL will be treated according to local guidelines. If new lesions ≥10 mm with AFP >20 ng/mL occur at Week 24, subjects may continue on study drug at the discretion of the investigator unless or until a clinical diagnosis of HCC is made (defined as LI-RADS 4 or 5 on MRI, or histological confirmation of HCC). For subjects with suspected HCC by ultrasound and AFP screening, additional imaging may be obtained, and data will be gathered for adjudication. Safety will be monitored by a data safety monitoring board (DSMB). All subjects will return to the clinic for the End-of-Treatment (EOT) visit at Week 48. Subjects will return to the clinic at Weeks 49 and 54 (or at 1 and 6 weeks after last dose of aldafermin) for a post-treatment response and End-of-Study (EOS) follow-up visits. Subjects may be contacted to participate in additional optional follow-up visits, if necessary, to monitor anti-drug antibody (ADA) response.
Number of Subjects:	Up to approximately 150 eligible subjects will be randomized
Number of Study Sites:	This is a global study planned in approximately 80 sites
Test Product, Dose, and Mode of Administration:	The investigational product is aldafermin, which will be administered once daily by subcutaneous injection. Subjects will receive 0.3 mg aldafermin, 1 mg aldafermin, 3 mg aldafermin, or matched placebo. Under protocol Version 5.0 and subsequent versions, randomization to the 0.3 mg aldafermin dose was discontinued. Rosuvastatin will be administered for subjects meeting pre-specified criteria at Week 2 with dose optimization opportunities at Weeks 6, 12, 18, 24, 30, 36, and 42. Subjects who do not meet dose escalation criteria will continue on their prior assigned dose of rosuvastatin/placebo. Study-labeled rosuvastatin/matched placebo is over-encapsulated and will be supplied in either 5 mg, 10 mg, 20 mg, or 40 mg total daily doses as outlined in Section 6.2.1.2 of the protocol to manage possible LDL-C increase during aldafermin treatment.

Synopsis	Study 282-CC-207
Duration of Treatment and Study:	Total study-drug treatment: 48 weeks. Total study duration: up to 74 weeks. Subjects will review and sign the Informed Consent Form at the Day 56 Screening Visit and will undergo screening assessments to verify eligibility for the study for up to 8 weeks (up to 16 weeks with Medical Monitor approval) from the date of consent. All subjects will be treated with aldafermin or matched placebo for 48 weeks and will be monitored for additional 6-10 weeks after completing their final dose of aldafermin or matched placebo. The total duration of individual subject participation, including screening (up to 8 weeks [up to 16 weeks with Medical Monitor approval]), the treatment period (48 weeks) and the safety follow-up (6-10 weeks) will be up to 74 weeks.
Statistical Considerations	**Analysis Populations:** • Intent to treat (ITT) population: all randomized subjects • Modified ITT (mITT) population: all subjects who receive at least 2 weeks of study drug and have at least one valid, post-dose, on-treatment ELF score • Safety population: all subjects who receive at least one dose (full or partial) of study drug • Full-Analysis population: all randomized subjects who receive at least one dose (full or partial) of study drug and have at least one valid, non-missing post-dose efficacy/PD parameter value • Per-Protocol (PP) population: a subset of subjects in the Full Analysis population; will include subjects who have valid, non-missing baseline and post-dose liver biopsy results and do not have protocol deviations that impact the liver biopsy assessments • PK population: all randomized subjects who receive at least one dose (full or partial) of drug, and have a qualified (i.e., above the lower limit of quantification) pre-dose and post-dose (at least one) PK assessment. **General Approach:** Descriptive statistics including the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum will be presented for continuous variables, frequency and percentage distribution for categorical variables, Kaplan-Meier estimates for time-to-event variables.

Primary Efficacy Analysis:

The primary efficacy endpoint is the change from baseline in ELF at Week 48. Missing change from baseline in ELF will be imputed with multiple imputation (MI) method under the assumption of missing at random (MAR). Sensitivity analysis under the assumption of missing not at random (e.g., pattern mixture model) will be performed, In addition, another sensitivity analysis using the last observation carried forward (LOCF) methods will be performed.

The primary efficacy endpoint will be analyzed using the Multiple Comparison Procedure – Modelling (MCP-Mod) approach to assess the dose-response relationship. Within the framework of the MCP-Mod procedure, the null hypothesis of no dose-response will be tested at the 5% significance level (two-sided) against the alternative hypothesis that there is a dose-response.

The primary efficacy analysis will be performed using the ITT population. The mITT, Full-Analysis, and PP populations will be used as sensitivity analyses.

Secondary Efficacy Analyses:

The between-group comparisons (aldafermin doses vs placebo) of the change from baseline in ELF at Week 48 will be performed using an analysis of covariance (ANCOVA) model with effects for treatment, baseline T2D status (Yes/No) and the baseline outcome value as a covariate.

The between-group comparisons (aldafermin doses vs placebo) of the histologic response at Week 48 will be performed using the Cochran Mantel Haenszel (CMH) test stratified by baseline T2D status (Yes/No).

Change from baseline in ALT, AST, Pro-C3, C4, serum bile acids, and liver stiffness measure will be analyzed using an analysis of covariance (ANCOVA) model with effects for treatment, baseline T2D status (Yes/No) and the baseline outcome value as a covariate.

All secondary efficacy analyses will be performed using the ITT population. Full-Analysis, and PP populations will be used as sensitivity analyses.

Subgroup Analyses:

[redacted]

Synopsis	Study 282-CC-207
	Pharmacokinetic Analyses:  Safety Analyses: Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be summarized by primary system organ class and preferred term. Actual values and change from baseline values for vital signs, ECGs, clinical laboratory (hematology and chemistry) tests, and other continuous safety variables will be summarized with descriptive statistics. Concomitant medications, injection site reactions, and other categorical safety variables will be summarized with frequency and percentage distribution. All safety analyses will be performed using the Safety population. Interim Analyses: One interim analysis (IA) may be conducted for organizational decision making. The IA, if conducted, will include a review of selected safety and efficacy endpoints by treatment group. No formal hypothesis testing will be conducted. The study will not be stopped early based on the results. Results for individual subjects will not be shared with study site staff or subjects. Further details of the IA will be included in the statistical analysis plan (SAP).

2. INTRODUCTION

2.1. Background

Aldafermin is an engineered analog of human fibroblast growth factor 19 (FGF19) that is currently being developed as a potential treatment for Nonalcoholic Steatohepatitis (NASH). Although the natural history of NASH is not fully elucidated, the risk of progression to end-stage liver disease is characterized by an increased fibrosis stage and cirrhosis, with increased risk for outcomes of hepatic decompensation, need for liver transplant, and mortality (Angulo 2015, Younossi 2018). Decompensation events include ascites, sepsis, variceal bleeding, encephalopathy, and nonobstructive jaundice.

The pathogenesis of NASH and progression to fibrosis/cirrhosis is not yet fully understood, despite recent advances in understanding complex metabolic and inflammatory pathways that are likely involved in disease progression. The most widely supported theory implicates insulin resistance as the key mechanism leading to hepatic steatosis and subsequent NASH (Cusi 2012). This initial dysfunction is likely followed by oxidative injury resulting in the necroinflammatory component of NASH (Cusi 2012). Hepatic iron, antioxidant deficiency, and intestinal bacteria have all been suggested as potential oxidative stressors (Cusi 2012). Several other factors known to be involved in the progression of NASH include inflammatory cytokines, adipokines, lipotoxicity, autophagy, and mitochondrial dysfunction (Tsochatzis 2009). There is also growing evidence of a genetic component for the progression of NAFLD to NASH as well as fibrogenesis in patients with NASH (Mehta 2014).

The natural history of NASH is variable from patient to patient and the non-alcoholic fatty liver disease (NAFLD) activity score (NAS) does not appear to be predictive of disease progression. The presence of fibrosis has been the only highly predictive factor of patients who will progress to cirrhosis. Approximately 10%–20% of patients with NAFLD will progress to NASH over a 7-year period (Argo 2009, Bhala 2013). Of these patients, roughly 20% will progress to cirrhosis over a 20-year period (Bhala 2013). A recent meta-analysis of paired biopsy studies in NASH patients demonstrated an annual fibrosis progression rate of 0.14 fibrosis stages in patients with NASH and 1 stage of progression over 7.1 years for patients with NASH (Singh 2015). The mortality rate of patients with NASH has been estimated at 1%–2% per year in patients with fibrosis, largely due to cardiovascular disease followed by liver-related causes (Kim 2013). Patients with NASH-related cirrhosis can progress to decompensated liver disease, complications of portal hypertension, and hepatocellular carcinoma (HCC). Recently, a growing number of cases of HCC in NASH patients have been reported without bridging fibrosis or cirrhosis, suggesting an independent pathogenic mechanism in this population (Paradis 2009). NASH is rapidly growing as the primary cause of end stage liver disease in the U.S. and European populations and is expected to be the primary indication for liver transplantation by 2020 (Charlton 2011, Afzali 2012).

The histologic criteria for the diagnosis of adult NASH include macrovesicular steatosis, hepatocyte ballooning, and mild lobular inflammation (Kleiner 2005, Brunt 2009). Portal and periportal fibrosis followed by bridging fibrosis and cirrhosis are seen in patients with the

progression of NASH. Steatosis may be absent in cases of bridging fibrosis or cirrhosis ("burnt-out NASH") and is often misdiagnosed as cryptogenic cirrhosis (Caldwell 2004).

The estimated global prevalence of NASH has risen rapidly in parallel with the dramatic rise in population levels of obesity and diabetes, resulting in NAFLD now representing the most common cause of liver disease in the Western world (Swinburn 2011, Centers for Disease Control US Obesity Trends 2014). The prevalence of NASH is estimated to be between 2% and 5% in Western adults, rising to as high as 40%–50% in the morbidly obese patients with type 2 diabetes (T2D) (Argo 2009, Williams 2011). The development of cirrhosis over the lifetime of patients with NASH is estimated to be at least 20%, with decompensation occurring in about 45% of patients with NASH related cirrhosis over a 10-year period (Rinella 2015, McCullough 2004, Sanyal 2006). In a recent study that evaluated the prevalence of NASH cirrhosis and NAFLD-associated fibrosis by the National Health and Nutrition Examination Survey (NHANES) (7,034 participants), the prevalence of NASH cirrhosis and NAFLD-associated fibrosis increased by 2.5 fold and 2-fold in 2009-2012 compared to 1999-2002. Significant increases in obesity, diabetes, and insulin resistance also increased significantly ($p < .005$ for all). Thus, regression or prevention of the progression of NASH-related cirrhosis represents an important unmet need.

2.2. Cirrhosis Pathophysiology

Cirrhosis is an advanced stage of liver fibrosis defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease. Liver fibrosis results from interference in the normal wound-healing response, thus preventing tissues from disassembly during inflammation, apoptosis, necrosis, and proteolysis (Schuppan 2008). With chronic liver disease and the development of cirrhosis, activated myofibroblasts deriving from proliferating hepatic stellate cells and portal fibroblasts result in fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular exclusions (Tsochatzis 2014). This process leads to sinusoidal remodeling and extracellular matrix (ECM) deposition with cross-linking of fibrillary collagen (Friedman 2010). The vascular distortion that occurs with cirrhosis leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma. The hepatic sinusoids are lined by fenestrated endothelia that rest on a sheet of permeable connective tissue in the space of Disse, which also contains hepatic stellate cells and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes that execute most of the known liver functions. In cirrhosis, the space of Disse is filled with scar tissue and endothelial fenestrations are lost. The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction, and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are intimately linked to the hepatic vascular alterations and resulting portal hypertension. Cirrhosis and its associated vascular distortion are traditionally regarded as irreversible, but recent data suggest that cirrhosis regression or even reversal may be possible (Schuppan 2008).

2.3. Current Treatments for NASH Cirrhosis

There are currently no approved therapies for affecting progression or regression of cirrhosis, though a variety of targets are being pursued with potential anti-fibrotic therapies. Many of these potential therapies are also being studied for earlier stages of NASH in a population of patients with F2/F3 fibrosis stage. (Friedman 2018).

The identification of a single therapeutic target has been complicated by the complexity of the pathogenesis of NASH. The treatment goals for NASH have focused on the prevention or reversal of liver injury either by treating the underlying metabolic and inflammatory conditions or through directly targeting fibrogenic pathways. Early-stage disease treatments have focused on insulin sensitization, decreasing lipids, and antioxidant activity.
The endpoints for these treatments have been both improvements in biochemical parameters and histologic improvement in the components of NAS with no worsening or improvement of fibrosis. More recently, the resolution of NASH on biopsy has been considered a more clinically meaningful treatment endpoint. Anti-fibrotic agents have targeted the advanced fibrosis and cirrhotic populations but have little activity on the underlying disease causing the chronic hepatic injury (Harrison 2018).

Weight loss through lifestyle management is considered the first-line treatment strategy for NASH and is associated with improvement in liver histology and a reduction in cardiovascular and metabolic complications (Promrat 2010, Glass 2015). However, the majority of patients are unsuccessful in achieving or maintaining adequate weight loss and require other interventions. In cases of morbid obesity, bariatric surgery has been successful in reversing the metabolic and hepatic injury associated with NASH.

Many agents are currently being studied in clinical trials. In current clinical practice, vitamin E is the most commonly used medication, though evidence of efficacy is limited in those with diabetes and cirrhosis and current American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines recommend its use be restricted to nondiabetic, non-cirrhotic patients with NASH (Chalasani 2017, EASL 2016). This recommendation has been largely generated by data from the PIVENS trial, in which subjects randomized to receive 800 IU/day of vitamin E for 96 weeks demonstrated improvement in steatosis, lobular inflammation and ballooning, as well as resolution of NASH, but no improvement in fibrosis (Sanyal 2010). There have also been subsequent safety concerns regarding the use of vitamin E as data suggest a possible increased risk of overall mortality and higher rates of prostate cancer, though this remains controversial. Of the insulin sensitizers, pioglitazone has been extensively evaluated in clinical trials with fairly consistent improvements in various features of NASH and less consistently fibrosis. The primary downside to the use of pioglitazone is fluid retention, weight gain, and bone fracture, limiting both patient and provider acceptance. Given the increasing disease burden and no approved treatment options, the development of pharmacologic therapies to treat NASH is critical.

There are several drugs in Phase 2 and Phase 3 development for the treatment of noncirrhotic and compensated cirrhotic patients with NASH. These drugs are targeting either modification of the underlying disease-related injury, fibrosis, or both. Despite the presence of numerous agents in clinical development, none have demonstrated a rapid or potent effect on liver

histology, and a significant medical need for new effective therapies with favorable safety and tolerability profiles remains.

The management of liver cirrhosis secondary to NASH currently focuses on reducing the complications of cirrhosis and preventing progression to decompensated hepatic events or death/liver transplant. This includes assessment and treatment of renal complications, treatment of ascites (low sodium diet, paracentesis, diuretics, or shunt) and screening for hepatocellular carcinoma with imaging techniques (e.g., MRI , CT scan, or ultrasonography) and screening for gastroesophageal varices with assessment of risk for bleeding to guide testing frequency (Rinella 2015). Prevention of bleeding in patients with varices includes variceal band ligation or a nonselective β-blocker to reduce hepatic venous pressure gradient (HVPG). Statins such as simvastatin have also been used to lower HVPG and improve liver hemodynamics, in patients with cirrhosis and varices. Statins have also demonstrated reduction in the incidence of HCC in patients with T2DM (Tsochatzis 2014).

2.4. Mechanism of Action of Aldafermin

Aldafermin is 95.4% identical to FGF19. FGF19 and its murine homologue FGF15 have been implicated in the regulation of hepatic bile acid (BA) metabolism. FGF19 interacts with the FGFR4/β-klotho receptor complex located in the liver to induce the expression of small heterodimer partner (SHP), an orphan nuclear receptor, in the liver to suppress the expression of *CYP7A1,* the gene encoding cholesterol 7α-hydroxylase. In catalyzing the first, and rate-limiting step in the conversion of cholesterol into BAs, cholesterol 7α-hydroxylase represents the key regulatory checkpoint in the control of BA synthesis, and changes in the level of this enzyme have been shown to have a significant effect on both the size and composition of the BA pool (Russell 2003). Additionally, FGF19 interacts with the FGFR1c/β-klotho receptor complex located in the adipose tissue and the brain to regulate insulin sensitivity, glucose metabolism, and energy homeostasis (Kliewer 2015).

Aldafermin differs from wild-type FGF19 in the amino terminus, a key region of the protein involved in receptor interactions and signaling modulation (Zhou 2014, DePaoli 2019, Luo 2014). In aldafermin, a 5-amino acid deletion (P24-S28) coupled with the substitution of three amino acids at critical positions (A30S, G31S, H33L) enable biased FGFR4 signaling so that aldafermin retains the ability to potently repress CYP7A1 expression but no longer triggers activation of signal transducer and activator of transcription 3, a signaling pathway essential for FGF19-mediated hepatocarcinogenesis (Zhou 2017). By engaging both FGFR4 and FGFR1c pathways to reduce bile acid toxicity and lipotoxicity, and to improve insulin sensitivity, aldafermin has demonstrated robust anti-steatotic, anti-inflammatory, and anti-fibrotic activities in multiple animal models of NASH (Zhou 2017, Zhou 2019).

2.5. Therapeutic Rationale for Aldafermin in NASH

The potential role of reduced FGF19 activity in the pathogenesis of NASH is not fully elucidated but may, in part, be due to accumulation of hepatic bile acids. For example, increased bile acid synthesis as well as serum bile acid 7-alpha-hydroxy-4-cholesten-3-one (C4) concentrations, a key marker of cholesterol 7α-hydroxylase activity, correlate with NASH disease severity and fibrotic activity (Bechmann 2013). Altered bile acid composition has been observed in patients with NASH, with a compensatory transition from

CYP7A1-mediated classic pathway (toxic bile acids) to the less toxic alternative pathway (Lake 2013). Increased hepatic concentrations of bile acids are also associated with increased apoptosis, Fas, and tissue necrosis factor (TNF) R1 activity, resulting in hepatocyte injury and stellate cell activation (Faubion 1999, Higuchi 2003). A significant correlation also exists between increases in specific bile acids and severity of NASH-related hepatic injury (Aranha 2008). FGF19 levels are also decreased in subjects with Type 2 diabetes (T2D) or metabolic syndrome and return to normal levels after bariatric surgery in diabetic subjects (Mingrone 2012).

2.6. Nonclinical Studies

Aldafermin has been evaluated in various mouse animal models of NASH, and has demonstrated significant reduction in steatosis, inflammation, ballooning and fibrosis in mouse models of NASH (Table 1).

Table 1. Summary of Aldafermin Efficacy in Mouse NASH Models

Mouse Model (Study No.)	Treatment	Duration (weeks)	NAS Score [a]	Fibrosis Score [b]
STAM (14-PD-NGM282-1001)	GFP-AAV	3	5.33 + 1.5	1.09
	aldafermin-AAV		1.5 + 1.0***	1.06
FXR Knockout on chow (13-PD- NGM282-1007)	GFP-AAV	24	4.0 ± 1.73	1.8 + 0.4
	aldafermin-AAV		2.0± 1.73	1.4 + 0.6
HFFCh/C57BL6 (15-PD- NGM282-1001; data on file)	GFP-AAV	34	7.3 ± 0.3	3.9 + 0.5
	aldafermin-AAV		3.0 ± 0.4***	0.8 + 0.1***
HFFCh/FXR Knockout (15-PD- NGM282-1002; data on file)	GFP-AAV	34	7.5 ± 0.5	3.8 + 0.2
	aldafermin-AAV		6.4 ± 0.7	1.4 + 0.2***
HFFCh/C57BL6 (data on file)	GFP-AAV	24	5.4	1.8
	V97[c]-AAV		2.2***	1.2

AAV=adeno-associated virus; FXR=farnesoid X receptor; HFFCh=high-fat, fructose, cholesterol diet; SC=subcutaneous.

[a] NAS score represents sum of steatosis, inflammation, and ballooning degeneration scores

[b] Fibrosis score estimated using Kleiner criteria

[c] V97 is a surrogate molecule for aldafermin

*** $P < 0.001$ vs. GFP-AAV

Importantly, aldafermin is devoid of proliferative activity based on chronic evaluation in rodents and non-human primates that is a potential limitation of FGF19 as a therapeutic. Aldafermin was selected from more than 160 variants of human FGF19 that were screened to retain robust efficacy, while lacking evidence of proliferative activity in db/db mice (Luo 2014, Zhou 2014, DePaoli 2019).

The nonclinical safety program for aldafermin includes general toxicity and pharmacokinetic (PK) studies in the mouse, rat and cynomolgus monkey for up to 26 weeks of treatment and embryofetal and developmental toxicity studies in the mouse and rabbit. Based on the cumulative nonclinical safety profile of aldafermin for up to 26 weeks of treatment, the no observed adverse effect levels (NOAELs) in the mouse, rat and monkey were determined to be 1, 1, and 3 mg/kg, respectively. A sufficient safety margin exists for aldafermin at the proposed maximal clinical dose of 3 mg (0.033 mg/kg based on a 90 kg subject).

Please refer to Appendix 1 and Appendix 2 of the Investigator's Brochure (IB) for Pharmacological and Toxicology studies supporting the development of aldafermin in NASH.

2.7. Clinical Experience

The clinical testing of aldafermin includes a completed first in human Phase 1 study (Study 12-0101) in healthy subjects in Australia; a completed Phase 1b study in subjects with functional constipation (Study 15-0107); a completed single-dose Phase 1 study in subjects with varying degrees of impaired renal function (Study 282-RI-103); a completed 28-day Phase 2a study in subjects with type 2 diabetes (T2D) (Study 13-0102) in Australia and New Zealand; a completed 28-day Phase 2a (Study 13-0103) in subjects with Primary Biliary Cholangitis (PBC) in the United States, Australia and New Zealand; a completed 52-week Phase 2b (Study 14-0104) study in subjects with PBC in the United States, Australia, and New Zealand; and a completed 12-week Phase 2 study in subjects with Primary Sclerosing Cholangitis (PSC) (Study 15-0106) in the United States, France, Netherlands and United Kingdom. Additionally, a Phase 2 study in subjects with NASH (Study 15-0105) has evaluated 3 mg and 6 mg doses of aldafermin in a double-blind cohort (DBC) for 12 weeks (completed [Part 1]), 0.3 mg, 1 mg, and 3 mg doses for 12 weeks in an open-label single-blind cohort (SBC) (completed [Part 2]), and 1 mg for 24 weeks in an ongoing placebo-controlled histology cohort (Part 3; new results from interim analysis included).

In the randomized, placebo-controlled, double-blind cohort of Study 15-0105 (Part 1), patients with biopsy-confirmed non-cirrhotic NASH had decreased absolute liver fat content (LFC) by -9.7% and -11.9% upon treatment with aldafermin doses of 3 mg and 6 mg ($p<0.001$), respectively, versus -0.9% with placebo (Table 2). 74% (20/27) of patients receiving aldafermin at 3 mg and 85% (22/26) of patients receiving aldafermin at 6 mg met the primary endpoint of decrease in absolute LFC of ≥5%, while only 7% (2/27) of patients in the placebo group met this criteria (Table 2). There were no significant differences between the two aldafermin doses in either absolute or relative LFC reductions. Patients receiving aldafermin had a mean relative change in LFC from Baseline to Week 12 of -47% and -61% with the 3 mg and 6 mg doses, respectively, versus -1% with placebo ($p < 0.001$) (Table 2). Overall, 89% (47/53) of patients receiving aldafermin for 12 weeks achieved a clinically meaningful change (≥30% relative change) in LFC, with normalization (below a threshold of <5% absolute LFC) observed in 34% of patients of aldafermin-treated subjects versus none in the placebo group.

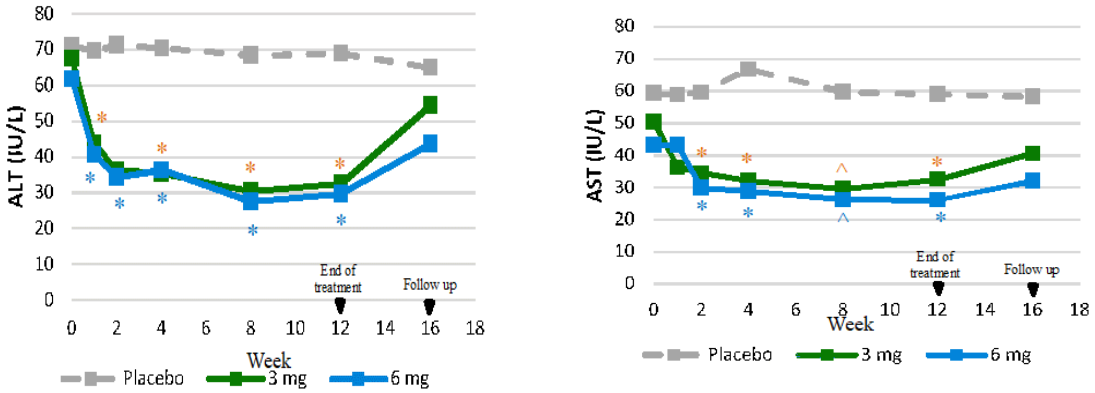
Table 2. Change from Baseline to Week 12 in MRI-PDFF in NASH Subjects

		Aldafermin	
	Placebo (N=27)	**3 mg (N=27)**	**6 mg (N=26)**
MRI-PDFF, Absolute % (Wk 12)	-0.9%	-9.7%	-11.9%
Absolute ≥5% (% pts.)	7%	74%	85%
MRI-PDFF, Relative % (Wk 12)	-1%	-47%	-61%
Relative ≥30% (% pts.)	7%	85%	92%
ALT, Absolute IU (Wk 12)	-2	-35	-32
ALT Normalization (female <19 IU, male <30 IU)	3.8%	37.0%	35.7%
ALT, Relative % (Wk 12)	1%	-43%	-44%

ALT=alanine aminotransferase; MRI-PDFF=magnetic resonance imaging-proton density fat fraction; pts=patients; Wk=week

Greater reductions from Baseline in mean absolute ALT levels were observed for both aldafermin 3 mg (−35 IU, p<0.0001) and 6 mg (−33 IU, p<0.0001) at Week 12 compared to placebo. The reductions achieved statistical significance as early as 1 week with a sustained reduction throughout the entire 12-week study treatment period. The mean relative percentage decreases in ALT levels from Baseline to Week 12 were also significant in both doses, ranging from -45% to -47% (p<0.001). ALT levels achieved normalization (defined as <19 IU in females and <30 IU in males) in 24% of aldafermin-treated patients by Week 2 and 36% of treated subjects by Week 12 (Figure 1). Similarly, treatment with aldafermin resulted in significant mean absolute reductions in AST levels from Baseline to Week 12 compared with placebo with the majority of subjects decreasing below the clinically meaningful threshold of 40 IU as soon as 2 weeks after starting treatment (Figure 1).

Figure 1. Absolute ALT and AST Values by Study Visit during and after Aldafermin Treatment



*p<0.001, ^p<0.05 change from baseline

In the single-blind cohort of Study 15-0105 (Part 2) evaluating 3 doses aldafermin (0.3 mg, 1 mg, 3 mg) in patients with biopsy-confirmed non-cirrhotic NASH, the primary endpoint (≥ 5% decrease in absolute LFC) was met in 57%, 90% and 100% of the 0.3 mg, 1 mg and 3 mg doses, respectively, at week 12. LFC normalization was achieved in 17%, 24% and

69% of the 0.3 mg, 1 mg, and 3 mg doses, respectively and was highly dependent on the Baseline MRI-PDFF for the 0.3 mg dose.

Importantly, similar to the LFC, by Week 12, ALT levels decreased to a similar magnitude in the 1 mg and 3 mg dose groups, whereas in the 0.3 mg dose group the ALT levels decreased to a lesser magnitude plateauing above the upper limit of the normal range (ULN) in the majority of subjects. The 1 mg and 3 mg dose groups demonstrated similar reductions of LFC and levels of ALT as those observed with the 3 mg dose in the double-blind cohort (Table 3).

Table 3. Changes in Noninvasive Imaging and Biomarkers from Baseline to Week 12 in the Single-Blind Cohort in Study 15-0105

	Aldafermin doses											
	0.3 mg (n=23)				1 mg (n=49)				3 mg (n=22)			
	Baseline	Week 12	Change from Baseline to Week 12	P*	Baseline	Week 12	Change from Baseline to Week 12	P*	Baseline	Week 12	Change from Baseline to Week 12	P*
Imaging												
Liver fat content by MRI-PDFF (%)	20.3 (7.1)	14.9 (8.5)	-5.34 (5.8)	0.0002	19.2 (6.5)	8.5 (5.0)	−11.0 (5.0)	<0.0001	17.5 (5.8)	6.6 (5.4)	−10.9 (4.3)	<0.0001
cT1 by Liver*MultiScan* (Whole Median (ms)					924.1 (82.8)	854.5 (77.6)	−77.0 (52.1)	<0.0001	901.0 (73.7)	830.8 (79.8)	−71.6 (58.3)	<0.0001
Serum markers of target engagement												
C4 (ng/mL)	45.9 (41.3)	16.4 (16.4)	-29.6 (43.4)	0.0043	33.1 (22.6)	7.3 (13.2)	−26.7 (26.1)	<0.0001	33.9 (24.1)	2.1 (2.7)	−31.8 (24.7)	<0.0001
Total bile acids (mmol/L)	4.9 (2.5)	3.1 (3.2)	-1.7 (3.0)	0.0138	5.4 (4.4)	1.7 (1.6)	−3.6 (3.9)	<0.0001	5.1 (3.2)	1.4 (1.0)	−3.7 (3.3)	<0.0001
Liver enzymes												
ALT (U/L)	74.3 (33.9)	51.8 (37.0)	-22.5(29.7)	0.0015	81.4 (48.6)	29.6 (18.9)	-51.8 (39.5)	<0.0001	78.4 (28.6)	-28.6 (14.0)	-49.8 (37.6)	<0.0001
AST (U/L)	50.6 (27.5)	39.2 (24.1)	-11.3 (19.4)	0.0105	61.3 (34.2)	28.3 (17.2)	−33.0 (30.9)	<0.0001	62.6 (32.3)	27.3 (9.1)	−35.3 (27.1)	<0.0001
Serum Fibrosis markers												
Pro-C3 (ng/mL)	18.2 (8.5)	15.3 (7.0)	-2.2 (7.6)	0.2097	16.8 (9.3)	12.3 (5.7)	−4.5 (6.4)	<0.001	25.4 (21.1)	14.7 (8.9)	−10.7 (18.0)	0.0155
ELF score	9.3 (0.7)	9.3 (0.8)	-0.02 (0.4)	0.7520	9.6 (0.8)	9.3 (0.8)	−0.3 (0.4)	<0.001	10.1 (.93)	9.6 (1.0)	−0.53 (0.6)	<0.0008

*Note: p-values are obtained using a one-sample t-test for the change from baseline at Week 12.

Liver histology was evaluated at 12 weeks in the 1 mg and 3 mg dosing groups in the single-blind cohort of the study (Part 2) in a total of 44 subjects. The Week 12 biopsy results in the 1 mg and 3 mg groups, are summarized as follows (Table 4):

- Fibrosis improved by at least 1 stage without NASH worsening in 25% and 42% of subjects in the 1 mg and 3 mg groups, respectively, with 3 subjects improving by 2 stages from Stage 3 to Stage 1 in the 3 mg group.

- 12% and 10% of subjects in the 1 mg and 3 mg groups, respectively, had resolution of NASH as currently defined by the FDA with no worsening in fibrosis
- NAS was decreased by ≥2 points (including inflammation and/or ballooning) without fibrosis worsening in 50% and 63% of subjects in the 1 mg and 3 mg groups, respectively.

Table 4. Histologic Measures in the 1 mg and 3 mg Single-blind Histology Cohorts in Study 15-0105

	Aldafermin Doses							
	1 mg (n=24)				3 mg (n=20)			
	Baseline	Week 12	Change from Baseline to Week 12	P*	Baseline	Week 12	Change from Baseline to Week 12	P*
Histology								
Total NAS score	5.4 (1.6)	3.5 (1.4)	−1.9 (1.6)	<0.001	5.6 (1.5)	3.6 (1.4)	−2.0 (2.1)	<0.001
Steatosis	2.0 (0.9)	0.9 (0.4)	−1.1 (0.8)	<0.001	1.7 (0.8)	0.7 (0.7)	−1.0 (1.0)	<0.001
Ballooning	1.4 (0.8)	1.0 (0.9)	−0.4 (0.9)	0.030	1.7 (0.7)	1.2 (0.8)	−0.6 (1.1)	0.030
Inflammation	2.0 (0.5)	1.6 (0.5)	−0.4 (0.6)	0.004	2.2 (0.7)	1.8 (0.5)	−0.4 (0.7)	0.017
Total Fibrosis score	2.3 (0.7)	2.2 (0.8)	−0.1 (0.7)	0.584	2.4 (0.8)	2.0 (0.9)	−0.4 (0.9)	0.048

* p-value is based on a one-sample t-test for change from baseline.

The double-blind, 24-week cohort of Study 15-0105 evaluates 1 mg aldafermin and placebo in patients with biopsy-confirmed non-cirrhotic NASH. A pre-specified interim analysis was conducted when ~50% of subjects randomized 2:1 to daily aldafermin or placebo completed Week 24 procedures. Thirty-eight subjects received placebo (n=13) or aldafermin 1 mg (n=25) at the interim data cut off. Key inclusion criteria included biopsy-proven NASH with NAS ≥4, Stage 2-3 fibrosis and absolute LFC ≥8%. Subjects underwent MRI-PDFF and liver biopsies at baseline and Week 24. The primary endpoint (≥5% decrease in absolute LFC) was achieved in 72% of patients receiving aldafermin 1 mg and in 17% of patients receiving placebo at Week 24. 72% and 17% of patients receiving aldafermin 1 mg or placebo, respectively, achieved a relative reduction of LFC ≥30%. At Week 24, reductions in markers of liver injury (ALT and AST) and liver fibrosis (Pro-C3 and ELF) were also observed with 1 mg aldafermin compared with placebo (Table 5).

Table 5. Change from Baseline to Week 24 in Key Parameters: Interim Analysis of a 24-week, Double-blind, Placebo-controlled Study of Aldafermin (15-0105, Part 3) in Patients with NASH

	PBO (n=13)	Aldafermin 1 mg (n=25)
Imaging Parameters		
Δ Absolute MRI-PDFF, %	−2.0 (2.0)	−7.9 (1.4)**** †
% subjects with ↓5% absolute	*17%*	*72%††
Δ Relative MRI-PDFF	−5.9%	−39.6%**** †
% subjects with ↓30% relative	*17%*	*72%††
Serum Parameters		
Δ Absolute ALT, U/L	−18.6 (5.6)**	−38.0 (4.1)****††
Δ Relative ALT	−2.0%	−38.7%****††
Δ Absolute AST, U/L	−9.4 (6.4)	−18.5 (4.8)***
Δ Relative AST	−4.1%	−23.4%**
Δ Pro-C3, ng/mL	0.3 (1.5)	−4.3 (1.0)*** †
Δ Relative Pro-C3	5.4%	−24.3%** †
Δ Absolute ELF	0.06 (0.18)	−0.21 (0.14)

Shown are least squares mean (SE).
****p<0.0001, ***p<0.001, **p<0.01, *p<0.05 vs baseline,
††p<0.01, †p<0.05 vs PBO

Overall, aldafermin has demonstrated robust activity in reducing LFC, transaminases, and serum markers of fibrogenesis, leading to improvement in liver fibrosis and histology in patients with biopsy-confirmed, non-cirrhotic NASH.

2.8. Rationale for Dose Selection

The planned aldafermin dose levels for Phase 2b Study 282-CC-207 in F4 subjects are 0.3, 1, or 3 mg. These doses are proposed based on assessment of safety, tolerability, and efficacy data from a total of 326 subjects obtained from the following studies:

- Phase 1 Study 12-0101 in healthy subjects: placebo, aldafermin dose range for single-ascending dose (SAD) from 0.1 mg to 30 mg and dose range for multiple-ascending dose (MAD) from 0.1 mg to 20 mg;
- Phase 2 Study 13-0102 in T2D (presumptive NASH subjects): placebo, aldafermin dose range from 2 mg to 10 mg; and
- Phase 2 Study 15-0105 in noncirrhotic NASH
  - Double-blind cohort (completed): placebo, aldafermin doses (3 and 6 mg),
  - Single-blind cohort (completed): aldafermin doses (0.3, 1 and 3 mg), and
  - Placebo-controlled cohort (ongoing): placebo and 1 mg aldafermin dose.

In the Phase 1 Study 12-0101, aldafermin demonstrated a favorable tolerability profile up to 30 mg in the SAD portion of the study and 10 mg in the MAD portion of the study. Significant rapid and dose-dependent biological action on BA synthesis and reduction in C4 (80 to 90%) was observed at doses of 0.3, 1, and 3 mg of aldafermin in healthy subjects. The 0.1 mg dose did not demonstrate any reduction in C4, suggesting it to be a “no effect” dose. This established the lowest dose for evaluation of aldafermin in other subject populations as 0.3 mg, and a dose range for evaluation of 0.3 to 10 mg.

In the Phase 2 Study 13-0102, data from the T2D study subjects (presumptive NASH patients) indicated that aldafermin demonstrated an increased frequency and severity of gastrointestinal (GI) symptoms and injection-site reactions (ISRs) in patients treated with 10 mg. Therefore, the dose range of 0.3 to 6 mg was selected for the Phase 2 Study 15-0105. In addition, aldafermin at doses >2 mg demonstrated greater decreases in body weight, fasting blood glucose, triglycerides, high-density lipoprotein (HDL), and ALT and C4 were suppressed by >95% in T2D patients treated with the 2 and 5 mg doses of aldafermin. Therefore, a dose range of 0.3 to 6 mg was evaluated in the NASH patients.

In the Phase 2 Study 15-0105, the integrated safety data from the noncirrhotic NASH subjects double-blind and single-blind cohorts demonstrated a dose-dependent increase in the incidence of most commonly-occurring treatment-emergent adverse events (TEAEs), i.e., ≥10%, comprising gastrointestinal symptoms, headache, fatigue, and injection site erythema, with incidence plateauing from 1 mg (90%), 3 mg (86%), to 6 mg (86%). The 6 mg dose of aldafermin was associated with more drug-related treatment discontinuations and study withdrawals compared to the 3 mg dose, and hence was not further evaluated.

In addition, data from the double-blind cohort suggest that both the 3 and 6 mg doses of aldafermin have equivalent efficacy in terms of reductions in LFC, liver transaminases, and anti-fibrotic markers. The primary endpoint of ≥5% decrease in absolute LFC was met in 57%, 90%, and 100% of the 0.3 mg, 1 mg, and 3 mg doses, respectively. Noninvasive marker analyses demonstrated a dose dependent and significant decrease in Pro-C3 and enhanced liver fibrosis (ELF) scores at these doses. ALT decreased rapidly and was similar for the 1 mg and 3 mg doses. The decrease in ALT levels was lesser in magnitude and plateaued above the ULN for most of the subjects in the 0.3 mg group. A total of 43 subjects were enrolled in the 1 and 3 mg single-blind dose cohorts and completed 12 weeks of treatment with paired biopsies. At Week 12, a greater proportion of subjects in the 3 mg arm (i.e., 68%) than 1 mg arm (i.e., 50%) met the histologic responder criteria.

These studies also showed that repeat dosing of aldafermin does not cause accumulation of aldafermin systemically due to the short (~5 hour) half-life. Additionally, NGM does not expect an increased risk of liver injury in well-compensated cirrhotic NASH subjects as aldafermin is not metabolized in the liver.
Therefore, based on the totality of the safety, tolerability, and efficacy data from these studies, NGM has selected aldafermin doses of 0.3, 1, and 3 mg for evaluation in this Phase 2b study. These selected doses are within the safety margins determined from the chronic toxicology studies in mice, rats, and monkeys.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary Objective and Endpoints

The primary objective of this study is to evaluate the efficacy and safety of aldafermin compared to placebo.

1. The primary efficacy endpoint is the change in Enhanced Liver Fibrosis (ELF) score from baseline to Week 48 with aldafermin or matched placebo.

2. The primary safety endpoint is frequency, severity, and timing of adverse events (AEs) and serious adverse events (SAEs).

3.2. Secondary Efficacy Objectives and Endpoints

The secondary objectives are to evaluate the efficacy of aldafermin and the effect of aldafermin on pharmacokinetics and on biomarkers of target engagement, fibrogenesis, and imaging.

The following endpoints will be measured:

1. Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis), after 48 weeks of treatment with aldafermin or matched placebo, in subjects who had a minimum 1 point in each category (hepatocellular ballooning, steatosis, and lobular inflammation) of NAFLD Activity Score (NAS) at baseline as determined by central pathologist evaluation.

2. Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) after 48 weeks of treatment with aldafermin or matched placebo.
3. Changes from baseline in fibrosis as measured by Collagen Proportional Area (CPA) and/or Second Harmonic Generation (SHG) methodologies at Week 48.

4. Aldafermin concentrations pre-dose at all treatment visits and 4-hours post-dose at Day 1, Week 24, and Week 48 in all subjects. In a subset of subjects participating in an optional PK study, full PK profiles up to 24 hours will be assessed at Day 1 and steady state at end of treatment (EOT), i.e., 48 weeks.

5. Changes from baseline over time in C4 and serum bile acids and compared to placebo.

6. Changes from baseline over time in Pro-C3 compared to placebo.

7. Changes from baseline over time in alanine transaminase (ALT) and aspartate transaminase (AST) and compared to placebo in subjects with elevated transaminases at baseline.

8. Changes from baseline over time in liver stiffness measure (LSM by FibroScan®) and compared to placebo.

3.3. Exploratory Endpoints

The following exploratory endpoints will be evaluated to understand change from baseline with aldafermin and compared to placebo:

4. STUDY DESIGN

4.1. Methodology/Study Design:

This study is a double-blind, randomized, placebo-controlled, multi-center study of aldafermin in subjects with histologically confirmed cirrhosis with NASH.

The study consists of a screening period, a double-blind treatment period of 48 weeks and a safety follow-up period of 6-10 weeks. Subjects will be treated with either aldafermin or matched placebo given as a subcutaneous injection daily for 48 weeks.

Eligible subjects will have histologically confirmed cirrhosis (NASH CRN fibrosis Stage 4, with a limited number of subjects with fibrosis Stage 3 with a clinical diagnosis of cirrhosis) due to NASH. Historical biopsy may be used for inclusion into the study. Otherwise, a liver biopsy must be obtained for eligibility assessment. Liver biopsy results of either historical or screening biopsy must be confirmed by a central pathologist reading.

At Screening, all subjects will undergo evaluation for risk of HCC. A gadolinium-enhanced MRI or multiphasic CT scan without any nodules evaluated as Liver Imaging and Reporting Data System (LI-RADS) score of ≥2 on central read will be required at Screening to rule out HCC risk. For potential subjects unable to obtain an MRI or CT scan, ultrasound that is negative for hepatic lesions/nodules (local read) at Screening may be used. In all cases, AFP must be ≤20 ng/mL.

Subjects with suspicious lesions/nodules at ultrasound followed by observation of nodules that are LI-RADS ≥2 by central read of gadolinium-enhanced MRI or multiphasic CT scan at Screening will be excluded from enrollment and will be referred for further evaluation for HCC per the standard of care (SOC). Subjects will also be excluded if EGD documented any signs of esophageal or gastric varices.

Up to approximately 150 eligible subjects will be randomized into 1 of 4 treatment groups in a 3:2:2:3 ratio to receive either subcutaneous placebo, 0.3 mg aldafermin, 1 mg aldafermin, or 3 mg aldafermin, respectively. Under protocol Version 5.0 and subsequent versions, eligible subjects will no longer be randomized into the 0.3 mg aldafermin treatment group. Instead, subjects will be randomized into 1 of 3 treatment groups in a 4:3:4 ratio to receive either subcutaneous placebo, 1 mg aldafermin or 3 mg aldafermin, respectively. Subjects randomized to the 0.3 mg aldafermin treatment group prior to protocol Version 5.0 will continue to receive the same dose until treatment completion. No more than 30% of the remaining population will be enrolled with the expanded Baveno VI criteria.

Randomization will be stratified by clinical diagnosis of T2D versus no T2D to ensure planned allocation ratio of treatment groups within each stratum (see Table 6 [Version 1.0-4.0], Table 7 [Version 5.0], and Figure 2).

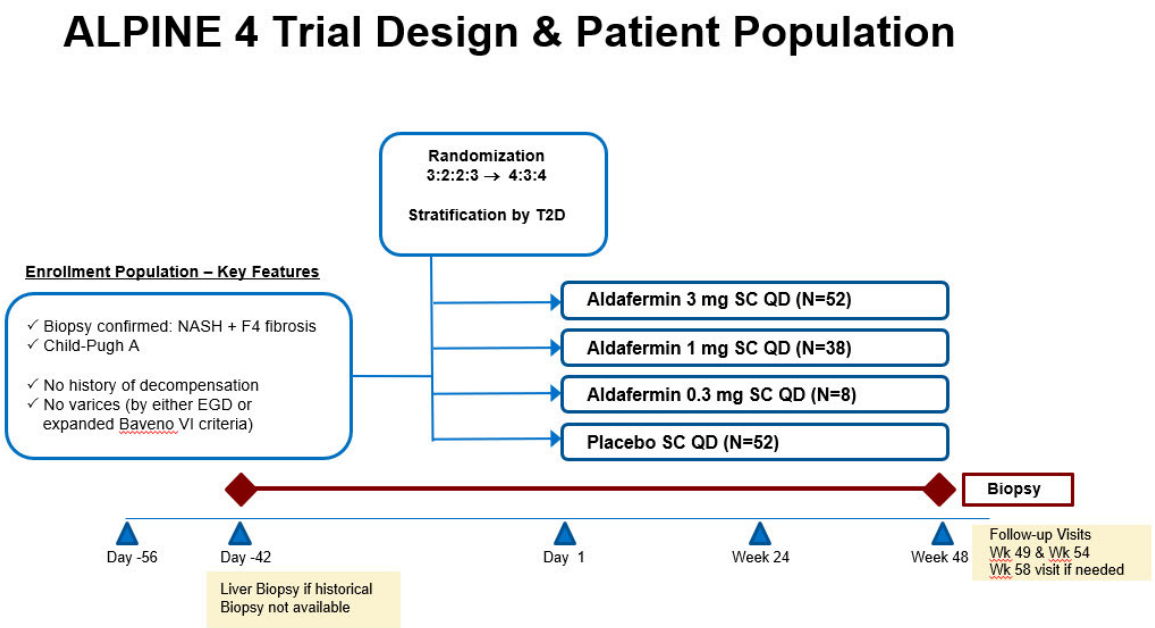
Table 6. Study Design 282-CC-207 (Versions 1.0-4.0)

Treatment Group	Dose of aldafermin (mg)	Mode of Treatment	Regimen	Number of Subjects Planned
1	0 (Placebo)	Subcutaneous	Daily	45
2	0.3			30
3	1			30
4	3			45
			Total Subjects Planned	150

Table 7. Study Design 282-CC-207 (Version 5.0)

Treatment Group	Dose of aldafermin (mg)	Mode of Treatment	Regimen	Number of Subjects Planned
1	0 (Placebo)	Subcutaneous	Daily	52
2	0.3			8
3	1			38
4	3			52
			Total Subjects Planned	150

Figure 2. Schematic Overview of the Study Design



Study drug self-administration instructions and training will be provided to the subjects and study drug kits will be dispensed. Subjects will self-administer in the clinic the first dose of aldafermin/ placebo (Day 1) and doses at Weeks 2, 6, 12, 18, 24, 30, 36, 42, and 48 study visits. Subjects will self-administer all other doses through Week 48 at home. Self-administration should occur at a similar time for every dose in both the clinic and at home.

Subjects will return to the clinic on Weeks 2, 6, 12, 18, 24, 30, 36, 42, and 48 for on treatment assessments.

Subject cholesterol levels will be followed during the course of the study, and treatment with over-encapsulated rosuvastatin/matched placebo will start at Week 2 according to the lipid management algorithm (Appendix 4).

LDL-C levels and related safety data will be evaluated at Weeks 2, 6, 12, 18, 24, 30, 36, and 42 in all subjects by an independent third-party Medical Monitor who will determine the need for initiation/titration of rosuvastatin according to the protocol. Rosuvastatin will be used to manage cholesterol levels according to the established lipid management algorithm described in Appendix 4.

Rosuvastatin and matched placebo are over-encapsulated to maintain the treatment blind. Initiation and ongoing dose adjustments of rosuvastatin/matched placebo will be managed through the [redacted] who is unblinded to subject lipid levels but blinded to the treatment assignment (aldafermin or matched placebo). The sponsor and study sites will be blinded to subject lipid levels, rosuvastatin/placebo allocation, and the specific rosuvastatin dosing decisions. A kit containing rosuvastatin or matched placebo bottles will be assigned based on assessment by the unblinded Medical Monitor, at each study visit from Week 2 through Week 42 (statin-naïve) or Week 48 (statin-experienced), according to the lipid management algorithm and will be delivered to subjects via a courier service vendor (Section 6.1.3.1) or to the study site for subjects to collect, depending on subject preference. Reference Appendix 4 for specific dosing algorithm for statin-naïve and statin experienced subjects.

Over-encapsulated rosuvastatin will be initiated at Week 2, starting at 5 mg QD in statin-naïve subjects whose ASCVD 10-year risk score is ≥7.5% (US) or ≥ moderate level risk (European), Appendix 4. In subjects who are statin-naïve with diabetes or a history of myocardial infarction or stroke, or other ASCVD risk-enhancing diagnoses, rosuvastatin will be initiated at 5 mg at Week 2 if LDL-C is not already at the goal of ≤70 mg/dL (1.8 mmol/L). Though there is incremental cardiovascular benefit to additional LDL-C lowering (Sabatine 2018), other reports, including the meta-analysis by Ma, et al. suggest an association between low LDL-C levels and hemorrhagic stroke (Ma 2019), and overall, controversy remains regarding the long-term safety of medications that can help achieve low LDL-C levels such as PCSK9 inhibitors (Pasta 2020, Bandyopadhyay 2018). Thus, for safety considerations, statin-naïve subjects with risk-enhancing diagnoses who are already at an LDL-C treatment goal of ≤ 70 mg/dL (1.8 mmol/L) will be initiated on over-encapsulated rosuvastatin placebo. At subsequent clinic visits, lipid levels will be evaluated and treatment with over-encapsulated rosuvastatin may be initiated or placebo may be continued.

Subjects who are statin-experienced (i.e., on statin concomitant medication), will be switched to an equivalent intensity rosuvastatin dose at Week 2. For self-identified Asians, 10 mg is

considered a high intensity dose, and 5 mg is considered a moderate intensity dose. Matched placebo will be given to statin-naive study subjects who do not meet initiation criteria at Week 2 or subsequent visits.

LDL-C values will be further evaluated at study visit Week 6, 12, 18, 24, 30, 36, and 42, in order to identify subjects who require rosuvastatin initiation or dose-escalation. Specific LDL goal or treatment success criteria are described in detail in Section 8.3.17. Subjects who do not meet rosuvastatin increase criteria will continue on their prior assigned dose of over-encapsulated rosuvastatin/ matched placebo. Subjects on the maximum dose of rosuvastatin 40 mg whose LDL-C levels are still not at goal will continue on the study with rosuvastatin 40 mg unless the subject experiences a cardiovascular-related SAE (e.g., myocardial infarction, CVA). Subjects experiencing a CV-related SAE on rosuvastatin 40 mg will discontinue both aldafermin and rosuvastatin for the remainder of the trial, and cardiovascular care will continue per the subject's regular physician and as per local standard of care practices. Subjects who experience rosuvastatin-related intolerance (by evaluation of muscular symptoms and creatine kinase (CK) levels) will be evaluated by follow-up laboratory testing after the over-encapsulated rosuvastatin/placebo has been held. Depending on the CK levels and clinical status, subjects may be allowed to restart over-encapsulated rosuvastatin/placebo at a reduced dose. Algorithm details are found in Section 7.1.1, part ii.

All subjects will be assessed at Weeks 49 and 54 to confirm their LDL-C levels have decreased to near baseline, at which point no additional follow-up is needed.

Subjects who do not meet LDL-C decrease criteria at Week 54 will have an additional 4-week follow-up visit at Week 58 to confirm that their LDL-C level returned to near baseline. Subjects may remain on statin through Week 58.

As part of safety monitoring, subjects will undergo ultrasound and alpha fetoprotein (AFP) testing at Weeks 24 and 48 to screen for HCC. Subjects with new lesions ≥10 mm with AFP >20 ng/mL will be treated according to local guidelines. If new lesions ≥10 mm with AFP >20 ng/mL occur at Week 24, subjects may continue on study drug at the discretion of the investigator unless or until a clinical diagnosis of HCC is made (defined as LI-RADS 4 or 5 on MRI, or histological confirmation of HCC). For subjects with suspected HCC by ultrasound and AFP screening, additional imaging may be obtained, and data will be gathered for adjudication.

Overall safety will be monitored by a data safety monitoring board (DSMB).

All subjects will return to the clinic for the End-of-Treatment (EOT) visit at Week 48. Subjects will return to the clinic at Weeks 49 and 54 (or at 1 and 6 weeks after last dose of aldafermin) for a post-treatment response and End-of-Study (EOS) follow-up visits. Subjects may be contacted to participate in additional optional follow-up visits, if necessary, to monitor anti-drug antibody (ADA) response.

4.2. Study Stop Criteria

The entire study may be discontinued at the discretion of the sponsor based on the occurrence of the following:

- AEs with respect to their nature, frequency, severity, and/or duration (reference Section 7.1 for details)
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects
- Cancellation of drug development

5. SUBJECT SELECTION

5.1. Inclusion Criteria

Subjects must meet the following criteria for study entry:

1. Males and females between 18 and 75 years of age, inclusive, who are able to comprehend and willing to sign an Informed Consent Form (ICF).
2. Liver biopsy consistent with a diagnosis of NASH Cirrhosis according to NASH CRN criteria and per the central pathologist evaluation.
   a. A historical biopsy is acceptable if tissue slides are available from within 12 months prior to Screening and are acceptable for the central pathologist evaluation.
   b. Liver biopsies must be consistent with cirrhosis according to the NASH CRN classification (NASH CRN fibrosis score of 4), as assessed by the central reader (see also Inclusion Criterion 4).
   c. NASH must be the etiology of cirrhosis (i.e., no other causes of cirrhosis; see also Inclusion Criterion 4).
   d. A limited number of subjects (capped at 10% of planned enrollment) with clinical diagnosis of NASH cirrhosis may be enrolled despite a NASH CRN fibrosis score of 3. Clinical diagnosis of NASH cirrhosis must meet at least one of the following:
      - Agile 4 score ≥0.57 (Younossi 2020, Boursier 2021)
      - Platelet count ≤140,000/mm^3 and Liver Stiffness Measure (LSM) by FibroScan® ≥13.6 kPA (Eddowes 2019)
      - FIB-4 ≥3.25

3. *Criterion deleted per protocol Version 5.0.*
4. Subjects must have Definitive NASH cirrhosis as defined in Noureddin 2020.
   a. Current biopsy shows cirrhosis with steatohepatitis. There is no evidence for a competing etiology.
   b. Previous biopsy showed steatohepatitis, but now with cirrhosis either by clinical history or current features, imaging, noninvasive tests, or biopsy. If there is a current biopsy, it does not show evidence of steatosis or steatohepatitis, as these histological findings may have disappeared (burn-out). There is no evidence for a competing etiology. There is at least 1 coexisting or history of metabolic comorbidity to corroborate a diagnosis of NAFLD.
   c. Current biopsy shows cirrhosis with steatosis. There is no evidence for competing etiology. There are at least 2 coexisting or history of metabolic comorbidities, including obesity and/or T2DM to corroborate a diagnosis of NAFLD.

Have AFP ≤20 ng/mL at Screening.

Negative for hepatic lesions/nodules indicating HCC risk:

a. MRI is the preferred imaging modality. There must be no nodules with a Liver Imaging and Reporting Data System (LI-RADS) score of ≥2 by central radiologist evaluation.

b. If MRI is not available or not possible to be performed, a multi-phasic CT scan may be used to assess HCC risk. There must be no nodules with a LI-RADS score ≥2 by central radiologist evaluation.

c. If MRI and CT are not available or not possible to be performed for screening a potential subject, then ultrasonography of the liver may be performed:

   1) If no hepatic lesions or nodules (local radiologist evaluation) and AFP ≤20 ng/mL, the potential subject may be considered further for enrollment.

   2) For any findings of hepatic lesions or nodules (local radiologist evaluation) that are not clearly benign cysts and have not been shown clearly benign by prior CT or MRI, follow-up MRI must be performed and meet criteria (no nodules with LI-RADS score of ≥2 evaluated centrally) in order for the potential subject to be considered further for enrollment.

7. Subjects with T2D or insulin resistance are permitted as long as diabetic medications are reasonably "stable" within 3 months prior to Screening, as outlined in Section 6.4.

8. Other concomitant medications/therapies used for the treatment of coexisting conditions are acceptable (Section 6.4), if on a stable regimen for at least 3 months prior to the Screening, except for non-statin lipid lowering agents, which can be used until Day 1 of Screening.

9. Statin use is acceptable based on the following criteria, as assessed by the investigator at Screening:

   a. **Statin-naïve** is defined as no administration of statins within 3 months prior to Screening

   b. **Statin-Experienced** is defined as currently receiving ≤50% of the maximal approved dose of statin therapy

      Requires a reasonably stable statin dose at least 3 months prior to Screening

   Note: The following are the acceptable daily doses of approved statin therapies, and other lipid lowering agents. Also listed under Section 6.4:

   i. Atorvastatin: ≤40 mg/day
   ii. Fluvastatin: ≤40 mg/day
   iii. Lovastatin: ≤40 mg/day (for both immediate and extended release)
   iv. Pitavastatin: ≤2 mg/day
   v. Pravastatin: ≤40 mg/day

vi. Simvastatin: ≤40 mg/day

vii. Rosuvastatin: ≤20 mg/day

10. The following additional laboratory parameters must be met at Screening

    a. Total bilirubin ≤1.3 mg/dL

        i. if Gilbert's Syndrome, with direct bilirubin within ULN.

    b. HbA1c ≤9.5%

    c. Platelet count ≥120,000/mm^3

        Subjects who meet the Baveno VI criteria with a platelet count >110,000/mm^3 and <120,000/mm^3 may be enrolled if they meet the expanded Baveno VI criteria. (Note: No more than 30% of the remaining population will be enrolled using the Baveno VI criteria.)

    d. Creatinine clearance ≥60 mL/min as calculated by Cockcroft-Gault equation

    e. Serum alanine amino transferase (ALT) levels ≤5 x ULN

    f. Serum aspartate amino transferase (AST) levels ≤5 x ULN

    g. Alkaline phosphatase ≤1.5 x ULN

    h. Serum albumin ≥3.5 g/dL

    i. International normalized ratio (INR) ≤1.7.

        Note: A 10% laboratory variability is allowed on platelets and bilirubin values. Platelet variability does not apply to Baveno VI.

11. Female subjects must be either of a) non-childbearing potential, defined as women who have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, documented postmenopausal, or a follicle stimulating hormone ≥40 mIU/mL, OR b) if of childbearing potential, defined as including women <55 years of age with ≤2 years of amenorrhea (absence of menstruation and not due to any reversible medical cause or any current medication use), then have a negative serum pregnancy test at Screening and urine pregnancy test at the Day 1 visit prior to first dose of study drug, and must be non-lactating and non-breastfeeding. Note: Females who do not meet this criterion can be included if they meet Inclusion Criterion 12.

12. Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must agree to consistent and adequate birth control from Screening to EOS (Week 54):

    - Recommended forms of contraception for males: condom, vasectomy, and sexual abstinence
        i. Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the female subject of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

ii. Condom use is not considered as a highly effective form of contraception alone and may be used effectively with a second method of contraception.
iii. Sexual abstinence is considered a highly effective method only if defined as abstaining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.

- Recommended forms of contraception for females: hormone containing contraceptive medication, Intrauterine device with failure rate <1% per year, cervical cap or diaphragm with spermicidal agent, bilateral tubal occlusion (tubal sterilization), sexual abstinence
  i. Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation
  ii. Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation
  iii. Cervical cap or diaphragm with spermicidal agent is not considered as a highly effective form of contraception alone and may be used effectively with a second method of contraception

  Sexual abstinence is considered a highly effective method only if defined as abstaining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.

13. Able and willing to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

5.2. Exclusion Criteria

The following will exclude potential subjects from participating the study:

1. Other causes of liver disease that are primary, secondary, or otherwise causes of cirrhosis or which may confound the intended patient population according to the investigator, including but not limited to alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders, primary biliary cirrhosis, drug-induced hepatotoxicity, Wilson's disease, hemochromatosis, and alpha-1-anti-trypsin deficiency based on medical history and/or centralized read of liver histology.

2. Evidence of drug induced steatohepatitis secondary to amiodarone, corticosteroids, estrogens, methotrexate, tetracycline, or other medications known to cause hepatic steatosis.

3. History of hepatic decompensation, including variceal bleeding, ascites, or hepatic encephalopathy.

4. Prior or pending liver transplantation.

5. Child Pugh class B and C status.

6. Model of end stage liver disease (MELD) score >12.

7. Evidence of worsening liver disease (defined below) between screening visits (i.e., Day -56 and Day -42) including measures of AST, ALT, alkaline phosphatase (ALP) or total bilirubin (TBL):

    a. For subjects with TBL, AST, ALT, or ALP baseline levels >ULN, the second assessment should not exceed an increase of 35% over the first assessment.

    Note: An unscheduled visit may be necessary to confirm eligibility if the difference exceeds the allowable percent difference. If performed, unscheduled visit results will be compared to the average of Day -56 and Day -42 results to determine eligibility. If liver function tests are repeated to verify eligibility criteria have been met, there must be a minimum of 14 days (2 weeks) between the Day -42 visit and any unscheduled visit.

8. History of porto-systemic shunt procedure.

9. No evidence of gastroesophageal varices as documented by one of the following assessments:

    a. A historical and locally evaluated EGD obtained within 365 days of screening or
    b. A locally evaluated EGD conducted during the screening period

    * If no EGD is available, the latest EGD assessment guidelines during a global pandemic† for patients with compensated cirrhosis (i.e., the expanded Baveno VI criteria, Petta 2018) as follows can be used as a replacement for the EGD to determine eligibility:

    c. Platelet count >110,000/mm^3, and a FibroScan® <30 kPa on a M probe or <25 kPa on a XL probe
    Note: No more than 30% of the remaining population will be enrolled with the expanded Baveno VI criteria.
    † *EGD waived in patients with compensated cirrhosis during a global pandemic per AASLD/ASGE guidelines.*

10. Clinically significant cardiovascular or cerebrovascular event or new diagnosis within 6 months of Screening, including but not limited to congestive heart failure, myocardial infarction, acute coronary syndrome, revascularization, stroke (hemorrhagic or ischemic), transient ischemic attack (TIA), or implanted defibrillator or pacemaker (for uncomplicated elective, non-biventricular pacemaker procedure, 3 months post procedure will be allowed).

11. Gastric bypass or bariatric surgery in the past 5 years or planned procedure during the study period.

12. 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.

13. Documented significant weight change (±5%) <3 months prior to Screening.

14. Screening ECG with clinically significant abnormalities that in the investigator's opinion, require evaluation and possible treatment.

15. Positive for HBsAg, antiHIV Ab, or antiHCV Ab plus HCV-RNA. Subjects who are antiHCV Ab- positive but HCV-RNA negative (secondary to treatment or viral clearance) are eligible with at least a 1-year period since documented sustained viral response at Week 12 post-treatment.

16. 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* or breast ductular carcinoma *in situ* is allowed if appropriately treated within 2 years prior to Screening); subjects under evaluation for suspected malignancy are not eligible. History of hepatocellular carcinoma at any point regardless of treatment or treatment success will be excluded.

17. A positive drug screen (e.g., morphine, heroin, cocaine) will exclude subjects unless it can be clearly explained by a prescribed medication. The diagnosis and prescription must be approved by the investigator and the Medical Monitor.

18. Significant alcohol intake as measured by a phosphatidylethanol (PEth) level ≥200 ng/mL AND significant alcohol use, as determined by the Alcohol Use Disorders Identification Test (AUDIT-C) alcohol consumption questionnaire (Appendix 3).

19. *Criterion deleted per protocol Version 3.0.*

20. Consumption of ≥21 units of alcohol per week in males and ≥14 units of alcohol per week in females for two years prior to screening, where a “unit” of alcohol is equivalent to a 12-ounce beer, 4-ounce glass of wine, or 1-ounce shot of hard liquor.

21. Use of any prohibited concomitant medications as described in Section 6.4 within 3 months prior to screening;

    a. Weight loss medications.

    b. Any medication that is contraindicated according to the rosuvastatin package insert (Appendix 5) or if subject has a known hypersensitivity to rosuvastatin product components (Section 6.1.3).

    c. Hepatotoxic medications (Appendix 6); allopurinol allowed.

    d. Anabolic steroids.

22. History of statin intolerance, as defined by presence of significant side effects while on statins and/or inability to take or use statins for treatment.

23. Prior participation in a clinical trial of aldafermin unless previously enrolled into a placebo arm of the trial.

24. History of severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies.

25. Participation in a study of another investigational agent within 28 days or five half-lives of the drug (whichever is longer) prior to Screening.

26. Any acute or chronic condition that, in the opinion of the investigator, would limit the subject's ability to participate, complete, and/or would confound data interpretation in this clinical study.

6. STUDY TREATMENT

6.1. Clinical Supplies

6.1.1. Aldafermin

Aldafermin is formulated in aqueous isosmotic buffer solution with 0.01% polysorbate-20. It is filled into 1-mL type I glass syringes, with a 29-g staked needle, needle shield, grey rubber plunger, and plastic plunger rod. Filled syringes are labeled and packaged into trays and cardboard cartons.

Aldafermin is provided as a sterile solution for injection in a single use prefilled syringe for SC administration at doses of 0.3 mg, 1 mg, and 3 mg (note: under protocol Version 5.0 and subsequent versions, randomization to the 0.3 mg aldafermin dose was discontinued). The drug product is manufactured for NGM under current Good Manufacturing Practice (cGMP) regulations [redacted], a contract manufacturing facility that has undergone FDA inspection.

6.1.2. Aldafermin-matched Placebo

Aldafermin placebo is formulated in aqueous isosmotic buffer solution with 0.01% polysorbate-20. It is filled into 1-mL type I glass syringes, with a 29-g staked needle, needle shield, grey rubber plunger, and plastic plunger rod. Filled syringes are labeled and packaged into trays and cardboard cartons.

Aldafermin placebo is provided as a sterile solution for injection in a single use- pre-filled syringe for SC administration. The drug product is manufactured for NGM under cGMP regulations [redacted], an FDA-inspected contract manufacturing facility.

6.1.3. Rosuvastatin / Placebo

Commercial rosuvastatin tablets will be over-encapsulated and will be supplied as 5 mg, 10 mg, 20 mg, or 40 mg strengths in multi-count bottles. Inactive ingredient microcrystalline cellulose will be used to backfill over-encapsulated rosuvastatin calcium tablets.
Placebo capsules for rosuvastatin calcium contains only microcrystalline cellulose and will be supplied in multi-count bottles. The capsules used for the active and placebo are opaque, Swedish Orange, size A, hard gelatin capsules containing gelatin, titanium oxide, and FDA/E172 red iron oxide. Refer to Appendix 5 for the rosuvastatin package inserts.

6.1.3.1. Rosuvastatin Supply

Upon subject consent, over-encapsulated rosuvastatin/placebo bottles will be delivered to his/her designated location (e.g., home, office) via a courier service vendor. Delivery can be done through either a depot or central pharmacy. In compliance with data privacy regulations, the vendor has a data privacy system in place to cover any local obligations. If subjects do not agree to use this courier service, they have the option to pick up the rosuvastatin/placebo bottles at the study site.

6.2. Preparation / Handling / Storage / Accountability

6.2.1. Preparation

6.2.1.1. Aldafermin

Subjects will be instructed to self-administer aldafermin/placebo at relatively the same time each day. Study drug/placebo syringes will be equilibrated to room temperature prior to use and will be administered as a SC injection in the abdomen. On Day 1, subjects will be trained on self-administering a SC injection. During the treatment visits, self-administration will occur in the clinic under observation by clinic staff. Re-training will be provided as required. Written dose preparation and administration instructions will be provided to subjects. Subjects will be required to complete a daily study drug/placebo administration diary.

6.2.1.2. Rosuvastatin / Placebo

Subjects will be instructed to take one capsule of rosuvastatin/placebo once a day by mouth at approximately the same time each day. All bottles will be blinded. The subject will be contacted by the site a few days after study visits and instructed as to which bottle to dose from. During the on-treatment visits, subjects will take their study drug to clinic visits and dose from the dosing bottle dispensed at the last visit in the clinic under observation by clinic staff. The subject will be required to complete a daily study drug/placebo dosing diary.

6.2.2. Storage

Aldafermin/placebo syringes are to be stored at the clinical site in the provided packaging and refrigerated at 2°C–8°C (36°F–46°F) in a secure, controlled access- location protected from light. At the subject's home, aldafermin/placebo syringes are to be stored in the provided packaging and refrigerated at 2°C–8°C (36°F–46°F) in a location protected from light (e.g., refrigerator).

Rosuvastatin /placebo bottles should be stored at room temperature, at 68°F–77°F (20°C-25°C) and in a dry place.

Subjects will be instructed to keep both study drugs out of the reach of children and other family members who may have access to the storage location.

6.2.3. Accountability

The principal investigator (PI) is responsible for ensuring that a current record of inventory/drug accountability (aldafermin/placebo and rosuvastatin/placebo) is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time.

Upon receipt of the investigational drug/placebo, the designated site personnel will visually inspect the shipment, verify the number and condition of study drug received, and confirm receipt of study drug.

At the completion of the study, all unused study drug supplies will be returned to the sponsor (or designee) or disposed of by the clinic, per the sponsor's (or designee's) written instructions.

6.3. Randomization and Blinding

Subjects will be randomized to a treatment group using [redacted]. Treatment assignment will be blinded to the sites, study subjects, sponsor study team, and sponsor Medical Monitor throughout the study period.

Rosuvastatin and matched placebo will be over-encapsulated to maintain the blind at the sites and with the sponsor study teams. Initiation and ongoing dose adjustments of rosuvastatin/matched placebo will be managed through the [redacted] but blinded to the treatment assignment (aldafermin or matched placebo). The sponsor and study sites will be blinded to LDL-C values and the specific rosuvastatin dosing decisions.

6.3.1. Removal of Study Blind (if applicable)

Breaking of any blind will be available to the PI [redacted] The subject's treatment assignment will be available to the PI in the event of a medical emergency or an AE that necessitates identification of the study drug for the welfare of that subject. Except in the case of a medical emergency, the PI and clinic staff will remain blinded during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock). The date and time when the PI removed the study blind for an individual subject will be documented by [redacted] to the sponsor.

6.4. Concomitant Medications

Any medication taken at least once within 90 days prior to Screening Visit and during the study period as well as the reason for use will be recorded in the source documents and the CRFs. Subjects should refrain from the use of any new prescription medications or products or changes in the dose or frequency of existing therapies from Screening to Day 1 until EOS.

The sponsor Medical Monitor or designee should be informed of any changes or addition of prohibited medications during this time.

6.4.1. Prohibited Medications:

- Investigational agents, other than aldafermin, or devices for any indication, within 28 days or 5 half-lives of the drug (whichever is longer) prior to Screening through the end of the study.
- Non-statin lipid lowering agents, from Day 1 of Screening through the end of the study
    - Example medications to avoid include: Cholestyramine, colesevelam, PCSK9 inhibitors (evolocumab or alirocumab), colestid, fibrates, fenofibrates, pharmacologic (dose of >1 g daily) fish oil
- Statins other than the study provided rosuvastatin from Week 2 through the end of the study:
    - Prior statin use must be at a reasonably stable dose for 3 months prior to Screening and will continue as a concomitant medication until Week 2.

- Agents used for the treatment of any condition listed in the exclusionary enrollment criteria (see Section 5.1).
- Weight loss medications including orlistat, phentermine, qsymia, lorcaserin hydrochloride, naltrexone hydrochloride, benzphentamine, diethylpropion, phendimetrazine, from 3 months prior to Screening through the end of the study.
- Contraindicated medications according to the rosuvastatin package insert (Appendix 5), including; cyclosporine, gemfibrozil, protease inhibitors (atazanavir, ritonavir, lopinavir, simeprevir), coumarin anticoagulants, fenofibrates, niacin, colchicine, from randomization through the end of the study.
- Known hepatotoxic agents (refer to Appendix 6).
- Anabolic steroids.

This list of prohibited medications along with Appendix 6, are not an inclusive list. investigator judgement must be used to avoid prohibited medications and to justify initiating any other medication during the study.

6.4.2. Restricted Concomitant Medications / Treatments:

- Statin Therapies:

For statin experienced subjects only, the following daily dose of approved statin therapies will allow for enrollment consideration if dosing is stable at least 3 months with reasonable dose adjustment (as per Medical Monitor's judgment) prior to Screening through Week 2. All subjects will transition to study rosuvastatin treatment at Week 2 according to the protocol. From Week 2 onward, over-encapsulated rosuvastatin or matched placebo will be dispensed according to the Lipid Lowering Algorithm (Appendix 4).

- Atorvastatin: ≤40 mg/day
- Fluvastatin: ≤40 mg/day
- Lovastatin: ≤40 mg/day (for immediate and extended release)
- Pitavastatin: ≤2 mg/day
- Pravastatin: ≤40 mg/day
- Simvastatin: ≤40 mg/day
- Rosuvastatin: ≤20 mg/day

- Other therapies for coexisting conditions require a stable regimen for at least 3 months prior to the Screening and throughout the study including:
  - Standard vitamin supplements
  - Vitamin E (>400 IU)
  - Milk thistle
  - Pentoxifylline

- Diabetic medications:
  - GLP1 agonists and pioglitazone: require a stable regimen for at least 3 months prior to Screening and throughout the study.
  - Insulin: require stable dosing, defined as reasonable dose adjustments (as per Investigator's judgment) to maintain glucose control, for at least 3 months prior to Screening.
  - All other diabetic medications: require a stable dose with reasonable dose adjustment (as per Investigator's judgment) for at least 3 months prior to Screening.
- Antibiotics (not listed in Appendix 6): Antibiotics for short-term use (<10 days) are allowed; however, chronic, continuous use is not allowed. Use will be at the discretion of the PI.
- Procedural medications (e.g., anti-anxiety medication for MRI scan, anesthetic for liver biopsy) use will be at the discretion of the PI.

7. STUDY TREATMENT DISCONTINUATION AND SUBJECT DISCONTINUATION / WITHDRAWAL FROM THE STUDY

7.1. Discontinuation of Study Treatment for an Individual Subject

Study treatment discontinuation, interruption or dose reduction will be considered if subjects experience the following:

- TEAE of Grade 3 or 4 (per CTCAE V5.0) with severity and relationship noted below
- Any suspected statin-related AE, as determined by the investigator (see below)
- Laboratory result(s) indicative of drug induced liver disease (DILI), based on assessment by the Medical Monitor and by the independent DILI adjudication
- Confirmed diagnosis of HCC
- Progression from Child-Pugh A to Child-Pugh B or C status
- Liver decompensation events
- Subjects with MELD score ≥15.

7.1.1. Specific Actions Taken Will Be As Follows:

i) TEAE of Grade 3 or 4 (per CTCAE V5.0):

- Any possibly or probably related Grade 3 TEAE, aldafermin and/or statin may be discontinued or interrupted; evaluation and determination by the PI or the unblinded Medical Monitor in the case of TEAEs possibly related to statin use.
- Any Grade 4 or higher TEAE, aldafermin and statin will be discontinued

ii) Any suspected statin-related AE:

Subjects will be allowed a rosuvastatin dose adjustment if the subject experiences a statin-related AE (as determined by the PI). The third-party Medical Monitor will be contacted by the study site to report a possible statin-related AE requiring intervention. Information will be collected on the AE including the specific description, history, and severity based on CTCAE grading. The study team should instruct the subject to refrain from administering the rosuvastatin/placebo therapy and to repeat safety laboratory examinations as indicated by the specific AE within 72 hours. If the subject is <2 weeks from their next visit, they should not dose the rosuvastatin/placebo therapy until the next scheduled visit. If they are >2 weeks from their next study visit, an unscheduled visit should be made to repeat laboratory examinations.

If the AE resolves, subjects will be restarted on a lower dose of over encapsulated rosuvastatin. Subjects on rosuvastatin 20 mg or 40 mg will be restarted on rosuvastatin 10 mg, and subjects on 5 mg or 10 mg will be restarted on rosuvastatin 5 mg. Subjects taking over-encapsulated placebo will be restarted on placebo. In the event that the AE re-occurs upon re-initiation at the lower dose, over encapsulated rosuvastatin/placebo should be discontinued. If the AE does not re-occur with the lower dose, an increase in the over encapsulated rosuvastatin dose may be considered at the subsequent clinic visits according to the protocol algorithm. If the AE re-occurs following administration of this new dose of

rosuvastatin, over encapsulated rosuvastatin/placebo may be reverted to the last tolerated dose. Aldafermin dosing will not be interrupted.

If a subject experiences a statin-related AE of myalgia or rhabdomyolysis (as determined by the PI), information will be collected on the AE including the specific description, history, and severity based on CTCAE grading and forwarded to the designated third-party Medical Monitor who is blinded to treatment assignment but unblinded to laboratory data and statin assignment and dose. The clinical study team will collect a blood sample for safety laboratory evaluations within 48-72 hours. For subjects that have signs or symptoms suggestive of rhabdomyolysis from either muscle symptoms (such as myalgia, pain, weakness, dark urine) or elevated creatine kinase (CK), the origin of the symptoms/CK elevation will be investigated. To this end, the subject will be interviewed about recent heavy exercise, trauma, convulsions, surgery, use of excessive alcohol, morphine, cocaine, or other contributing factors. Additional laboratory tests (creatinine, AST/ALT, total and conjugated bilirubin, potassium, calcium, and/or myoglobin (serum and urine)) will also be performed.

If the subject experienced statin-related increased CK>3 x ULN with clinical symptoms, administration of over-encapsulated rosuvastatin/placebo should be held and may be re-initiated at half the prior dose if follow-up CK is <3 x ULN. If CK rises to >3 x ULN again, the administration of over-encapsulated rosuvastatin/placebo should be held until CK <3 x ULN and can be re-initiated at 5 mg. For subjects experiencing symptoms and CK elevation on 5 mg, over-encapsulated rosuvastatin/placebo should be discontinued. Aldafermin dosing will continue.

For subjects with suspicion of statin-related myalgia or rhabdomyolysis AND CK 3-5 x ULN, administration of over-encapsulated rosuvastatin/placebo should be held until CK<3 x ULN and may be reinitiated at half the original dose. If symptoms persist and if CK increases >3 x ULN, rosuvastatin should be discontinued. For CK>5 x ULN with clinical suspicion of rhabdomyolysis (ruling out other causes, e.g., recent heavy exercise, trauma, convulsions, surgery, use of excessive alcohol, morphine, cocaine, or other contributing factors), rosuvastatin will be discontinued. Throughout, aldafermin dosing should continue.

iii) Laboratory value(s) suggestive of DILI:

a) Elevation of AST or ALT >2 x above subject-specific baseline value (calculated using the average of the Day -56 and the Day 1 values) and total bilirubin >1.5 x subject specific baseline value, repeat testing of ALT, AST, and bilirubin must be performed within 48-72 hours. If there are persistent elevations (AST or ALT >2 x baseline or TBL >1.5 x baseline values) upon repeat testing, then close observation (testing and physical examination 2-3 times per week) should be implemented and discontinuation of aldafermin and rosuvastatin should be considered (see below). Note: the unblinded study Medical Monitor will be notified of acute suspected cases and upon identification of suspected DILI cases, the Liver Events Adjudication Committee chair will be notified.

b) A decision to discontinue or temporarily interrupt the study drug will be considered based on factors that include how much higher than baseline ALT and AST were relative to the ULN and how much the on-study ALT and AST levels have increased

relative to baseline, in addition to whether there is concomitant elevation of bilirubin or INR. aldafermin and rosuvastatin will be discontinued or temporarily interrupted as follows:

- If baseline measurements (BLM) were <2 x ULN, discontinue if ALT or AST increases to >5 x BLM
- If BLM ≥2 x ULN but <5 x ULN, discontinue if ALT or AST increases to >3 x BLM
- Discontinue if ALT or AST increase >2 x BLM AND the increase is accompanied by a concomitant increase in TBL to >2 x BLM OR the INR concomitantly increases by >0.2
- Discontinue if total bilirubin >3.0 mg/dL
- In any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

c) If a subject resides in a remote area, laboratory testing can be performed locally, and the results should be promptly communicated to the investigator site.

d) Close observation for suspected DILI will include:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
- Obtaining or re-confirming a detailed history of symptoms and prior or concurrent diseases.
- Obtaining or re-confirming the history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.

Outside of situations listed above, no aldafermin/matched placebo dose reductions will be allowed. Temporary drug holidays from aldafermin dosing <5 days will be allowed on a case-by-case basis for subjects for safety or tolerability but must be approved by the sponsor Medical Monitor or designee. If drug is restarted and is still not tolerated, the subject should stop the medication as multiple drug holidays will not be allowed.

7.2. Discontinuation of Subjects from Study Participation

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The PI may remove a subject from the study if, in the PI's opinion, it is not in the best interest of the subject to continue the study. Subjects may be discontinued due to a change in compliance with an inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, or administration of non-permitted concomitant medication that might affect subject safety or study assessments/objectives. In addition, for any AEs noted, the PI will determine whether there is impact, or a potential for impact, on subject safety or study assessments/objectives, and will remove such subjects. Subjects will be discontinued due to clinically relevant changes in a subject's status related to Inclusion and Exclusion criteria that significantly affect subject safety or study integrity, development of pregnancy, or necessary administration of non-permitted concomitant medications that might affect subject safety or study assessments/objectives. Notification of discontinuation will be made immediately to the sponsor Medical Monitor or designee. In case of premature discontinuation of study participation, efforts will be made to perform all final EOT and EOS visits/assessments. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's Case Report Form (CRF). All withdrawn subjects will be followed until resolution of any AEs or until any unresolved AEs are judged by the PI to have stabilized.

8. STUDY PROCEDURES

8.1. Schedule of Study Procedures

The Schedule of Study Procedures is shown in Table 8. The visits should occur as close to the intended dates as possible. However, there is an acceptable ±3-day window from Week 2 through Week 6, and Week 54 (Week 58 if needed). Visit window from Weeks 12 through 48 is ±7 days. Visit window for Week 49 is +3 days.

Subjects attending any visits out of windows from Day 1 to Week 48/Early Withdrawal (EOT) visit should be brought back into compliance with the overall study visit schedule as soon as possible thereafter.

The PI has discretion to repeat assessments if he/she believes the results are erroneous or to rule out worsening of liver disease (Exclusion #7) for Day -56 and Day -42 visits. Repeat assessments must be conducted within the 8-week Screening Period. The screening window may be increased up to 16 weeks (112 days) to obtain all screening assessments, with Medical Monitor approval. Only assessments that need to be repeated should be done rather than a full re-screening of the subject. The results of the repeat testing will be used for evaluation.

All subjects will be assessed at Weeks 49 and 54 to confirm their LDL-C levels have returned to near baseline. At that point, no additional follow-up will be performed.

Subjects who do not meet criteria at Week 54 (Day 1 levels within 15 mg/dL or at the protocol-defined LDL-C goal) will have an additional 4-week follow-up visit at Week 58 to confirm that their LDL-C level returned to near baseline or at the protocol-defined LDL-C goal. Subjects may remain on over-encapsulated rosuvastatin through Week 58.

All subjects will have pre-dose PK blood collection on all treatment visits as well as 4-hours post-dose on Day 1, Week 24, and Week 48.

All subjects will be offered the opportunity to participate in a PK sub-study, which will involve a few additional procedures, including blood draws (i.e., on Day 1 and Week 48 at pre-dose, and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours). Reference Table 8 for more details.

Table 8. Schedule of Assessments

	Screening [a]		Treatment Visits									Follow-up		LDL-C monitor
Study Procedure	D-56	D-42 to -1	Day 1	Wk 2	Wk 6	Wk 12	Wk 18	Wk 24	Wk 30	Wk 36	Wk 42	Wk 48/EW (EOT)	Wk 49	Wk 54 (EOS)	Wk 58 [x]
Visit Window (Days) [b]				± 3	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+3	± 3	± 3
Informed consent	X														
Inclusion/exclusion criteria	X		X												
Demographics	X														
Medical history	X														
Smoking status	X														
Height	X														
Alcohol Consumption [c]	X														
Body weight [d], BMI [e], waist circumference	X		X				X		X	X		X		X	
Physical exam and RUQ pain assessment	X		X		X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X		X				X			X		X		X	
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	
Chronic Liver Disease Questionnaire-NASH (CLDQ-NASH)		X						X				X		X	
Gadolinium-enhanced MRI, CT, or ultrasound for HCC screening [f]		X													
Ultrasound scan (local read) for HCC surveillance								X				X			
FibroScan® (VCTE™)/ (CAP™) [g]	X							X				X			
EGD		X													
Liver biopsy [h]		X										X			
Randomization			X												
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedure	Screening [a]		Treatment Visits										Follow-up		LDL-C monitor
	D-56	D-42 to -1	Day 1	Wk 2	Wk 6	Wk 12	Wk 18	Wk 24	Wk 30	Wk 36	Wk 42	Wk 48/EW (EOT)	Wk 49	Wk 54 (EOS)	Wk 58 [x]
Visit Window (Days) [b]				± 3	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+3	± 3	± 3
Adverse event (AE) evaluations [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LISSA evaluations			X	X	X	X	X	X	X	X	X	X			
Chemistry, including creatine kinase (fasted ≥ 10 hrs) [j, k]	X		X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory assessments for worsening liver disease [l]		X													
Complete blood count (CBC)	X		X	X	X	X	X	X	X	X	X	X	X	X	
HbA1c	X		X									X		X	
Insulin level and HOMA-IR	X		X					X				X		X	
[redacted]			[redacted]									[redacted]		[redacted]	
International Normalized Ratio (INR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Alpha fetoprotein (AFP)	X							X				X	X		
Pregnancy test [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis and HIV Ab screen	X														
Urinalysis (UA)	X		X					X				X		X	
Urine drug screen [n]	X		X					X				X			
PEth alcohol screen	X														
Fasting lipid panel	X		X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X [j]	X
Lipoprotein particles			X	X	X	X	X	X	X	X	X	X		X	
Lipase			X		X	X		X		X		X		X	
Serum bile acids [o]			X									X			
C4 [p]			X	X	X	X	X	X	X	X	X	X			
PK blood samples [q,r]			X	X	X	X	X	X	X	X	X	X			
Anti-drug antibodies (ADAs)			X	X	X	X		X		X		X		X	
Neutralizing antibodies (NAbs)			X	X	X	X		X		X		X		X	
ELF Panel			X					X				X[y]		X	
Pro-C3			X					X				X		X	
Pro-C3X			X					X				X		X	

Study Procedure	Screening [a]		Treatment Visits										Follow-up		LDL-C monitor
	D-56	D-42 to -1	Day 1	Wk 2	Wk 6	Wk 12	Wk 18	Wk 24	Wk 30	Wk 36	Wk 42	Wk 48/EW (EOT)	Wk 49	Wk 54 (EOS)	Wk 58 [x]
Visit Window (Days) [b]				± 3	± 3	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+3	± 3	± 3
CTX-III			X					X				X		X	
C3M			X					X				X		X	
PNPLA3/Genetic Biomarkers [s]			X												
Exploratory Biomarker 1, 2, 3			X	X	X	X	X	X	X	X	X	X	X	X	
Aldafermin/placebo in clinic self-administration [t]			X	X	X	X	X	X	X	X	X	X			
Dispense aldafermin and diary			X	X	X	X	X	X	X	X	X				
Dispense rosuvastatin [u] and diary				X	X	X	X	X	X	X	X	X			
Medication compliance				X	X	X	X	X	X	X	X	X		X [v]	
Lipid management				X	X	X	X	X	X	X	X	X	X [w]	X [w, x]	

[a] There must be a minimum of 14 days (2 weeks) between Day -56 and Day -42 Screening Visits to allow for adequate separation of liver function testing prior to randomization in order to evaluate worsening liver function, per Exclusion #7. If liver function tests are repeated to verify eligibility criteria have been met, there must be a minimum of 14 days (2 weeks) between the Day -42 visit and any unscheduled visit. The screening window may be increased up to 16 weeks (112 days) to obtain all screening assessments, with Medical Monitor approval.

[b] Acceptable window from Week 2 through Week 6, and Week 54 (Week 58 if needed) is ±3-days. Visit window from Weeks 12 through 48 is ± 7 days. Visit window for Week 49 is +3 days.

[c] During screening, sites will complete; i) AUDIT-C alcohol consumption questionnaire and, ii) document subject- reported alcohol consumption to confirm whether amounts are within protocol defined limits, and iii) PEth level ≥200 ng/mL (refer to exclusion criteria #18, 20).

[d] Subjects should maintain their normal level of physical activity, diet, and lifestyle throughout the entire study.

[e] BMI will be calculated with height obtained at Screening.

[f] Gadolinium-enhanced MRI and multiphasic CT imaging must not have any nodules with LI-RADS ≥2. If nodules/lesions discovered on ultrasound that have not been previously defined by MRI or CT as clearly benign or LI-RADS <2, follow-up imaging with MRI or CT must be conducted for eligibility.

[g] FibroScan® (transient elastography (VCTE™) or ultrasound attenuation rate (CAP™) should be collected at Screening Day -56, Week 24, and Week 48 at sites with available technology.

[h] All subjects are required to have a liver biopsy result at Screening and additional liver biopsy at Week 48. A Screening liver biopsy will be performed only in subjects who do not have a qualified historical biopsy available for central pathology evaluation. The Week 48 biopsy should be obtained before the last dose of aldafermin with a visit window of 7 days prior to the end of treatment period.

[i] Adverse events will be monitored and recorded from subject signing informed consent through follow-up.

[j] Serum chemistry will include ALT, AST, ALP, bicarbonate, bilirubin (direct and total), BUN, calcium, chloride, creatinine, CK, GGT, glucose, HDL, LDL, phosphate, potassium, proteins (albumin, total protein), sodium, total cholesterol, and TG. Lab results for ALT, AST, total cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor from Week 2 onward.

[k] Creatine kinase will be collected at all time points as serum chemistry.
[l] Per Exclusion #7, total bilirubin, AST, ALT, ALP
[m] A serum pregnancy test will be performed on all female subjects of childbearing potential at Day -56 Screening visit, Week 24, and Week 48. A urine pregnancy test will be performed on all female subjects of childbearing potential at all study visits through EOS.
[n] Urine drug and alcohol tests may be repeated during treatment for subjects suspected of excessive alcohol intake or to rule out association with a safety event.
[o] Serum bile acids will be collected pre-dose Day 1 and Week 48/early withdrawal.
[p] C4 will be collected pre-dose on Day 1 and Weeks 2, 6, 12, 18, 24, 30, 36, 42, 48 and 4-h post dose on Days 1, Weeks 24, and 48. In addition, for subjects participating in the optional PK sub-study, additional C4 will be tested at the same time points as the PK blood sample collections: Day 1 and Week 48 at pre-dose, and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. The window for sample collection for the pre-dose through 4 hours is ±5 minutes, 6-12-hour time points is ±30 minutes. The window for sample collection for the 24-hour time points is -2 hours.
[q] PK blood samples will be collected in all subjects before dosing themselves in the clinic (pre-dose) on Day 1, Weeks 2, 6, 12,18, 24, 30, 36, 42, and 48 and 4-hours post-dose on Day 1, Week 24 and Week 48 .
[r] For subjects participating in the optional PK sub-study, blood samples will be collected when the subjects dose themselves in the clinic on Day 1 and Week 48 at pre-dose, and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. The window for sample collection for the pre-dose through 4 hours is ±5 minutes, 6-12-hour time points is ±30 minutes. The window for sample collection for the 24-hour time points is -2 hours.
[s] A single buccal swab sample for PNPLA3/other genetic biomarkers will be collected pre-dose on Day 1.
[t] Subjects will be instructed to self-inject aldafermin/placebo in the abdomen at a similar time each day. Subjects will not self-inject aldafermin/placebo at home on clinic visit day.
[u] Rosuvastatin will be dispensed at Weeks 2, 6, 12, 18, 24, 30, 36, and 42 visits and subjects will be provided further dosing instruction based on their ASCVD risk assessment, prior statin history (statin naïve or statin experienced), and LDL-C levels or LDL reduction levels. Subjects on a statin at Screening will switch from their current statin to an equivalent intensity dose of rosuvastatin at Week 2 and will be dispensed additional rosuvastatin at Week 48 and continue through Week 54 (or Week 58 if LDL-C follow-up is needed).
[v] For subjects who were statin experienced at Baseline, medication compliance will be assessed at Week 54 only.
[w] All subjects will be assessed at Weeks 49 and 54 to confirm their LDL-C levels are decreasing to near baseline, at which point, no additional follow-up is needed. Subjects who do not meet LDL-C decrease criteria at Week 54 will have an additional 4-week follow-up visit at Week 58 to confirm their LDL-C has returned to near baseline.
[x] ONLY for subjects who were identified at Week 49 as needing re-assessment of LDL-C at Week 54, the third-party Medical Monitor will evaluate LDL-C results to assess the need to schedule a 4-week LDL-C safety follow-up visit (Study Week 58) to confirm their LDL-C value has returned to near baseline.
[y] For EW patients only, the last, on-treatment ELF values at the visit prior to the EW visit will also be measured, in addition to the EW visit. This measurement will be done using the banked serum samples for the Exploratory Biomarker.

8.2. Study Visit Procedures

8.2.1. Screening - Day -56 (Screening) Procedures

Subjects will report to clinic fasted. The Screening procedures must be completed within 56 days from consent in order to randomize the subject.

- Obtain informed consent
- Collect demographic data
- Ascertain medical history and smoking status
- Assess inclusion/exclusion criteria
- Measure height
- Measure body weight, BMI, waist circumference
- Conduct physical examination and right upper quadrant (RUQ) pain assessment with numeric rating scale (NRS)
- Obtain 12 lead ECG (after subject has been supine for at least 5 minutes)
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Complete AUDIT-C alcohol consumption questionnaire
- Record prior and concomitant medications
- Record AEs (starting from the when the subject signs informed consent)
- Obtain FibroScan® scores (transient elastography, VCTE™ and in steatosis by ultrasound attenuation rate CAP™), where available
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry, including creatine kinase
  - CBC
  - HbA1c
  - Insulin level
  - HOMA-IR calculation
  - INR
  - Alpha fetoprotein (AFP)
  - Serum pregnancy test (all female subjects of childbearing potential)
  - Hepatitis and HIV Ab screen
  - PEth alcohol screen
  - Lipid panel

- Obtain urine sample for:
  - Urinalysis
  - Urine drug screen

8.2.2. Day –42 to Day -1 (Screening) Procedures

Subjects will report to clinic fasted. Day -42 Screening procedures must be completed no sooner than 14 days (2 weeks) days after the Day -56 Screening visit to allow for adequate separation of liver function tests.

- Conduct Chronic Liver Disease Questionnaire for NASH (CLDQ-NASH)
- Obtain imaging (MRI, CT, or ultrasound) for HCC screening (preferably prior to any histologic evaluation unless a historical biopsy is available)
- Gadolinium-enhanced MRI (if necessary, based on ultrasound screening result)
- Obtain an EGD (see Section 8.3.6 for additional details regarding EGD requirement)
- Obtain viable tissue slides from eligible historical liver biopsy or undergo a liver biopsy procedure to obtain new tissue
- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Laboratory assessments for worsening liver disease per Exclusion #7, total bilirubin, AST, ALT, ALP
  - INR
- Obtain urine for pre-dose urine pregnancy in all female subjects of childbearing potential

8.2.3. Day 1 Procedures

Subjects will report to clinic fasted. The following procedures will be performed at the Day 1 Visit:

Pre-dose:

- Reassess inclusion/exclusion criteria
- Measure body weight, BMI, and waist circumference
- Conduct physical examination and RUQ pain assessment with NRS
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes)
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record new and/or changes to AEs
- Obtain 10-hour fasted clinical laboratory samples for the following:

  - Chemistry, including creatine kinase.
  - CBC
  - HbA1c
  - [redacted]
  - Insulin level
  - HOMA-IR calculation
  - INR
  - Lipid panel
  - Lipoprotein particles
  - Lipase
  - C4
  - Serum bile acids
  - PK
  - Anti-drug antibodies (ADAs)
  - Neutralizing antibodies (NAbs)
  - ELF panel
  - Pro-C3
  - Pro-C3X
  - CTX-III
  - C3M
  - Exploratory Plasma biomarker #1
  - Exploratory Plasma biomarker #2
  - Exploratory Serum biomarker #3
  - Single exploratory buccal swab sample for PNPLA3/other genetic biomarkers
- Obtain urine sample for:
  - Pre-dose urine pregnancy in all female subjects of childbearing potential
  - Urinalysis
  - Urine drug screen
- Randomize subject [redacted]

<u>In-clinic dosing and post-dose assessments/activities:</u>

- Dispense initial aldafermin study drug kit and home diary
- Provide aldafermin study drug self-administration training
- Oversee subject's aldafermin study drug self-administration

- Perform local injection site symptom assessment (LISSA) evaluation.
- Obtain PK blood sample [redacted]
- C4 blood sample [redacted]

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next clinic visit and not to self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 2 visit

[redacted]

8.2.4. Week 2 Procedures

Subjects will report to clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted clinical laboratory samples
  - Chemistry, including creatine kinase.
  - CBC
  - INR
  - Lipid panel
  - Lipoprotein particles
  - C4
  - PK
  - ADAs
  - NAbs
  - Exploratory Plasma biomarker #1

- Exploratory Plasma biomarker #2
- Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:

Pre-dose urine pregnancy in all female subjects of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary
- Rosuvastatin/ matched placebo diary. Inform Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next visit and not to self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 6 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

8.2.5. Week 6 Procedures

Subjects will report to clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:

- Conduct physical examination and RUQ pain assessment with NRS
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted clinical laboratory samples:
  - Chemistry, including creatine kinase
  - CBC
  - INR
  - Lipid panel
  - Lipoprotein particles

- Lipase
- C4
- PK
- ADAs
- NAbs
- Exploratory Plasma biomarker #1
- Exploratory Plasma biomarker #2
- Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:

Pre-dose urine pregnancy in all female subjects of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin or matched placebo bottles and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary
- Re-dispense rosuvastatin or matched placebo bottles and diary. Remind subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next visit and not to self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 12 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

8.2.6. Week 12 Procedures

Subjects will report clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:

- Conduct physical examination and RUQ pain assessment with NRS
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)

- Record prior and concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry, including creatine kinase
  - CBC
  - INR
  - Lipid panel
  - Lipoprotein particles
  - Lipase
  - C4
  - PK
  - ADAs
  - NAbs
  - Exploratory Plasma biomarker #1
  - Exploratory Plasma biomarker #2
  - Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:

Pre-dose urine pregnancy in all female subjects of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin or matched placebo bottles and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary
- Re-dispense rosuvastatin medication or matched placebo bottles and diary.
  Remind Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next visit and not to self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 18 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

8.2.7. Week 18 Procedures

Subjects will report to clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:

- Measure body weight, BMI, and waist circumference
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes)
- Conduct physical examination and RUQ pain assessment with NRS
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry, including creatine kinase.
  - CBC
  - INR
  - Lipid panel
  - Lipoproteins
  - C4
  - PK
  - Exploratory Plasma biomarker #1
  - Exploratory Plasma biomarker #2
  - Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:

Pre-dose urine pregnancy in all female subjects of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin medication or matched placebo bottles and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary

- Re-dispense rosuvastatin or matched placebo bottles and diary. Remind Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next visit and to not self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 24 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

8.2.8. Week 24 Procedures

Subjects will report clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:

- Conduct physical examination and RUQ pain assessment with NRS
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Conduct Chronic Liver Disease Questionnaire for NASH (CLDQ-NASH)
- Obtain an ultrasound of the liver for HCC surveillance
- Obtain FibroScan® scores (for transient elastography, VCTE™ and steatosis by ultrasound attenuation rate CAP™), where available
- Record prior and concomitant medications
- Record AEs (starting from the when the subject signs informed consent)
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry, including creatine kinase.
  - CBC
  - INR
  - AFP
  - Insulin level
  - HOMA-IR calculation
  - Lipid panel
  - Lipoprotein particles

- Lipase
- C4
- PK
- ADAs
- NAbs
- ELF panel
- Pro-C3
- Pro-C3X
- CTX-III
- C3M
- Exploratory Plasma biomarker #1
- Exploratory Plasma biomarker #2
- Exploratory Serum biomarker #3
- Serum pregnancy test (all female subjects of childbearing potential)

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:
  - Urinalysis
  - Urine drug screen

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin or matched placebo bottles and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary
- Re-dispense rosuvastatin or matched placebo bottles and diary. Remind Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation
- Obtain PK blood sample 4-hours post dose.
- Obtain C4 blood sample 4-hours post dose.

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next visit and to not self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 30 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

8.2.9. Week 30 Procedures

Subjects will report to clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:

- Measure body weight, BMI, and waist circumference
- Conduct physical examination and RUQ pain assessment with NRS
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry
  - CBC
  - INR
  - Lipid panel
  - Lipoproteins
  - C4
  - PK
  - Exploratory Plasma biomarker #1
  - Exploratory Plasma biomarker #2
  - Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:

Pre-dose urine pregnancy in all female subjects of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin or matched placebo bottles and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary

- Re-dispense rosuvastatin or matched placebo bottles and diary. Remind Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:
- Remind subject to bring study drug kit and diary at the next visit and to not self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 36 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

8.2.10. Week 36 Procedures

Subjects will report to clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:
- Measure body weight, BMI, and waist circumference
- Conduct physical examination and RUQ pain assessment with NRS
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes)
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry
  - CBC
  - INR
  - Lipid panel
  - Lipoproteins
  - Lipase
  - C4
  - PK
  - ADAs
  - NAbs

- Exploratory Plasma biomarker #1
- Exploratory Plasma biomarker #2
- Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:

Pre-dose urine pregnancy in all female subjects of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin or matched placebo bottles and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary
- Re-dispense rosuvastatin or matched placebo bottles and diary. Remind Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next visit and to not self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 42 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17)

8.2.11. Week 42 Procedures

Subjects will report to clinic fasted and not dosed with aldafermin. The following procedures will be performed:

Pre-dose:

- Conduct physical examination and RUQ pain assessment with NRS
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry
  - CBC
  - INR

- Lipid panel
- Lipoproteins
- C4
- PK
- Exploratory Plasma biomarker #1
- Exploratory Plasma biomarker #2
- Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

- Obtain urine sample for:

Pre-dose urine pregnancy in all female subjects of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin or matched placebo bottles and diary and conduct reconciliation
- Dispense new aldafermin study drug kit and diary
- Re-dispense rosuvastatin or matched placebo bottles and diary. Remind Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study drug kit and diary at the next visit and to not self-administer aldafermin/placebo at home on clinic visit days
- Schedule Week 48 visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

8.2.12. Week 48 / Early Withdrawal (End of Treatment) Procedures

Subjects will report to this visit fasted and not dosed with aldafermin.

The following procedures will be performed at the Week 48/Early Withdrawal visit:

Pre-dose:

- Measure body weight, BMI, and waist circumference
- Conduct physical examination and RUQ pain assessment with NRS
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes)

- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Conduct Chronic Liver Disease Questionnaire for NASH (CLDQ-NASH)
- Obtain FibroScan® scores (for transient elastography, VCTE™ and steatosis by ultrasound attenuation rate CAP™), where available
- Obtain an ultrasound liver for routine HCC surveillance
- Undergo a liver biopsy procedure to obtain new tissue
- Record concomitant medications
- Record AEs
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - HbA1c
  - [redacted]
  - Insulin level
  - HOMA-IR calculation
  - INR
  - AFP
  - Serum pregnancy test (all female subjects of childbearing potential)
  - Lipid panel
  - Lipoprotein particles
  - Lipase
  - C4
  - Serum bile acids
  - PK
  - ADAs
  - NAbs
  - ELF panel
  - Pro-C3
  - Pro-C3X
  - CTX-III
  - C3M
  - Exploratory Plasma biomarker #1

- Exploratory Plasma biomarker #2
- Exploratory Serum biomarker #3

Results for ALT, AST, Total Cholesterol, LDL, HDL, and triglycerides are blinded to the site and sponsor.

Obtain urine sample:
- Urinalysis
- Urine drug screen

In-clinic dosing:
- Collect old aldafermin study drug kit and diary and conduct reconciliation
- Collect old rosuvastatin bottle and diary and conduct reconciliation
- Re-dispense rosuvastatin study drug and diary (only for subjects who were statin experienced at Baseline). Remind Subjects that they will be contacted in a few days regarding the delivery or pick up of their rosuvastatin/placebo drug bottles.
- Oversee subject's aldafermin study drug self-administration (from old kit) (not applicable for Early Withdrawal subjects)
- Perform LISSA evaluation.
- Obtain PK blood sample 4-hours post dose.
- Obtain C4 blood sample 4-hours post dose

Before clinic discharge:
(NOTE: PK sampling before clinic discharge is not applicable for Early Withdrawal subjects; however, Early Withdrawal subjects should be scheduled for a 6-week Follow-up visit.)

- Schedule subject for Week 49 Post-Treatment Response Visit

Lipid Lowering Therapy Assessment:

The third-party Medical Monitor will evaluate LDL-C results to assess the need for lipid lowering therapy (refer to Section 8.3.17).

[redacted]

8.2.13. Week 49 Procedures

Subjects will report to this visit fasted. The following procedures will be performed at the Week 49 visit:

- Conduct physical examination and RUQ pain assessment with NRS
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)
- Record concomitant medications
- Record new and/or changes to AEs
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - INR
  - AFP
  - Lipid panel
  - Exploratory Plasma biomarker #1
  - Exploratory Plasma biomarker #2
  - Exploratory Serum biomarker #3

Obtain urine sample for:

- Urine pregnancy in all female subjects of childbearing potential

Before clinic discharge:

- Schedule Week 54 (EOS) visit

Lipid Lowering Therapy Assessment:
The third-party Medical Monitor will evaluate LDL-C (refer to Section 8.3.17).
All subjects will be assessed at Weeks 49 and 54 to confirm their LDL-C levels are decreasing to near baseline, at which point, no additional follow-up is needed.
Subjects who do not meet LDL-C decrease criteria at Week 54 will have an additional 4-week follow-up visit at Week 58 to confirm their LDL-C change has returned to near baseline.

8.2.14. Week 54 (End of Study) Procedures

This visit will be performed 6 weeks after the EOT visit. Subjects will report to this visit fasted.

- Measure body weight, BMI, and waist circumference
- Conduct physical examination and RUQ pain assessment with NRS
- Obtain 12-lead ECG (after subject has been supine for at least 5 minutes)
- Measure vital signs (including temperature, respiratory rate, and seated blood pressure and pulse)

- Conduct Chronic Liver Disease Questionnaire for NASH (CLDQ-NASH)
- Record concomitant medications
- Record new and/or changes to AEs
- Obtain 10 hour fasted clinical laboratory samples for the following:
  - Chemistry
  - CBC
  - HbA1c
  - Insulin level
  - HOMA-IR calculation
  - [redacted]
  - INR
  - Lipid panel
  - Lipoprotein particles
  - Lipase
  - ADAs
  - NAbs
  - ELF panel
  - Pro-C3
  - Pro-C3X
  - CTX-III
  - C3M
  - Exploratory Plasma biomarker #1
  - Exploratory Plasma biomarker #2
  - Exploratory Serum biomarker #3
- Obtain urine sample for urinalysis and urine pregnancy in all female subjects of childbearing potential
- Collect old rosuvastatin bottles/diary and conduct reconciliation ***(only for subjects who were on statin therapy at Baseline and continued on rosuvastatin after EOT visit).***
- Invite consent for ADA follow-up study (reference Section 8.2.16).
- For subjects who do not require additional lipid monitoring (Section 8.2.15), this Week 54 visit will mark their end of participation in this clinical trial. For subjects who do need the additional 4-week lipid monitoring follow-up visit, the end of their trial participation will occur at Week 58 (Section 8.2.15).

Lipid Lowering Therapy Assessment:
For subjects who were identified at Week 49 as needing re-assessment of LDL-C at Week 54, the third-party- Medical Monitor will evaluate LDL-C results to assess the need to schedule a 4-week LDL-C safety follow-up visit (**Study Week 58**, Section 8.2.15) to confirm their LDL-C value has returned to near baseline (refer to Section 8.3.17). Based on this lipid assessment, the third-party Medical Monitor may recommend specific follow-up with the subject's regular physician. Otherwise, all subjects should be advised to follow-up with their regular physician regarding any lipid management needs going forward.

8.2.15. Week 58 (Lipid Monitoring Assessment 4 Week Follow-up Visit Procedures)

This visit will be performed only for those subjects who are determined to require additional lipid monitoring at the Week 54 visit. The following procedures will be performed at this visit:

- Record concomitant medications
- Record AEs
- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Lipid panel

Based on this lipid assessment, the third-party Medical Monitor may recommend specific follow-up with the subject's regular physician. Otherwise, all subjects should be advised to follow-up with their regular physician regarding any lipid management needs going forward.

8.2.16. Monitoring of Anti-Drug Antibody Response

Subjects may be contacted to participate in additional optional follow-up visits, if necessary, to monitor anti-drug antibody (ADA) responses.

8.3. Clinical Evaluations

8.3.1. Alcohol Consumption

8.3.1.1. AUDIT-C

During Screening, clinical sites will implement the AUDIT-C, a 3-item alcohol screen that can help identify persons who are hazardous drinkers or have active alcohol use disorders (Appendix 3). The AUDIT-C is scored on a scale of 0-12. Each AUDIT-C question has 5 answer choices. Points allotted are: a=0 points, b=1 point, c=2 points, d=3 points, e=4 points. For men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. For women, a score of 3 or more is considered positive.

However, when the points are all from Question #1 alone (#2 & #3 are zero), it can be assumed that the patient is drinking below recommended limits and it is suggested that the provider review the patient's alcohol intake over the past few months to confirm accuracy.

8.3.1.2. PEth Screening

Subjects with PEth levels ≥200 ng/mL AND a positive AUDIT-C at Screening will be excluded from the study.

8.3.1.3. History of Alcohol Consumption

Subjects will also be asked to report their history of alcohol consumption and will be excluded from study participation if they consume ≥21 units per week (males) or ≥14 units per week (females) for two years prior to Screening and where a unit of alcohol is equivalent to a 12-ounce beer, 4-ounce glass of wine, or a 1-ounce shot of hard liquor.

8.3.2. Liver Biopsy

Subjects who meet the Screening criteria of having a historical liver biopsy if tissue slides are available from within 12 months prior to Screening and are acceptable for central pathologist evaluation will not be required to undergo a liver biopsy. All other subjects will be required to undergo a liver biopsy during the Screening period and prior to randomization according to the study site's local standard of care. Liver biopsy procedures have inherent risks and benefits, and qualified study personnel will discuss these risks and benefits with each potential participant prior to enrollment.

The common procedure for obtaining a liver biopsy sample involves a percutaneous approach using an appropriate gauge needle for sample collection. Other means of obtaining liver biopsy may be used if found appropriate by the study investigator. The primary risks involved include bleeding, pain, and infection at the incision site. Premedication (for example, midazolam can be used, if consistent with local procedures) and post-biopsy care will be according to the study site's standard of care. Adverse events will be collected, and subjects followed as appropriate.

Sites should not perform a local reporting of the NAS or fibrosis score at either Screening or Week 48 in order to maintain the blinding of the primary endpoint. Tissue from all subjects will be collected, prepared, and sent to the Central Study Pathologist for review and determination of NASH. Liver biopsies with histologically confirmed NASH will be further assessed using the NAS established and validated by the NASH CRN (see Appendix 1), and liver biopsies will also be assessed for fibrosis stage for primary endpoint analysis.
The Week 48 biopsy should be obtained before the last dose of aldafermin with a visit window of -7 days.

Sites will collect a liver biopsy sample for subjects who received at least 24 weeks of aldafermin dose and terminate early from the study.

8.3.3. CPA and SHG

CPA (collagen proportional area, with staining) and SHG (Second Harmonic Generation, stain-free) technologies for assessment of fibrosis involve digital pathology system to characterize and accurately quantify collagen fibers area in the liver biopsies. For SHG, when a scan begins with an unstained liver tissue sample, the laser produces two photons (tiny light

particles), which – upon interaction with the collagen fibers – results in the combination of both photons into a single new photon, with twice the energy and therefore twice the frequency and half the wavelength of the initial photons. This is known as SHG, and the detection of SHG signals lead to a high-resolution imaging of collagen fibers within the tissue. Subjects will be assessed using this methodology at baseline and following 48 weeks of treatment with study drug. All testing will be through a central read.

8.3.4. CLDQ NASH

A chronic liver disease questionnaire will be conducted at Screening and on Weeks 24, 48, and 54.

8.3.5. Transient Elastography and Ultrasound Attenuation Rate (Steatosis) using (FibroScan®) Device

A noninvasive device (FibroScan®), where available, will be used for assessing liver stiffness as a measure of fibrosis via elastography (VCTE™) at the Screening Day -56, Weeks 24 and 48. Currently, there are no imaging techniques that can directly detect the specific stage of fibrosis. Most attempt to detect fibrosis indirectly using proposed biomarkers, which include stiffness, diffusion, perfusion, metabolites, and image texture with the leading biomarker being liver stiffness (Younossi 2018). The rationale for using "stiffness" or "elasticity" is that the collagen deposition associated with fibrosis imparts parenchymal rigidity, which on imaging tests is considered as assessing "stiffness" or "elastography." In addition, the FibroScan® device will provide steatosis information using an ultrasound attenuation rate method (CAP™). For individual subjects, the same FibroScan® device and the same probe (medium [M] or extra large [XL]) must be used for all assessments. Where available, the median Controlled Attenuation Parameter (CAP) value will be recorded from FibroScan® examinations.

8.3.6. Esophagogastroduodenoscopy (EGD)

No evidence of gastroesophageal varices as documented by one of the following assessments:

a. A historical and locally evaluated EGD obtained within 365 days of screening or
b. A locally evaluated EGD conducted during the screening period

*If no EGD is available, the latest EGD assessment guidelines during a global pandemic† for patients with compensated cirrhosis (i.e., the expanded Baveno VI criteria, Petta 2018) as follows can be used as a replacement for the EGD to determine eligibility:

c. Platelet count >110,000/mm^3, and a FibroScan® <30 kPa on a M probe or <25 kPa on a XL probe

Note: No more than 30% of the remaining population will be enrolled with the expanded Baveno VI criteria.

† EGD waived in patients with compensated cirrhosis during a global pandemic per AASLD/ASGE guidelines.

8.3.7. Pharmacokinetic Blood Sample Collection and Processing

In all subjects, blood samples for PK analysis of aldafermin levels will be collected pre-dose on all treatment visits and 4-hours post dose on Day 1, Week 24, and Week 48. The window for sample collection for the pre-dose time points is ± 5 minutes.

Subjects participating in the optional PK sub-study will have blood samples collected at the Day 1 and Week 48 visits at the following time points: pre-dose, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours post-dose. The window for sample collection for the pre-dose through 4 hours is ±5 minutes, 6-12-hour time points is ±30 minutes. The window for sample collection for the 24-hour time points is -2 hours.

Processing, storage, and shipping instructions for these PK blood samples will be presented in the study Lab Manual.

8.3.8. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be collected as outlined in Section 8.

Serum chemistry will include ALT, AST, ALP, bilirubin (direct and total), creatinine, CK, GGT, glucose, HDL, LDL, lipase, total cholesterol, TG, bicarbonate, calcium, BUN, chloride, phosphate, potassium, proteins (albumin, total protein), and sodium. Samples for analysis of ADAs, NAbs will be collected. All NAb samples will be collected as scheduled, and analyzed only if necessary, based on ADA results.

Liver function tests, including AST, ALT, TBL, and ALP, will be compared between Day -56 and Day -42 to assess whether there is worsening of liver disease during screening according to Exclusion #7. An unscheduled visit may be necessary to confirm eligibility if the difference exceeds the allowable percent difference. If performed, unscheduled visit results will be compared to the average of Day -56 and Day -42 results to determine eligibility. If liver function tests are repeated to verify eligibility criteria have been met, there must be a minimum of 14 days (2 weeks) between the Day -42 visit and any unscheduled visit.

Processing, storage, and shipping instructions for the above will be presented in a separate Lab Manual.

8.3.9. C4 Testing

C4 testing will be collected at pre-dose at all treatment visits as well as 4-hours post-dose on Day 1, Week 24, and Week 48.

Subjects participating in the optional PK study will undergo additional C4 testing at the same time points as their PK blood sample collections: Day 1 and Week 48 at pre-dose, and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. The window for sample collection for the pre-dose through 4 hours is ±5 minutes, 6-12-hour time points is ±30 minutes. The window for sample collection for the 24-hour time points is -2 hours.

8.3.10. Serum Bile Testing

Serum bile acids samples will be collected pre-dose Day 1 and Week 48/early withdrawal.

8.3.11. 12 -Lead Electrocardiograms

12 -lead ECGs will be performed after the subject has been supine for at least 5 minutes, and as outlined in the Schedule of Study Procedures.

8.3.12. Vital Signs

Vital signs (including temperature, respiratory rate, and seated blood pressure and pulse) will be obtained at Screening and at all study visits as outlined in Section 8. Seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes.

8.3.13. Physical Examinations and RUQ Pain Assessment

A routine physical examination will be performed at Screening Day -56, Day 1, and Weeks 6, 12, 18, 24, 30, 36, 42, 48, 49 and 54. A specific assessment of RUQ pain will be collected and scored based on 10-point NRS. During the physical examination, the PI directly palpitates the RUQ region and asks the subject to provide a number between 0, equal to no pain and 10, being equal to worst pain.

8.3.14. Weight, Body Mass Index, and Waist Circumference Measurements

Subjects will be weighed, BMI calculated, and waist circumference measured at Screening Day -56, Day 1, and Weeks 18, 30, 36, 48 and 54. Formal instructions for recording weight and measuring waist circumference will be provided to sites.

8.3.15. Local Injection-Site Symptom Assessments (LISSA)

Injection site evaluation will be made and documented by the PI or clinic staff using a LISSA.

LISSA evaluations are to be performed at each clinic visit from Day 1 through Week 48.

The LISSA is intended to be a “snapshot” of the ISRs at the time of clinic assessment. The LISSA is not intended to capture ISR data (frequency, severity, duration, etc.) in between clinic visits. As with any other potential AE, investigator judgment should be used as to whether any ISR is recorded as an AE. Mild to Severe Reactions (LISSA Grades 1–3) are reported as AEs at the discretion of the investigator unless standard SAE criteria are met and then must be reported as an SAE. Life-threatening (LISSA Grade 4) meet SAE criteria and must be reported as such.

LISSAs may be performed if necessary and as clinically indicated by the PI to capture ISRs outside of the routine scheduled assessment time points.

The FDA Toxicity Grading Scale will be used to assess any ISRs (U.S. Department of Health and Human Services 2007). The documented record will include all of the symptoms, severity, and any local reaction (including pain, tenderness, redness, and swelling) and size of injection-site skin reactions identified and observed by the subject or clinic personnel. LISSA scores will be documented on the subject’s CRF.

8.3.16. Evaluation of Biomarkers

A single buccal swab sample for evaluation of PNPLA3/other genetic biomarkers will be collected pre-dose on Day 1.

8.3.17. Lipid Lowering Therapy Assessment

LDL-C will be evaluated at all study visits beginning at Week 2 for possible increases in lipid levels associated with aldafermin administration. Rosuvastatin will be used to manage cholesterol levels and initiated if protocol-defined lipid management criteria are met.

Rosuvastatin and matched placebo are over-encapsulated and provided in multi-capsule bottles (Section 6.2.1.2). Initiation and ongoing dose adjustments of rosuvastatin will be managed by a third-party Medical Monitor who is blinded to treatment assignment but unblinded to LDL-C values and related safety laboratory results. Rosuvastatin dose changes will be managed through the IxRS. Lipid levels and titration recommendations will be blinded to the sponsor, sponsor's Medical Monitor, investigators, subjects, and site. Initiation and dose adjustments will be determined by the lipid levels collected at Week 2 through Week 54, with lipid levels at Day 1 serving as baseline. LDL-C samples will be analyzed and reported to the third-party Medical Monitor. A kit containing rosuvastatin or matched placebo bottles will be assigned as instructed through the IxRS system and based on subjects LDL-C level assessment at each study visit from Week 2 through Week 42 (statin-naïve) or Week 48 (statin-experienced), and will be delivered to subjects via a courier service vendor (Section 6.1.3.1). The site will communicate to the subject the assigned bottle(s) and dosing should be immediately initiated.

Group A

Statin-experienced subjects (definition from Exclusion Criteria 9b) will be switched to an equivalent intensity rosuvastatin dose (high intensity dose – 20 mg rosuvastatin, moderate intensity dose – 10 mg rosuvastatin, low intensity dose – 5 mg rosuvastatin). For subjects who are self-identified Asians, the high intensity rosuvastatin dose is 10 mg, and the moderate intensity rosuvastatin dose is 5 mg. The treatment goal for this group of statin-experienced subjects is LDL-C level of ≤70 mg/dL (1.8 mmol/L) or ≥50% LDL-C reduction from the Week 2 level, starting at Week 6.

Group B

Subjects who are statin-naïve (definition from Exclusion Criteria 9a) AND who have risk-enhanced diagnoses (e.g., clinical ASCVD, CVA) AND LDL-C level of >70 mg/dL (1.8 mmol/L) will initiate over-encapsulated rosuvastatin at 5 mg daily with a treatment goal of LDL-C level of ≤70 mg/dL (1.8 mmol/L) or ≥50% LDL-C reduction from the Week 2 level. Those subjects who are already at LDL-C level of ≤70 mg/dL (1.8 mmol/L) will initiate over-encapsulated rosuvastatin placebo, and LDL-C initiation criteria will be re-evaluated at subsequent clinic visits (i.e., Week 6, 12, 18, 24, 30, 36, 42).

Group C

Statin-naïve subjects without risk-enhanced diagnoses AND with a 10-year ASCVD risk ≥7.5% (US) >1% (Europe) will initiate over-encapsulated rosuvastatin at 5 mg daily.

The treatment goal is LDL-C level of ≤70 mg/dL (1.8 mmol/L) or ≥ 50% LDL-C reduction from the Week 2 level.

Statin-naïve subjects without risk-enhanced diagnoses AND with a 10-year ASCVD risk <7.5% will initiate over-encapsulated rosuvastatin placebo. ASCVD risk and LDL-C laboratory assessment will be evaluated at subsequent clinic visits (i.e., Week 6, 12, 18, 24, 30, 36, 42) in order to determine whether rosuvastatin should be initiated at 5 mg daily.

All Subjects

At subsequent clinic visits, subjects who have achieved the protocol-defined LDL-C treatment goal will continue on their most recent assigned dose of rosuvastatin/placebo. If a subject fails to achieve the determined LDL-C goal despite increasing the rosuvastatin dose, those subjects will be reassigned to the lowest dose used to achieve the current LDL-C level.

Subjects on the maximum dose of rosuvastatin 40 mg whose LDL-C levels are still not at the protocol-defined LDL-C goal will continue on the study with rosuvastatin 40 mg unless the subject experiences a cardiovascular-related SAE(e.g., myocardial infarction, CVA).

All subjects will be assessed at Weeks 49 and 54 to confirm their LDL-C levels have either decreased to near baseline or at the protocol-defined LDL-C goal. At that point, no additional follow-up will be performed.

Subjects who do not meet criteria at Week 54 (Day 1 levels within 15 mg/dL or at the protocol-defined LDL-C goal) will have an additional 4-week follow-up visit at Week 58 to confirm that their LDL-C level returned to near baseline. At this point, the third-party Medical Monitor may recommend specific follow-up with the subject's regular physician. Otherwise, all subjects should be advised to follow-up with their regular physician regarding any lipid management needs going forward.

8.3.18. Diet and Activity Control

Subjects should maintain their normal level of physical activity, diet, and lifestyle throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion). For subjects enrolled in the optional PK sub-study, participants may be domiciled during dosing and 24-hour sampling and receive a standardized diet at scheduled times that do not conflict with other study-related activities.

8.3.19. MRI, CT, and Ultrasound for HCC Testing

As part of safety monitoring, subjects will undergo liver imaging and AFP testing to screen for HCC, followed by liver ultrasound and AFP testing at Weeks 24 and 48 for surveillance. Lesions detected on ultrasound at 24 weeks or 48 weeks, without significant change in AFP levels, will be managed according to the SOC at the clinical site. Subjects with an AFP level >20 ng/mL at either Week 24 or 48, without detectable lesions on ultrasound, will be managed according to the SOC at the clinical site. Subjects with a lesion ≥10 mm detected on ultrasound at 24 weeks with an AFP level >20 ng/mL at 24 weeks may continue on study drug at the discretion of the investigator unless or until a clinical diagnosis of HCC is made (defined as LI-RADS 4 or 5 at MRI, or histological confirmation of HCC). Abnormal readings with an AFP test results or suspicious ultrasound lesions will have follow-up and adjudication as defined by the Hepatocellular Carcinoma Adjudication Charter (see Section 8.5.2).

8.3.20. Evaluation of Biomarkers

Blood samples will be collected for evaluation of exploratory biomarkers 1, 2, and 3, as outlined in Table 8.

8.4. Safety and Other Assessments

8.4.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigational subject who has been administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. A TEAE is an AE that is reported after a dose of study drug.

AEs are all:

- unfavorable changes in general condition
- subjective or objective signs/symptoms
- concomitant diseases or accidents
- clinically relevant adverse changes in laboratory parameters observed in a participant in the course of a clinical study

AEs comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free, and post-treatment periods, or under placebo, are also to be designated as AEs.

All AEs, whether volunteered, elicited, or noted on physical examination, will be recorded throughout the study (i.e., from screening until EOS).

Subjects will be queried for resolution of ongoing AEs or until any unresolved AEs are judged by the PI to have stabilized or if lost to follow-up. Resolution of all AEs will be promptly documented by the clinic in the subject's CRF.

Any pregnancy diagnosed during the study must be reported immediately to the investigator and sponsor, including pregnancy in female partners of male subjects. The pregnancy will be followed to term and/or outcome and this outcome must be reported to the sponsor. Pregnancy, in and of itself, is not regarded as an AE or SAE unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication or method.

8.4.2. Definition of Serious Adverse Events and SAE Reporting

An SAE is any untoward medical occurrence at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (i.e., puts the subject, in the view of the PI, at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical event that may require medical or surgical intervention to prevent one of the above outcomes

An unexpected adverse drug event is any adverse drug event the specificity or severity of which is not consistent with the current IB or, if an IB is not required or available, the general investigational plan or elsewhere in the current application.

An AE is associated with the use of the drug if a reasonable possibility exists that the event may have been caused by the drug.

SAEs that are unexpected and related to either aldafermin or rosuvastatin are reportable to Regulatory Authorities. All SAEs will be reported by the PI to the sponsor and will be reported to the responsible Ethics Committee (EC) in accordance with local requirements.

The sponsor's assigned Safety Representative will be notified in writing (e.g., email or facsimile) within 24 hours of when an SAE is first recognized or reported. The Safety Representative will subsequently notify the sponsor and the sponsor's assigned Medical Monitor or designee of all reported SAEs.

Suspected statin-related AEs requiring either dose reduction or discontinuation should be reported to the third-party Medical Monitor by the PI. These subjects will be managed as outlined in Section 8.3.17.

8.4.3. Classification of Severity of Adverse Event

The severity of AEs will be categorized as shown below, based on common terminology criteria for adverse events (CTCAE) Version 5.0 criteria.

Table 9. Categorization of Severity of Adverse Events

Mild	The event is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL); participant is aware of symptoms, but symptoms are easily tolerated.
Moderate	The event is an inconvenience or concern to the subject and causes interference with ADL, but the participant is able to continue with ADL.
Severe	The event significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL.
Potentially life threatening	An event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction, which hypothetically might have caused death if it were more severe.

8.4.3.1. Relationship to Study Drug

The investigator will make a determination of the relationship of the AE to the study drug using a 4-category system (not related, possible, probable, definite), as shown below, based on common terminology criteria for adverse events (CTCAE) Version 5.0 criteria.

Table 10. Categorization for Determining Relationship of AEs to Study Treatment

Not related	An AE that does not follow a reasonable temporal sequence from administration of the drug and that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
Possible	An AE that follows a reasonable temporal sequence from the administration of the drug (including the course after withdrawal of the drug) and that cannot be excluded as being possibly caused by the drug (e.g., existence of similar reports attributed to the drug and/or its analogues; reactions attributable to the pharmacological effect of the drug), although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
Probable	An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and that can be excluded as being possibly caused by other factors, such as underlying disease, complications, concomitant drugs, or concurrent treatment.
Definite	An AE that follows a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug), follows a known or hypothesized cause–effect relationship, and (if appropriate) satisfies the following: • Positive results obtained in drug sensitivity tests • Toxic level of the drug present in blood or other body fluids

8.5. Safety Monitoring

8.5.1. Data Safety Monitoring Board

The study will be performed under review by an external independent Data Safety and Monitoring Board (DSMB) to closely monitor the safety and welfare of the study subjects. The DSMB will be comprised of experienced hepatologists and other relevant specialists. The DSMB will review study data at regular intervals and determine whether it is safe to

continue the study according to the protocol. The DSMB members will be independent of the sponsor, the clinical study sites, and investigators. The event definitions information relevant to the operation of the committee will be described in a DSMB Charter.

8.5.2. Independent Adjudication

In addition to the DSMB, NGM will incorporate a formal Adjudication process for: a) drug-induced liver injury (DILI) monitoring as part of the Liver Events Adjudication Committee, b) hepatocellular carcinoma (HCC), and c) cardiovascular events. Adjudication of possible/suspected cases will be conducted by independent clinicians with relevant clinical expertise. A cardiovascular adjudication committee is already in place across all aldafermin studies and performs blinded review of known and suspected cardiovascular events with focus on CV death, MI and hospitalization for heart failure and cerebrovascular accident (stroke). The Cardiovascular adjudication also reviews off-target effects of the potential investigational products on parameters potentially influencing the overall cardiovascular risk, such as: plasma lipids, glucose homeostasis, and (systemic) inflammatory (and fibrosis) parameters.

9. STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan (SAP) will be provided and finalized prior to the study database lock or unblinding. No discrepancies are expected between the SAP and the protocol. However, if there are discrepancies between this section of the protocol and the final SAP, the SAP will override the protocol.

In general, descriptive statistics including the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum will be presented for continuous variables, frequency and percentage distribution for categorical variables, and Kaplan–Meier estimates for time-to-event variables.

9.1. Sample Size Determination

The sample size for this study is determined based on power simulations for the modified primary efficacy endpoint (the change in ELF at Week 48) and using the analysis method described in Klingenberg (2009). Based on the ALPINE 2/3 study, the change from baseline in ELF at Month 6 (24 weeks) are 0.066, 0.083, -0.013, and 0.224 for placebo and aldafermin 0.3 mg, 1.0 mg, and 3.0 mg, respectively. Assuming a change in ELF of 0.1 for subjects treated with placebo, and a change in ELF of -0.4 at Month 12 (48 weeks) for subjects treated with aldafermin 3 mg, and a 15% subject drop-out rate at Week 48, a sample size of 150 subjects will provide at least 92% power to detect an upward dose-response trend at the 5% significance level (two-sided) (Table 11). Under protocol Version 5.0 and subsequent versions, eligible subjects will no longer be randomized into the 0.3 mg aldafermin treatment group. Instead, subjects will be randomized into 1 of 3 treatment groups in a 4:3:4 ratio to receive either subcutaneous placebo, 1 mg aldafermin or 3 mg aldafermin, respectively. Subjects randomized to the 0.3 mg aldafermin treatment group prior to protocol Version 5.0 will continue to receive the same dose until treatment completion. No more than 30% of the remaining population will be enrolled with the expanded Baveno VI criteria. The power under the new randomization is expected to be higher than that under the original randomization (3:2:2:3). More details of the power simulations will be provided in the SAP.

Based on the modified primary endpoint of the change from baseline in ELF at Week 48 and the analysis results from ALPINE 2/3, the following table presents the change from baseline needed for different powers.

Table 11. Power Simulations for the Primary Efficacy Analysis

Assumed Change from Baseline in ELF at Week 48		Power
Aldafermin 3 mg	**Placebo**	
-0.224	0.066	51.00%
-0.3	0.066	69.83%
-0.3	0.1	77.33%
-0.4	0.066	88.35%
-0.4	0.1	92.33%
-0.5	0.1	99.25%

9.2. Analysis Populations

Subjects will be analyzed using the following analysis populations:

- Intent to treat (ITT) population: all randomized subjects
- Modified ITT (mITT) population: all subjects who receive at least 2 weeks of study drug and have at least one valid, post-dose, on-treatment ELF score
- Safety population: all subjects who receive at least one dose (full or partial) of study drug
- Full-Analysis population: all randomized subjects who receive at least one dose (full or partial) of study drug and have at least one valid, non-missing post-dose efficacy/PD parameter value
- Per-Protocol (PP) population: a subset of subjects in the Full Analysis population who have valid, non-missing baseline and post-dose liver biopsy results and do not have protocol deviations that impact the liver biopsy assessments
- PK population: all randomized subjects who receive at least one dose (full or partial) of drug and have a qualified (i.e., above the lower limit of quantification) pre-dose and post-dose (at least one) PK assessment

9.3. Demographics and Other Baseline Characteristics

Demographics (e.g., age, sex, race, body weight, height, etc.) and other baseline characteristics will be summarized with descriptive statistics by treatment group for each analysis population.

9.4. Efficacy Analyses

9.4.1. Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in ELF at Week 48. Missing change from baseline in ELF will be imputed using a multiple imputation (MI) method under the assumption of missing at random (MAR).

Sensitivity analysis under the assumption of missing not at random (e.g., pattern mixture model) will be performed. In addition, another sensitivity approach to impute the missing ELF measurement at Week 48 using the last observation carried forward (LOCF) method will be performed.

The primary efficacy endpoint will be analyzed using the Multiple Comparison Procedure – Modeling (MCP-Mod) approach to assess the dose-response relationship. Within the framework of the MCP-Mod procedure, the null hypothesis of no dose-response will be tested at the 5% significance level (two-sided) against the alternative hypothesis that there is a dose-response.

The primary efficacy analysis will be performed using the ITT population. The mITT, Full-Analysis and PP populations will be used as sensitivity analyses. Both MI approaches and LOCF approaches will be applied to the missing change from baseline ELF as sensitivity analysis for ITT, mITT, Full-Analysis, and PP populations.

9.4.2. Secondary Efficacy Analyses

The between-group comparisons (aldafermin doses vs placebo) of the change from baseline in ELF at Week 48 will be performed using an analysis of covariance (ANCOVA) model with effects for treatment, baseline T2D status (Yes/No) and the baseline outcome value as a covariate.

Between-group comparisons (aldafermin doses vs placebo) of the histologic response at Week 48 (by NASH CRN criteria) will be performed using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline T2D status (Yes/No).

In addition, analyses will be performed for the following secondary efficacy endpoints:

- Changes from baseline in C4 and serum bile acids
- Changes from baseline in Pro-C3
- Changes from baseline in ALT, AST
- Changes from baseline in liver stiffness measure (LSM by FibroScan®)

All secondary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model with effects for treatment, baseline T2D status (Yes/No) and the baseline outcome value as a covariate.

All secondary efficacy endpoints will be performed using the ITT population. Full-Analysis, and PP populations will be used as sensitivity analyses.

No multiplicity adjustment will be made between the primary and secondary efficacy analyses to control the experiment-wise type I error rate, and thus all secondary efficacy analyses are exploratory in nature.

9.4.3. Other Efficacy Analyses

The details of other efficacy analyses will be provided in the SAP.

9.4.4. Subgroup Analyses

[redacted]

9.5. Safety Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be summarized by primary system organ class and preferred term. Actual values and change from baseline values for vital signs, ECGs, clinical laboratory (hematology and chemistry) tests, and other continuous safety variables will be summarized with descriptive statistics. Concomitant medications, injection site reactions, and other categorical safety variables will be summarized with frequency and percentage distribution.

All safety analyses will be performed using the Safety population.

9.6. Interim Analysis

One interim analysis (IA) may be conducted for organizational decision making. The IA, if conducted, will include a review of selected safety and efficacy endpoints by treatment group. No formal hypothesis testing will be conducted. The study will not be stopped early based on the results. Results for individual subjects will not be shared with study site staff or subjects. Further details of the IAs will be included in the SAP.

9.7. Pharmacokinetics

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

This study will be conducted in accordance with the protocol and with the following:

- Ethical principles for medical subjects involving human subjects derived from the Declaration of Helsinki
- Applicable ICH Good Clinical Practice Guidelines
- Applicable laws and regulations

10.1.1. Informed Consent Process

This study will be conducted in compliance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidance pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, subjects must give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits.
The informed consent document must be signed and dated by the subject prior to study participation. A copy of the informed consent document must be provided to the subject. Signed consent forms must remain in the subject's study file and be available for verification by sponsor or its representative at any time.

10.1.2. Ethics Committee

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/EC for approval. IRB/EC approval of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated.

The PI is responsible for keeping the IRB/EC advised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The PI is also responsible for notifying the IRB/EC of any reportable AEs that occur during the study.

10.1.3. Data Safety Monitoring Board (DSMB)

Please refer to Section 8.5.

10.1.4. Protocol Adherence

The investigator must adhere to the protocol as detailed in this document and agree that the sponsor must approve any changes to the protocol prior to seeking approval from the institutional review board (IRB). There will be no alterations in the protocol without agreement between the sponsor and the investigator. There will be no alterations in the protocol affecting subject safety without the express written approval of the sponsor, investigator, and the IRB.

10.1.5. Confidentiality and Privacy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The investigator agrees not to disclose such information in any way without prior written permission from the sponsor.

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the investigator or their representative(s), shall require prior notification and review, within a reasonable time frame, by the sponsor, and cannot be made in violation of the sponsor's confidentiality restrictions or to the detriment of the sponsor's intellectual property rights.

10.1.6. Clinical Monitoring

The sponsor or designee (e.g., Clinical Research Associate [CRA]) will be responsible for monitoring this clinical trial. The CRA will monitor the study conduct, proper CRF and source documentation completion and retention, and accurate study drug accountability. To this end, the CRA will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The investigator will grant access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the CRA will adhere to all requirements for participant confidentiality as outlined in the informed consent form (ICF). The investigator and investigator's staff will be expected to cooperate with the CRA, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

10.1.7. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan may be developed to describe a site's quality management.

10.1.8. Records

The results from Screening and data collected during the study will be recorded in the subject's CRF. To maintain confidentiality, the subjects will be identified only by numbers and initials.

The completed CRFs will be transferred to the sponsor or designee. Copies of each CRF will be retained by the PI. All source documents, records, and reports will be retained by the clinic.

All primary source data or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, photographs, and computer records) that are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the clinic archives.

The sponsor will inform the PI of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest (longest) standard applicable to that site for the study, as dictated by any institutional

requirements or local laws or regulations, or sponsor standards/procedures; otherwise, the retention period will default to the retention period of 15 years following completion of the clinical trial.

Blood and tissue samples will be collected and any remaining or back-up study samples may be used for future exploratory and biomarker analysis related to aldafermin treatment or metabolic diseases. The samples will be stored for up to 15 years.

10.1.9. Financing and Insurance

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

10.1.10. Publication Policy

NGM will retain ownership of all data. All proposed publications based on this study will be subject to sponsor's approval requirements.

11. REFERENCES

11.1. Clinical Studies Referenced in this Protocol

Study No.	Phase	Study Title	Study Population
12-0101	1	A Phase 1 Randomized, Double Blind, Placebo Controlled, Single Ascending Dose and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of NGM282 in Healthy Adult Participants	Normal volunteers
282-RI-103	1	A Phase 1, Single-center, Open label, Parallel group Study to Evaluate the Pharmacokinetics, Safety & Tolerability of a Single Dose of Aldafermin (NGM282) in Subjects with Impaired Renal Function	Renally impaired and normal volunteers
13-0102	2a	A Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Activity of NGM282 Administered for 28 Days to Participants with Type 2 Diabetes Mellitus	T2D
13-0103	2a	A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Pharmacodynamic Activity of NGM282 in Combination with Ursodeoxycholic Acid (UDCA) Administered for 28 Days in Patients with Primary Biliary Cirrhosis (PBC)	PBC
14-0104	2b	A Phase 2, Multicenter Study to Evaluate Four Doses of NGM282 Administered For 52 Weeks in Patients with Primary Biliary Cirrhosis (PBC)	PBC
15-0105	2a	A Phase 2, Randomized, Double-Blind, Placebo Controlled, Parallel Group and An Open-Label Single-Blind Cohort Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for 12 Weeks in Patients with Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)	NASH
15-0106	2	A Phase 2, Randomized, Double Blind, Placebo Controlled, Parallel Group, Multiple Center Study to Evaluate the Safety, Tolerability, and Efficacy of NGM282Administered for 12 Weeks in Patients with Primary Sclerosing Cholangitis (PSC)	PSC
15-0107	1b	A Phase 1b, Double-Blind, Placebo-controlled, Parallel-Group Multidose Study of the Pharmacodynamics of NGM282 on Colonic Transit, Bile acid Homeostasis, and Fecal Fat in Subjects with Functional Constipation Individuals	Functionally Constipated and Healthy Volunteers

11.2. Nonclinical Studies Referenced in this Protocol

Study No.	Study Title
13-PD-NGM282-1007	A 24-Week Study of Ectopic NGM282 Expression following Intravenous Adeno-Associated Viral Delivery in FXR-deficient Mice
14-PD-NGM282-1001	Effects of NGM282 administration on disease progression in the STAM mouse model of NASH
15-PD-NGM282-1001	Effect of Human FGF-19 and NGM282 in a High Fat/Fructose/Cholesterol Diet-Induced Animal Model of NASH (data on file)
15-PD-NGM282-1002	Effect of Human FGF-19 and NGM282 in FXR-null mice fed a High Fat/Fructose/Cholesterol Diet-Induced Animal Model of NASH (data on file)

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12. APPENDICES

Appendix 1. NASH Clinical Research Network NAFLD Activity Score and Fibrosis Score

Steatosis	S Score	Lobular Inflammation	L Score	Hepatocyte Ballooning	B Score
<5%	0	None	0	None	0
5%–33%	1	<2	1	Few ballooned cells	1
34%–66%	2	2–4	2	Many ballooned cells	2
>66%	3	>4	3	—	—

NAFLD=nonalcoholic fatty liver disease.
Note: NAFLD activity grade score=total score: S + L + B (range 0–8).

Fibrosis Stage	Score
0	No Fibrosis
1a	Zone 3, Mild
1b	Zone 3, Moderate
1c	Periportal Only
2	Zone 3 and Periportal
3	Bridging
4	Cirrhosis

Appendix 2. Food and Drug Administration Toxicity Grading Scale: Clinical Abnormalities in Local Injection Site Symptom Assessments

Local Reaction to Injection Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/ Redness [a]	2.5–5cm	5.1–10cm	>10cm	Necrosis or exfoliative dermatitis
Induration/ Swelling [b]	2.5–5cm and does not interfere with activity	5.1–10cm or interferes with activity	>10cm or prevents daily activity	Necrosis

ER=emergency room.
Note: The FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials can be found at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775 htm.
[a] In addition to grading the measured local reaction at the greatest single diameter, the measurements should be recorded as a continuous variable.
[b] Induration or swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Appendix 3. AUDIT-C Alcohol Consumption Questionnaire

AUDIT-C - Overview

The AUDIT-C is a 3-item alcohol screen that can help identify persons who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence). The AUDIT-C is a modified version of the 10 question AUDIT instrument.

Clinical Utility

The AUDIT-C is a brief alcohol screen that reliably identifies patients who are hazardous drinkers or have active alcohol use disorders.

Scoring

The AUDIT-C is scored on a scale of 0-12.

Each AUDIT-C question has 5 answer choices. Points allotted are:
a = 0 points, b = 1 point, c = 2 points, d = 3 points, e = 4 points

- **In men**, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders.
- **In women**, a score of 3 or more is considered positive (same as above).
- However, when the points are all from Question #1 alone (#2 & #3 are zero), it can be assumed that the patient is drinking below recommended limits and it is suggested that the provider review the patient's alcohol intake over the past few months to confirm accuracy.[3]
- Generally, the higher the score, the more likely it is that the patient's drinking is affecting his or her safety.

Psychometric Properties

For identifying patients with heavy/hazardous drinking and/or Active-DSM alcohol abuse or dependence

	Men[1]	Women[2]
≥3	Sens: 0.95 / Spec. 0.60	Sens: 0.66 / Spec. 0.94
≥4	Sens: 0.86 / Spec. 0.72	Sens: 0.48 / Spec. 0.99

For identifying patients with active alcohol abuse or dependence

≥ 3	Sens: 0.90 / Spec. 0.45	Sens: 0.80 / Spec. 0.87
≥ 4	Sens: 0.79 / Spec. 0.56	Sens: 0.67 / Spec. 0.94

1. *Bush K, Kivlahan DR, McDonell MB, et al. The AUDIT Alcohol Consumption Questions (AUDIT-C): An effective brief screening test for problem drinking. Arch Internal Med. 1998 (3): 1789-1795.*
2. *Bradley KA, Bush KR, Epler AJ, et al. Two brief alcohol-screening tests from the Alcohol Use Disorders Identification Test (AUDIT): Validation in a female veterans affairs patient population. Arch Internal Med Vol 163, April 2003: 821-829.*
3. *Frequently Asked Questions guide to using the AUDIT-C can be found via the website: www.oqp.med.va.gov/general/uploads/FAQ%20AUDIT-C*

AUDIT-C Questionnaire

Patient Name _____ Date of Visit _____

1. How often do you have a drink containing alcohol?

- ☐ a. Never
- ☐ b. Monthly or less
- ☐ c. 2-4 times a month
- ☐ d. 2-3 times a week
- ☐ e. 4 or more times a week

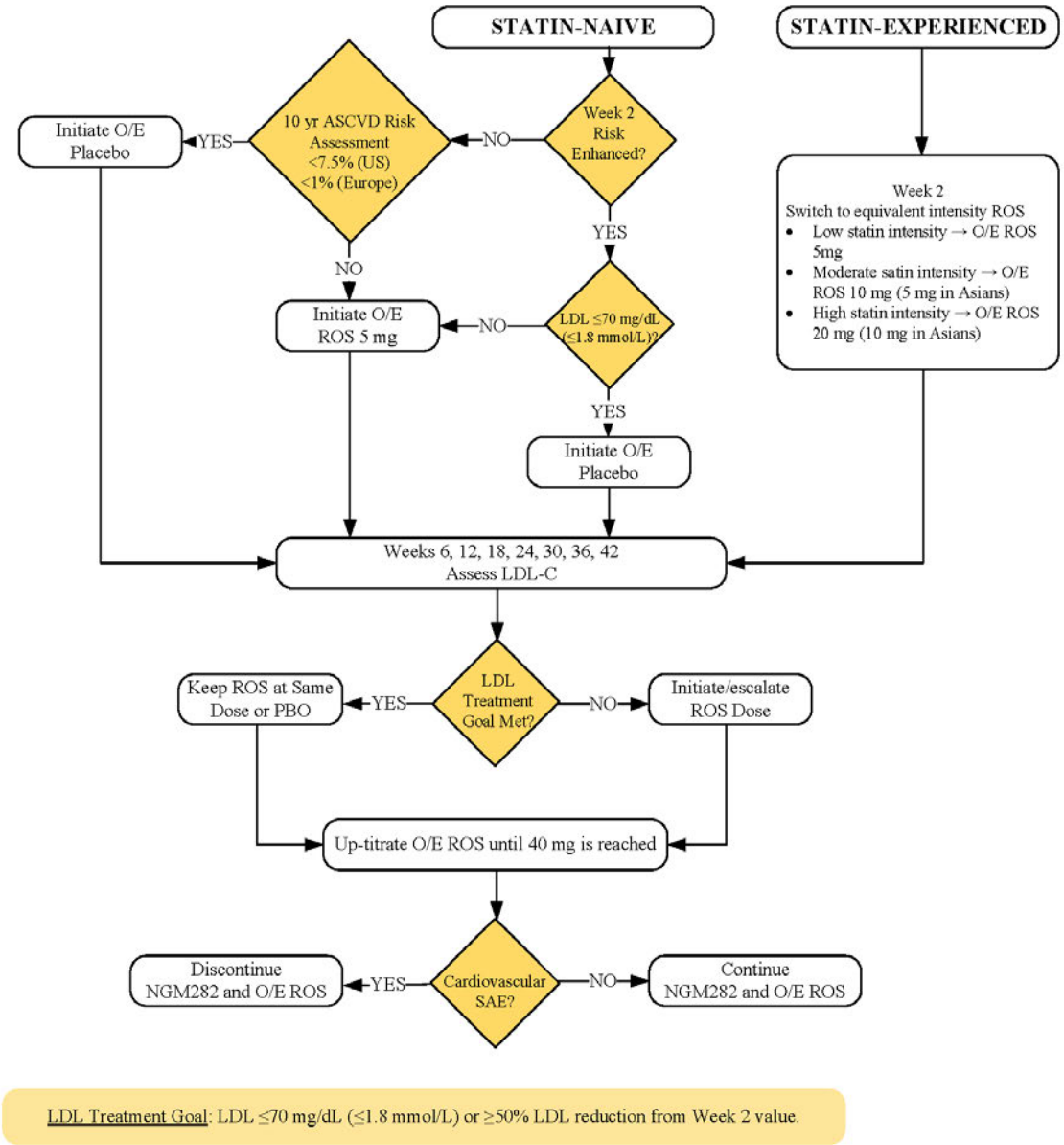
2. How many standard drinks containing alcohol do you have on a typical day?

- ☐ a. 1 or 2
- ☐ b. 3 or 4
- ☐ c. 5 or 6
- ☐ d. 7 to 9
- ☐ e. 10 or more

3. How often do you have six or more drinks on one occasion?

- ☐ a. Never
- ☐ b. Less than monthly
- ☐ c. Monthly
- ☐ d. Weekly
- ☐ e. Daily or almost daily

Appendix 4. Lipid Lowering Algorithm: Statin Naïve and Stain Experienced Subjects



Appendix 5. Rosuvastatin Package Insert

The package insert for rosuvastatin being used in the study can be found at the following web link:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021366s016lbl.pdf

Appendix 6. Prohibited Hepatotoxic Agents

All other hepatotoxic agents will be left to the discretion of the PI.

If a patient is on stable therapy for an appropriate period of time (e.g., 3 months) or received short-term therapy without hepatotoxicity, continuation of a listed agent may be appropriate per PI discretion and Medical Monitor approval without exclusion from the study.
There should be clear documentation in the subject's study records of investigator assessment of safety and approval of use of the listed medication to support the eligibility and/or continued use during the study.

Generic Name	Drug Class/Common Use
Acetaminophen >3000 mg/day	Analgesic
Albendazole	Anthelmintics (parasitic infections)
Amiodarone	Antiarrhythmic
Amodiaquine,	Antimalarial
Azathioprine/6-Mercaptopurine	Antineoplastic/Antirheumatic, autoimmune
Buspirone	Sedatives, hypnotics, Psychoactive drug – for anxiety
Busulfan	Antineoplastic/Alkylating, cancer
Carbamazepine	Anticonvulsant
Chemotherapies	
Chlorpromazine	GI, antipsychotic
Dantrolene	Muscle relaxant
Didanosine	Antiviral
Dimethyl Fumarate	For MS
Disufiram	Alcohol Deterrents
Dronedarone	Antiarrhythmic (AFib/flutter)
Efavirenz	Antiviral
Fenofibrate	Anti-lipemic Hypertriglyceridemia, hypercholesterolemia
Floxuridine	Antineoplastic, cancer
Flutamide	Antineoplastic, nonsteroidal antiandrogen (NSAA)
Glatiramer acetate	For MS
Gold Salts	Antirheumatic, RA
Halothane	Anesthetics for surgery
Hydralazine	Antihypertensive
Infliximab	Antirheumatic, Dermatologic, GI
Interferon alpha	Antiviral
Interferon beta	MS
Isoniazid	Anti TB
Methotrexate	Antineoplastic, Antirheumatic, Dermatologic
Methyldopa	Antihypertensive
Nefazodone,	antidepressant
Nevirapine	Anti-viral (HIV/AIDS therapy)
Nimesulide,	NSAID – COX-2
Norethisterone	For menstrual issues
Phenytoin	anticonvulsant
Pirfenidone	Pulmonary fibrosis
Propylthiouracil	Antithyroid
Pyrazinamide	Anti TB
Quinidine	Antiarrhythmic
Rifampin	Anti TB
Sulfasalazine	Anti-infective (DMARD, anti-inflammatory)
Suramin	Injectable – antiprotozoal agent

Thioguanine	Antineoplastic/Antirheumatic,
Ticlopidine	Antithrombotic, platelet inhibitor
Valproate	Anticonvulsant (epilepsy), mood stabilizer (Bipolar)