Aldafermin (NGM282) Clinical Protocol, Study 18-0108 (ALPINE 2/3)

NCT03912532

A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy, Safety, and Tolerability of Three Doses of Aldafermin Administered for 24 Weeks for the Treatment of Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)

for

NGM Biopharmaceuticals, Inc.
333 Oyster Point Boulevard
South San Francisco, CA 94080

Original Protocol: 08 August 2018
Amendment 1: 21 January 2019
Amendment 2: 03 July 2019
Amendment 3: 31 October 2019
Amendment 4: 15 January 2020

1 Study Identification

Sponsor:	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 Contact:	[redacted] Executive Director, Clinical Operations NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: [redacted] Fax: [redacted]
Sponsor Medical Monitor:	[redacted] Sr. Director, Clinical Development NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080, USA Phone: [redacted] Mobile: [redacted] Fax: [redacted]

2 Summary of Changes

Protocol Section	Modification	Justification for Change
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

Protocol Section	Modification	Justification for Change
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3 Table of Contents

3.1 List of Tables

3.2 List of Appendices

3.3 List of Abbreviations

Abbreviation	Definition/Explanation
AAV	Adeno-associated virus
ADA	Anti-drug antibody
AE	Adverse event
AFP	Alpha fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration–time curve
BMI	Body mass index
C_{2h}	Concentration at 2 hours post-dose

Abbreviation	Definition/Explanation
C4	7-alpha-hydroxy-4-cholesten-3-one
CBC	Complete blood count (hematology clinical laboratory evaluations)
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CI	Confidence interval
CL/F	Clearance divided by the bioavailable fraction
C_{max}	Maximum drug concentration
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form
CRN	Clinical Research Network
CTCAE	Common Terminology Criteria for Adverse Events
C_{min}	Minimal observed concentration during a dosing interval
D	Day
DILI	Drug-Induced Liver Injury
EC	Ethics Committee
ECG	Electrocardiogram
ELF	Enhanced liver fibrosis
EOS	End of Study
EOT	End of Treatment
ER	Emergency room
FDA	Food and Drug Administration
FGF19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
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
HOMA-IR	Homeostasis model assessment–estimated insulin resistance
H	Hour(s)
hs-CRP	High-sensitivity C-reactive protein
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
LISSA	Local injection-site symptom assessment
LLN	Lower Limit of Normal
LLT	Lowest Level Term (MedDRA)
MAD	Multiple ascending dose
Max	Maximum
MCP-Mod	Multiple Comparison Procedure – Modelling
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model of end-stage liver disease
MI	Multiple imputation
Min	Minimum
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging–proton density fat fraction

Abbreviation	Definition/Explanation
n	Number / number of non-missing observations
Nab	Neutralizing antibody
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
NGM	NGM Biopharmaceuticals, Inc.
Aldafermin/NGM282	A Recombinant protein of 190 amino acids; engineered variant of humanized FGF19
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
PI	Principal Investigator
Peth	Phosphatidylethanol
PIIINP	Propeptide of type III procollagen
PK	Pharmacokinetics; pharmacokinetic
PNPLA3	Patatin-like phospholipase domain-containing protein 3
PP	Per protocol
Pro-C3	N-terminal type III collagen
PSC	Primary sclerosing cholangitis
PT	Preferred term
REML	Restricted maximum likelihood
[redacted]	[redacted]
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SOP	Standard Operating Procedure
$t_{1/2}$	Apparent terminal elimination half-life
T2D	Type 2 diabetes
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TIMP-1	Tissue inhibitor of metalloproteinase 1
T_{max}	Time to maximum concentration
TNF	Tissue necrosis factor
Tx	Treatment
ULN	Upper limit of normal
US/U.S.	United States
V_z/F	Volume of distribution based on the terminal portion of the concentration–time curve divided by the bioavailable fraction
W	Week

4 Synopsis

Title of Study:	A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy, Safety, and Tolerability of Three Doses of NGM282 Administered for 24 Weeks for the Treatment of Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)
Protocol Number:	18-0108
Phase:	2b
Investigational Product:	NGM282, henceforth aldafermin
Study Objectives and Endpoints:	**Primary Objectives and Endpoints:** The primary objectives are to evaluate the efficacy, safety and tolerability of aldafermin based on liver histology at 24 weeks versus placebo. 1. The primary efficacy endpoint is the histologic response defined as an improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis at Week 24 compared with baseline. 2. The primary safety endpoint is frequency, severity, and timing of adverse events (AEs) and serious adverse events (SAEs). Safety and tolerability of aldafermin in subjects with NASH as a function of dose level after up to 24 weeks of treatment with aldafermin will be assessed. **Secondary Objectives and Endpoints:** The secondary objectives of this study are to evaluate the effect of aldafermin on pharmacokinetics, biomarkers of target engagement, fibrogenesis, and imaging. The secondary endpoints are as follows: 1. Resolution of NASH (defined as an NAS score of 0 or 1 for inflammation and 0 for ballooning) with no worsening of fibrosis as determined by the NASH CRN criteria at Week 24 compared with baseline. 2. Subjects with improvement in liver fibrosis by > 1 stage by CRN criteria with no worsening of steatohepatitis **and** resolution of NASH with no worsening of fibrosis as determined by the NASH CRN criteria at Week 24. 3. Subjects with improved, no change, and worsening of fibrosis and NAS (total score and individual components) at 24 weeks compared to baseline 4. Subjects with the following changes in liver fat content (LFC) by MRI-PDFF at Week 24 o Normalization for LFC (defined as < 5% absolute LFC) o ≥ 5% decrease in absolute LFC o ≥ 30% relative decrease in LFC 5. Absolute and percentage changes from Baseline to Week 24 of the following: o ALT, AST, total bilirubin, ALP and gamma glutamyl transpeptidase (GGT) o Total cholesterol, high-density lipoprotein-cholesterol (HDL-C), LDL-C, triglycerides

- Lipoprotein particles [redacted]
- Homeostasis model assessment–estimated insulin resistance (HOMA-IR)
- N-terminal Type III collagen (Pro-C3)
- Total ELF Score and individual components (i.e., hyaluronic acid, PIIINP, TIMP-1)
- 7-alpha-hydroxy-4-cholesten-3-one (C4) and serum bile acids (total and individual bile acids)
- [redacted]

6. Subjects with normalization of ALT and AST at Week 24

Exploratory Objectives and Endpoints:

[redacted]

Study Population Inclusion Criteria:

Subjects who meet the following criteria may be included in the study:

1. Males and females 18 to 75 years of age (inclusive) who are able to comprehend and willing to sign an Informed Consent Form (ICF)
2. Histologically confirmed NASH diagnosis as defined by the NIH NASH CRN (see Appendix 1, Kleiner 2005) and liver biopsy criteria outlined below.
   A historical biopsy is acceptable if performed within the required 6-months of Screening and tissue slides are available for a qualified central pathologist reader:
   - NAS ≥ 4 with a minimum of 1 point in each component
   - Histologic evidence of Stage 2 or Stage 3 fibrosis without cirrhosis
3. Total liver fat content of ≥ 8% as measured by MRI-PDFF
4. Subjects with T2D or insulin resistance are permitted as long as diabetic medications are stable as outlined in Section 9.3 Concomitant Medications and subject attempts to maintain a stable regimen during the study period.
5. Other concomitant medications/therapies for NAFLD or NASH: requires a stable regimen for at least 3 months prior to the Screening biopsy of record and throughout the study (Refer to Section 9.3 Concomitant Medications).
6. Statin use based on the following criteria for statin-naïve or statin-experienced at Screening:
   - **Statin naïve** is defined as no administration of statins within 3 months prior to Screening.

- **Statin experienced** is defined as administration of the following stable daily doses of approved statin therapies taken for at least 3 months prior to Screening through Week 2:
  - Atorvastatin: ≤ 40 mg/day
  - Fluvastatin: ≤ 40 mg/day
  - Lovastatin: ≤ 40 mg/day (immediate release), ≤ 30 mg/day (extended release)
  - Pitavastatin: ≤ 2 mg/day
  - Pravastatin: ≤ 40 mg/day
  - Simvastatin: ≤ 40 mg/day
  - Rosuvastatin: ≤ 20 mg/day

7. The following laboratory parameters must be met at Screening:
   - Total bilirubin ≤ULN (Upper Limit of Normal) based on the Day -42 value or average of at least 2 Screening values obtained during the Screening Period, except for subjects with an established diagnosis of Gilbert's Syndrome provided the direct bilirubin level is ≤ULN and hemoglobin and reticulocyte count are normal.
   - Aspartate aminotransferase (AST) ≥ 30 IU/L and ≤ 250 IU/L in all subjects, based on the Day -42 value or average of at least 2 screening values obtained during the Screening Period
     i. Exception: subjects with an average AST ≥ 20 and < 30 IU/L will be permitted provided that at least one of the following criteria are met:
        1. Local historical biopsy within 6 months with a NAS of 4 with at least 1 point in each component and fibrosis Stage 2 or 3. Subjects with a historical biopsy will have their slides evaluated by the central reader prior to undergoing MRI-PDFF.
        2. Vibration-controlled transient elastography (VCTE® by Fibroscan) ≥ 9.5 kPa within 6 months of Screening. If no historical Fibroscan is available, it may be conducted and evaluated as per local "standard-of-care" prior to Day -28.
   - Hemoglobin A1c (HbA1c) ≤ 9.5%
   - Platelet count ≥ Lower Limit of Normal (LLN) (i.e., 140,000/mm^3)
   - Creatinine clearance ≥ 60 mL/min as calculated by Cockcroft-Gault equation
   - Alpha fetoprotein (AFP) < 100 ng/mL
8. Female subjects who are of non-childbearing potential must have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, are documented postmenopausal, OR a follicle stimulating hormone > 40 mIU/mL
9. Female subjects of child-bearing potential must not be pregnant or nursing. Female subjects of childbearing potential are defined as women < 55 years of age with ≤ 2 years of amenorrhea and who meet both of the following criteria:
   i. A negative serum pregnancy test at Screening and urine pregnancy test prior to randomization

ii. Correct and consistent use of one of the following methods of birth control in addition to a male partner using a condom from Screening to 30 days after the last dose of study drug:
   1. hormone containing contraceptive
   2. intrauterine device with a failure rate < 1% per year
   3. cervical cap or diaphragm with spermicidal agent
   4. tubal sterilization
   5. vasectomy in male partner
   6. complete abstinence of sexual intercourse

10. Male subjects are eligible for the study if they meet the following criteria:
   a. Male subjects must agree to consistently and correctly use a condom in combination with one of the following from the date of consent to 30 days after the last dose of study drug:
      ii. Condom with spermicide
      iii. Vasectomy
      iv. Complete abstinence of sexual intercourse.

   AND

   a. Female partner(s) must use any of the approved methods of birth control in inclusion criterion #9.
11. Able and willing to comply with the dosing instructions for study-drug administration and able to complete the study schedule of assessments
12. BMI ≥ 25 kg/m^2 for subjects self-identified of Asian descent only

Exclusion Criteria

The following will exclude potential subjects from the study:

1. Clinically significant acute or chronic liver disease of an etiology other than NASH
2. Evidence of drug-induced steatohepatitis secondary to amiodarone, corticosteroids, estrogens, methotrexate, tetracycline, or other medications known to cause hepatic steatosis
3. History or presence of cirrhosis (compensated or decompensated) as determined by histology and/or relevant medical complications and/or laboratory parameters
4. Prior or pending liver transplantation
5. Model of end-stage liver disease (MELD) score ≥ 12 (except for subjects with established Gilbert's syndrome)
6. Evidence of worsening liver disease (defined below) between Screening visits (i.e., Day -42 and Day -28) including measures of AST, ALT, TBL, and ALP:
   - For subjects with AST, ALT, TBL or ALP baseline levels > ULN on Day -28, the Day -28 assessment should not exceed an increase of 35% over the Day -42 assessment.
   - For subjects with Gilbert's syndrome and a total bilirubin > ULN at the Day -42 assessment, the total bilirubin assessment at Day -28 should not exceed an increase of 50% over the Day -42 assessment.

   Note: For AST, ALT, TBL and ALP, if the percent increase in laboratory values between Day -42 and Day -28 is > 35%, repeat blood samples will be collected at an unscheduled visit at a minimum of two weeks from the Day - 28 visit. The average of Day -42 and Day -28 values will be compared

to the 3rd value to determine if eligibility ranges (i.e., % agreement ≤ 35%) are met.

7. 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 (except for uncomplicated elective pacemaker procedure, 3 months post procedure will be allowed).
8. History of gastric bypass or bariatric surgery or planned procedure during the study period. Removal of a gastric balloon or lap band is permitted if surgery performed within 6 months prior to Day 1.
9. Type 1 diabetes
10. History of clinically significant unstable or untreated illness or any other major medical disorder that may interfere with patient treatment, assessment, or compliance with the protocol
11. Any contraindication or inability to obtain an MRI
12. Inability to obtain or any contraindication to liver biopsy (if a historical biopsy with viable tissue slides are not available within the required time period)
13. Screening ECG with clinically significant abnormalities or unexplained findings that the investigator feels needs further evaluation and treatment
14. Positive for HBsAg, anti-HIV, or anti-HCV plus HCV-RNA. Subjects who are anti-HCV- 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
15. History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to Screening); subjects under evaluation for malignancy are not eligible
16. Clinically-relevant drug use within 12 months of Screening. A positive drug screen 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 Sponsor Medical Monitor or designee. Marijuana is not part of the drug screen.
17. Significant alcohol intake as measured by a phosphatidylethanol (PEth) level ≥ 200 ng/mL AND positive results from AUDIT-C alcohol consumption questionnaire (Appendix 8)
18. *Criterion eliminated per protocol amendment 3*
19. Consumption of ≥ 21 units of alcohol per week in males and ≥ 14 units of alcohol per week in females for two years prior to enrollment, where a "unit" of alcohol is equivalent to a 12-ounce beer, 4-ounce glass of wine, or 1-ounce shot of hard liquor
20. Use of any prohibited concomitant medications as described in Section 9.3 from Day -42 to the end of the study including:
    - Investigational agents, other than aldafermin, or devices for any indication
    - Combination preparations of statins and other lipid-lowering agents (other than approved statin therapies listed in inclusion criterion #6)
    - Weight loss medications
    - Any medication that is contraindicated according to the rosuvastatin package insert (Appendix 6) or if subject has a known hypersensitivity to rosuvastatin product components (Section 10.1.3).

- Any medication that is contraindicated according to the ezetimibe package insert (Appendix 7) or if subject has a known hypersensitivity to ezetimibe product components.
- Hepatotoxic medications (Appendix 9). For subjects who have been on stable therapy with no related hepatotoxicity, the MM may be contacted to assess the medical context and eligibility of the subject. Allopurinol to treat gout is permitted provided there is no prior history of intolerability.
- Anabolic steroids; Low levels of estrogen or testosterone as replacement therapy are allowed per Medical Monitor approval.

21. History of statin intolerance as evidenced by presence of ALT elevations, adverse event(s), or other significant side effects attributed to statins
22. Prior participation in a clinical trial of aldafermin is excluded **unless** previously enrolled into a placebo treatment group of the trial.
23. Subject with severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies
24. Participation in a study of another investigational agent:
    - NASH investigational agents: < 3 months prior to Screening if treated with active study drug or < 28 days if treated with placebo)
    - All other investigational agents: within 28 days or five half-lives of the drug (whichever is longer) prior to Screening
25. Any acute or chronic condition that, in the opinion of the Investigator or the Sponsor Medical Monitor, would limit the subject's ability to complete and/or participate in this clinical study
26. Pregnancy or lactation
27. *Criterion eliminated per protocol amendment 4*

Methodology/ Study Design:

This is a multiple-center evaluation of aldafermin in a randomized, double-blind, placebo-controlled study, when administered for 24 weeks as a daily subcutaneous (SC) injection in patients with histologically confirmed NASH.

Approximately 152 subjects, of which no more than 15% (approximately 22 subjects) will be self-identified Asian subjects, will be randomized at approximately 40 sites in the US. Depending on the overall enrollment rate and the proportion of subjects enrolled with F2 or F3, the sponsor may limit the enrollment of F2 subjects to be no greater than approximately 65% (99/152 subjects).

Subjects to be studied will have histologically confirmed NASH as defined by the NIH NASH CRN (Kleiner 2005) and determined by a qualified central pathologist's reading (see Appendix 1). Historical biopsy results within 6 months of the first Screening visit may be used for inclusion into the study; otherwise, a liver biopsy must be obtained for assessment. Subjects must have a NAS of at least 4, with a minimum of 1 point in each of the three components, along with the presence of either Stage 2 or 3 fibrosis. Subjects with no (Stage 0) or minimal (Stage 1) fibrosis and cirrhosis (Stage 4) will be excluded from this study. Subjects will undergo MRI during the Screening period, which must demonstrate ≥8% total liver fat content (LFC) by MRI-PDFF.

Subjects may be rescreened once with Medical Monitor approval. Note: certain laboratory parameters of interest (e.g., AST, TBL, creatinine clearance) may be retested at the investigators' discretion after discussing with the Medical Monitor.

On Day 1, eligible subjects will be randomized into one of the four treatment groups (0.3 mg aldafermin, 1 mg aldafermin, 3 mg aldafermin, or placebo) in a 1:1:1:1 ratio

(Table 3). Randomization will be stratified by baseline stage of fibrosis (Stage 2 versus 3) on the qualification liver biopsy as determined by the Central Pathologist. Treatment assignment will be blinded to the investigational sites, study subjects, and sponsor (both Study Team and sponsor Medical Monitor or designee) throughout the study period and managed through the [redacted] Study-drug self-administration instructions and training will be provided to the subjects and study-drug kits will be dispensed.

The first dose of aldafermin (Day 1) and doses at Weeks 2, 4, 8, 12, 18, and 24 study visits will be self-administered in the clinic, with all other daily doses through Week 24 self-administered at home. Self-administration should occur daily at a similar time at home. Subjects will return to the clinic on Weeks 2, 4, 8, 12, and 18 for on-treatment assessments and to receive aldafermin study-drug kits.

LDL-C will be evaluated at Weeks 2, 4, 8, 12 and 18 in all subjects for possible increases in lipid levels associated with aldafermin administration. Rosuvastatin will be started in subjects meeting specific LDL-C level criteria at Week 2. Rosuvastatin and matched placebo are 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 by an unblinded third-party medical monitor and through the [redacted]. The sponsor and study sites will be blinded to LDL-C values and the specific rosuvastatin dosing decisions as outlined in Section 9.4.14. Subjects who have not achieved an adequate response or cannot tolerate rosuvastatin as defined in Section 9.4.14 will be considered for the addition of ezetimibe as second-line lipid management therapy. Ezetimibe 10 mg tablets can be administered with or without food at the same time as rosuvastatin and aldafermin. Subjects whose LDL-C values are not adequately managed by their maximum tolerated rosuvastatin dose plus ezetimibe will be discontinued from study and an early withdrawal study visit will be completed. The follow-up visit/EOS should be scheduled for 6 weeks after the early withdrawal study visit. The specific rosuvastatin dosing algorithm is outlined in detail in Appendix 3.

Rosuvastatin or matching placebo will be dispensed at each study visit through Week 18 (statin-naïve) or Week 24 (statin-experienced). If the subject is taking statins, evaluate tolerability and continue therapy to Week 24 if statin naïve or Week 30 if statin experienced.

All subjects will return to the clinic at Week 25 for post-treatment LDL-C assessment. Subjects who have an LDL-C value of >100 mg/dL and > 15 mg/dL above their Day 1 value at Week 25 will be re-assessed at Week 30. Subjects who have an LDL-C value of > 100 mg/dL and >15 mg/dL above their Day 1 value at Week 30 will have an additional 4-week follow-up visit to confirm their LDL-C value is ≤ 100 mg/dL or ≤ 15 mg/dL above their Day 1 value.

The study visit at Week 24 will be the aldafermin EOT clinic visit and subjects will return to the clinic at Weeks 25 and 30 (or at 1 and 6 weeks after last dose of aldafermin) for a post- treatment response and EOS follow-up visits. Subjects are required to undergo MRI performed during Screening Day -28 and at Weeks 12, 24 / Early Withdrawal (EOT), and 30 (EOS) visits.

	All subjects will have blood samples drawn for [redacted]
Number of Subjects:	A total of approximately 152 subjects (38 per treatment group) will be randomized.
Number of Study Sites:	Approximately 40 sites in the United States
Test Product(s), Dose, and Mode of Administration:	Aldafermin final product will be supplied in pre-filled syringes intended to deliver 0.3 mL containing 0.3 mg, 1 mg, or 3 mg aldafermin for SC injection. Placebo will be provided in volume-matched syringes. Subjects will be instructed to dose aldafermin at home at a similar time each day; however, study drug will be taken in the clinic on study visit days. Rosuvastatin will be administered for subjects meeting pre-specified LDL-C criteria (statin-naïve subjects) or automatically at Week 2 (statin-experienced). Study-labeled rosuvastatin/matching placebo is over-encapsulated and will be supplied in 5 mg, 10 mg, 20 mg, or 40 mg total daily doses as outlined in Section 10.1.3 of the protocol to manage possible LDL-C increase during aldafermin treatment.
Duration of Treatment:	Subjects will sign the Informed Consent Form at the Day -42 Screening Visit and will undergo screening assessments to determine study eligibility. All subjects will be treated with aldafermin or matched placebo for 24 weeks and will be monitored for 6 weeks after completing their final dose of aldafermin or placebo. The total duration of individual subject participation will be approximately 36 weeks.
Statistical Methods:	**Analysis Populations:** Subjects will be analyzed using the following analysis populations: • **Intent-to-Treat Population** All randomized subjects will be included in the Intent-to-Treat (ITT) population. The ITT population will be based on randomized treatment if this differs from actual treatment received. • **Safety Population** All subjects who receive at least one dose (full or partial) of study drug will be included in the Safety population. All safety endpoints will be summarized using the Safety population and will be based on actual treatment received if this differs from the randomized/enrolled treatment. • **Full Analysis Population** All randomized/enrolled 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 will be included in the Full Analysis population. The Full Analysis population will be based on randomized/enrolled treatment if this differs from actual treatment received. • **Per Protocol (PP) Population** The Per Protocol (PP) population will constitute a subset of the Full Analysis population and will include subjects that have at least one valid, non-missing baseline and post-dose

liver biopsy results and do not have protocol deviations that impact the liver biopsy assessments.

- [redacted]

[redacted]

General Statistical Considerations:

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

Primary Efficacy Analysis:

The primary efficacy endpoint for this study is the histologic response at Week 24, defined as a subject achieving an improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) with no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis) after 24 weeks of treatment.

Subjects with two biopsies (baseline and post-baseline) will be considered for this analysis only if the second biopsy is taken after at least 12 weeks (i.e., 50% of the intended duration of 24-week treatment period) of treatment on the study drug. For the primary efficacy analysis, missing histologic responses at Week 24 will be imputed using a multiple imputation (MI) method under the assumption of missing at random. The details of the MI method will be provided in the SAP.

The primary efficacy endpoint will be analyzed using the MCP-Mod (Multiple Comparison Procedure – Modelling) 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 against the alternative hypothesis that there is a dose-response. The details of the MCP-Mod approach will be provided in the SAP.

Sensitivity analyses will include imputations with missing histologic responses as both responders and non-responders, and analysis with the assumption of missing not at random (e.g., pattern mixture models).

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

Secondary Efficacy Analyses:

Secondary efficacy analyses include the analyses of the primary efficacy endpoint (i.e., histologic response at Week 24) based on pair-wise comparisons between treatment groups and the analyses of the secondary efficacy endpoints.

	All binary efficacy endpoints (i.e., responders) will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline fibrosis stage. All continuous efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model with effects for treatment, baseline fibrosis stage and 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. 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. **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 Analysis	No Interim Analysis is planned for this study.

5 Introduction

5.1 Background

5.1.1 Nonalcoholic Steatohepatitis (NASH)

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease ranging from simple steatosis to inflammatory steatohepatitis (NASH). 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 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 NAFLD Activity Score (NAS) is a validated score used to grade disease activity in patients with NAFLD and NASH (Appendix 1). The NAS is the sum of the biopsy's individual scores for steatosis (0–3), lobular inflammation (0–2), and hepatocellular ballooning (0–2). Fibrosis staging is assessed using a separate (0–4) scoring system from the NAS (Kleiner 2005).

Most patients with NASH are asymptomatic, although some patients may present with fatigue, malaise, and vague right-upper abdominal discomfort. Patients are more likely to initially be identified by elevated liver aminotransferases on routine exams or hepatic steatosis detected incidentally on abdominal imaging. Patients with NASH often have one or more components of the metabolic syndrome such as obesity, hypertension, dyslipidemia, and insulin resistance or T2D, with NASH considered to be the hepatic manifestation of metabolic syndrome (Torres 2012). Most patients are diagnosed with NASH in their forties or fifties. Studies vary with regard to the sex distribution of NASH, with some studies suggesting it is more common in women while others suggest it is more common in men (Pan 2014). There appear to be ethnic differences in the prevalence of NASH, with a higher prevalence of hepatic steatosis in Hispanics compared with whites or blacks (Pan 2014).

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 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 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).

5.1.2 Treatment of NASH

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. Antifibrotic agents have targeted the advanced fibrosis and cirrhotic populations but have little activity on the underlying disease causing the chronic hepatic injury.

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 (Cazzo 2015). Currently, no agents have been approved by regulatory authorities for the treatment of NASH; the majority of interventions have utilized agents approved for other indications.

However, the interpretation of the data with many of these agents has been complicated by the study designs and endpoints. The majority of studies are uncontrolled or retrospective cohorts, have small sample sizes and/or are insufficiently powered, were comprised of heterogeneous populations, have treatment durations too short (< 12 months) to demonstrate a treatment effect, and lack consistent definitions of response. Evaluated agents including metformin, fibrates, ursodeoxycholic acid, and orlistat have failed to show a significant histologic benefit in NASH (Torres 2012). Pilot studies with PPARγ agonists (pioglitazone, rosiglitazone) have been undertaken based on their effects on insulin resistance, inflammatory signaling, and fibrogenesis. Both agents have demonstrated improvements in alanine aminotransferase (ALT) and steatosis with pioglitazone having a marginally better anti-inflammatory and anti-fibrotic activity (Belfort 2006, Neuschwander-Tetri 2003). Vitamin E has also been evaluated in NASH patients based on its antioxidant properties. Small pilot studies have demonstrated histologic improvement with daily doses of 400-800 IU (Harrison 2003). The PIVENS trial comparing pioglitazone or vitamin E to placebo was the first well-controlled study to show an impact on steatosis, inflammation, hepatocyte ballooning, and fibrosis, with vitamin E having slightly better improvements in fibrosis (Sanyal 2010). Although a treatment benefit was demonstrated in this study, the improvements in fibrosis were modest. Additionally, near- and long-term safety and tolerability concerns were observed with both pioglitazone (weight gain, edema, bone fractures, malignancy) and vitamin E (hemorrhagic stroke, inhibition of platelet aggregation, malignancy). More recently, the farnesoid X receptor (FXR) agonist obeticholic acid (OCA) was evaluated in the FLINT trial in a population similar to that in the PIVENS study with comparable primary and secondary endpoints (Neuschwander-Tetri 2015). OCA demonstrated results comparable to vitamin E versus placebo in terms of improvements in NAS and fibrosis whereas vitamin E and pioglitazone demonstrated better results compared to OCA in terms of resolution of NASH. Additionally, significant increases in pruritus and lipids (requiring treatment on study) were associated with OCA. Although these agents have demonstrated some histologic improvement in NASH, a significant medical need for new effective therapies with favorable safety and tolerability profiles remains.

5.2 Nonclinical Studies

Aldafermin has been evaluated in a series of in vitro and in vivo nonclinical studies to support its clinical development in patients with NASH. Please refer to the Investigator's Brochure (IB) for additional information on these studies.

5.2.1 Nonclinical Safety Assessment

The nonclinical safety of aldafermin has been assessed in general toxicity studies in CD-1 mice, Sprague-Dawley rats, and cynomolgus monkeys (*Macaca fascicularis*) for up to 26 weeks of treatment and in embryo–fetal toxicity studies in CD-1 mice and New Zealand White (NZW) rabbits. Aldafermin is pharmacologically active in the mouse and monkey for up to 26 weeks of treatment. Aldafermin was generally well tolerated in animals.

Based on the cumulative nonclinical safety profile of aldafermin for up to 26 weeks of treatment, the NOAELs in the mouse, rat, and monkey were determined to be 3, 3, and 1 mg/kg, respectively. A sufficient safety margin exists for aldafermin at the proposed maximal clinical dose of 3 mg (0.0864 mg/kg) where estimated exposure is estimated to be 5- or 28-fold below that at the NOAELs in the mouse or monkey, respectively (see Table 1).

Table 1. Estimated Safety Exposure Margin of Aldafermin

Nonclinical Species	NOAEL (mg/kg) [a]	Plasma AUC (hr • ng/mL) [b]	Exposure Margin Relative to Maximum Human Therapeutic Dose [c]
Monkey	1	6610	~28X
Mouse	3	1062	~5X
Rat	3	6580	~28X

AUC = area under the concentration–time curve; hr = hour; NOAEL = no-observed-adverse-effect level.
[a] Determined from the 6-month chronic toxicity studies.
[b] Systemic exposure at Day 1 after a single dose was used as the most conservative estimate of exposure given the presence of anti-drug antibody formation with repeat dosing in animals leading to drug accumulation (plasma AUC 7-fold above Day 1 levels).
[c] Based on a maximal therapeutic dose of 3 mg (0.033 mg/kg based on a 90-kg patient) where plasma AUC is projected to be 233 hr • ng/mL (Study 12-0101).

5.2.2 Therapeutic Rationale for Aldafermin in NASH

Aldafermin (also known as NGM282 or M70) is a recombinant protein with an amino acid sequence 95.4% identical to that of human FGF19. Aldafermin was engineered to retain the beneficial functions of FGF19 including improved metabolic parameters and regulation of hepatic bile acid synthesis (Zhou 2014, Luo 2014, DePaoli 2019).

The pathogenesis of NASH involves complex interactions of insulin resistance, dysregulation of lipid and triglyceride metabolism, and bile acid synthesis that leads to steatohepatitis and fibrogenic activity. Interestingly, decreased FGF19 serum levels are inversely correlated with severity of fibrosis/cirrhosis in NASH related liver disease (Alisi 2013). Moreover, patients with biopsy-proven NAFLD and NASH have decreased serum levels of FGF19 (Eren 2012, Bechmann 2013), which correlates with a reduced hepatic response to FGF19. These changes in FGF19 levels also correlate to increased hepatocyte ballooning (Schreuder 2010, Wojcik 2012).

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 CYP7A1 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 T2D or metabolic syndrome and return to normal levels after bariatric surgery in diabetic subjects (Mingrone 2012).

The potential therapeutic benefits of increased FGF19 pathway activity in metabolic disease and NASH is well documented in various animal models of disease. For example, aldafermin has been evaluated in various mouse animal models of NASH, and has demonstrated improvement in the histologic, biochemical, and fibrogenic biomarkers associated with NASH-related hepatic injury (Study 13-PD-NGM282-1007). Furthermore, aldafermin produced significant reduction in steatosis, inflammation, and ballooning in mouse models of NASH (Zhou 2017). 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 agent (Zhou 2014). 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 safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of aldafermin have been studied in a blinded, placebo-controlled, single-ascending-dose (SAD) and multiple-ascending-dose (MAD) study in normal subjects (Study 12-0101) and in subjects with T2D (Study 13-0102). Aldafermin was safe and generally well tolerated with dose-dependent mild to moderate injection-site reactions (ISRs), increases in total cholesterol and gastrointestinal (GI) symptoms (loose stools, abdominal cramping, nausea) the most common drug-related adverse events (AEs), which were observed mainly with higher doses. Dose-dependent significant reductions in serum C4 levels were also observed after administration of aldafermin in both populations supported target engagement and suppression of CYP7A1.

Aldafermin is being evaluated in an ongoing 3-Part Phase 2 trial in patients with biopsy-confirmed NASH (Study 15-0105). In the now complete Part 1, the randomized, placebo-controlled, double-blind cohort, patients with biopsy-confirmed non-cirrhotic NAS H had decreased absolute 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%

pts=patients

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 with 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 the 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. 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.

In the completed Part 2, the single-blind cohort 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 in a lesser magnitude plateauing above the ULN in the majority of subjects. The 1 mg and 3 mg dose groups show similar reductions of LFC and levels of ALT to those observed with the 3 mg dose in Part 1.

Liver histology was evaluated at 12 weeks in the 1 mg and 3 mg dosing groups in Part 2 in a total of 44 subjects. Based on the data, 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; and 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.

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

Thus, based on the favorable safety and tolerability profiles in normal volunteers as well as T2D and NASH patients as well as the potent treatment effects as measured by imaging, laboratory markers, and histology, aldafermin represents a potentially important therapeutic option for the treatment of NASH.

5.3 Clinical Studies

NGM has completed a Phase 1 clinical study in healthy volunteers and Phase 2 clinical studies in T2D, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), in addition to the interim analyses from the ongoing NASH study, to further support the clinical development of aldafermin in patients with NASH. Please refer to Section 5.2.2 and the current version of the NASH IB for additional detailed information on these studies.

5.4 Study Rationale

This is a Phase 2b study being conducted to evaluate the efficacy and safety and tolerability of aldafermin in patients with histologically confirmed NASH upon treatment for 24 weeks. The doses selected are supported by both the nonclinical and clinical data generated to date and are within the current safety margins in both monkeys and mice obtained in the GLP 26-week toxicology program. Based on efficacy of aldafermin observed NASH patients (Study 15-0105 Section 5.2.2), the selected doses of 0.3 mg, 1 mg, and 3 mg of aldafermin are expected allow a balance of optimizing biologic activity versus safety and tolerability in the studied population.

Additionally, while the efficacy obtained with 12 weeks of aldafermin treatment in Study 15-105, as measured by non-invasive assessment and liver histology, equals or exceeds the effects seen with available treatments per the current clinical guidelines and mid- and late-stage investigational agents that have been studied in Phase 2 and is encouraging, longer exposures are desirable in the further development of the molecule. Recent publications endorsed by the FDA have supported that 24 weeks is a sufficient duration to determine histologic response, depending on the mechanism of action of the drug being tested. Therefore, this study will evaluate the efficacy of aldafermin at 24 weeks.

Moreover, given that aldafermin has been shown to cause as increase serum levels of total and LDL-C cholesterol in normal volunteers (Study 12-0101) and T2D patients (Study 13-

0102), 5, 10, 20, and 40 mg of rosuvastatin will be studied in this study to further evaluate co-administration of a statin on lipid levels, safety, and tolerability in a larger population of aldafermin-treated subjects.

[redacted]

6 Study Objectives

6.1 Primary Objectives and Endpoints:

The primary objectives are to evaluate the efficacy, safety and tolerability of aldafermin based on liver histology at 24 weeks versus placebo.

1. The primary efficacy endpoint is the histologic response defined as an improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis at Week 24 compared with baseline.
2. The primary safety endpoint is frequency, severity, and timing of adverse events (AEs) and serious adverse events (SAEs). Safety and tolerability of aldafermin in subjects with NASH as a function of dose level after up to 24 weeks of treatment with aldafermin will be assessed.

6.2 Secondary Objectives and Endpoints

The secondary objectives of this study are to evaluate the effect of aldafermin 2 on pharmacokinetics, biomarkers of target engagement, fibrogenesis, and imaging.

The secondary endpoints are as follows:

1. Resolution of NASH (defined as an NAS score of 0 or 1 for inflammation and 0 for ballooning) with no worsening of fibrosis as determined by the NASH CRN criteria at Week 24 compared with baseline.
2. Subjects with improvement in liver fibrosis by > 1 stage by CRN criteria with no worsening of steatohepatitis **and** resolution of NASH with no worsening of fibrosis as determined by the NASH CRN criteria at Week 24.
3. Subjects with improved, no change, and worsening of fibrosis and NAS (total score and individual components) at 24 weeks compared to baseline
4. Subjects with the following changes in liver fat content (LFC) by MRI-PDFF at Week 24
   - Normalization for LFC (defined as < 5% absolute LFC)
   - ≥ 5% decrease in absolute LFC
   - ≥ 30% relative decrease in LFC
5. Absolute and percentage changes from Baseline to Week 24 of the following:
   - ALT, AST, total bilirubin, ALP and gamma glutamyl transpeptidase (GGT)
   - Total cholesterol, high-density lipoprotein-cholesterol (HDL-C), LDL-C, triglycerides
   - Lipoprotein particles (including ApoB)
   - Homeostasis model assessment–estimated insulin resistance (HOMA-IR)
   - N-terminal type III collagen (Pro-C3)
   - Total ELF Score and individual components (i.e., hyaluronic acid, PIIINP, TIMP-1)

- 7-alpha-hydroxy-4-cholesten-3-one (C4) and serum bile acids (total and individual bile acids)
- High-sensitivity C-reactive protein (hs-CRP)

6. Subjects with normalization of ALT and AST at Week 24

6.3 Exploratory Objectives and Endpoints:

[redacted]

7 Study Design

This is a multiple-center evaluation of aldafermin in a randomized, double-blind, placebo-controlled study, when administered for 24 weeks as a daily subcutaneous (SC) injection in patients with histologically confirmed NASH.

Approximately 152 subjects, of which no more than 15% (approximately 22 subjects) will be self-identified Asian subjects, will be randomized at approximately 40 sites in the US.

Subjects to be studied will have histologically confirmed NASH as defined by the NIH NASH CRN (Kleiner 2005) and determined by a qualified central pathologist's reading (see Appendix 1). Historical biopsy results within 6 months of the first Screening visit may be used for inclusion into the study; otherwise, a liver biopsy must be obtained for assessment. Subjects must have a NAS of at least 4, with a minimum of 1 point in each of the three components, along with the presence of either Stage 2 or 3 fibrosis. Subjects with no (Stage 0) or minimal (Stage 1) fibrosis and cirrhosis (Stage 4) will be excluded from this study. Subjects will undergo MRI during the Screening period, which must demonstrate ≥ 8% total liver fat content (LFC) by MRI-PDFF.

Subjects may be rescreened once with Medical Monitor approval. Note: certain laboratory parameters of interest (e.g., AST, TBL, creatinine clearance) may be retested at the investigators' discretion after discussing with the Medical Monitor.

On Day 1, eligible subjects will be randomized into one of the four treatment groups (0.3 mg aldafermin, 1 mg aldafermin, 3 mg aldafermin, or placebo) in a 1:1:1:1 ratio (Table 3). Randomization will be stratified by baseline stage of fibrosis (Stage 2 versus 3) on the qualification liver biopsy as determined by the Central Pathologist. Treatment assignment will be blinded to the investigational sites, study subjects, and sponsor (both Study Team and sponsor Medical Monitor or designee) throughout the study period and managed [redacted]. Study-drug self-administration instructions and training will be provided to the subjects and study-drug kits will be dispensed.

Table 3. Study Design

Study Treatment Group	Dose of aldafermin [1]	Mode of Administration	Volume of Injection [2]	Number of Subjects Planned
A	0.3 mg	Subcutaneous	0.3 mL	38
B	1 mg			38
C	3 mg			38
D	Matched-Placebo			38
Total number of Subjects Planned:				152

[1] In clinic dosing will occur on Day 1 and Study Week 2, 4, 8, 12, 18, and 24.
[2] Presented in single-use prefilled syringes.

The first dose of aldafermin (Day 1) and doses at Weeks 2, 4, 8, 12, 18, and 24 study visits will be self-administered in the clinic, with all other daily doses through Week 24 self-administered at home. Self-administration should occur daily at a similar time at home. Subjects will return to the clinic on Weeks 2, 4, 8, 12, and 18 for on-treatment assessments and to receive aldafermin study-drug kits.

LDL-C will be evaluated at Weeks 2, 4, 8, 12, and 18 in all subjects for possible increases in lipid levels associated with aldafermin administration. Rosuvastatin will be started in subjects meeting specific LDL-C level criteria at Week 2. Rosuvastatin and matched placebo are 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 by an unblinded third-party medical monitor and through the [redacted] The sponsor and study sites will be blinded to LDL-C values and the specific rosuvastatin dosing decisions as outlined in Section 9.4.14. Subjects who have not achieved an adequate response or cannot tolerate rosuvastatin as defined in Section 9.4.14 will be considered for the addition of ezetimibe as second-line lipid management therapy. Ezetimibe 10 mg tablets can be administered with or without food at the same time as rosuvastatin and aldafermin. Subjects whose LDL-C values are not adequately managed by their maximum tolerated rosuvastatin dose plus ezetimibe will be discontinued from study and an early withdrawal study visit will be completed. The follow-up visit/EOS should be scheduled for 6 weeks after the early withdrawal study visit. The specific rosuvastatin dosing algorithm is outlined in detail in Appendix 3.

Rosuvastatin or matching placebo will be dispensed at each study visit through Week 18 (statin-naïve) or Week 24 (statin-experienced). If the subject is taking statins, evaluate tolerability and continue therapy to Week 24 if statin naïve or Week 30 if statin experienced.

All subjects will return to the clinic at Week 25 for post-treatment LDL-C assessment. Subjects who have an LDL-C value of >100 mg/dL and >15 mg/dL above their Day 1 value at Week 25 will be re-assessed at Week 30. Subjects who have an LDL-C value of > 100 mg/dL and > 15 mg/dL above their Day 1 value at Week 30 will have an additional 4- week follow-up visit to confirm their LDL-C value is ≤ 100 mg/dL or ≤ 15 mg/dL above their Day 1 value.

The study visit at Week 24 will be the aldafermin EOT clinic visit and subjects will return to the clinic at Weeks 25 and 30 (or at 1 and 6 weeks after last dose of aldafermin) for a post-treatment response and EOS follow-up visits. Subjects are required to undergo MRI performed during Screening Day -28 and at Weeks 12, 24 / Early Withdrawal (EOT), and 30 (EOS) visits.

All subjects will have blood samples drawn for [redacted]

7.1 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 frequency, severity, and/or duration
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects
- Cancellation of drug development

8 Enrollment Criteria

8.1 Inclusion Criteria

Subjects who meet the following criteria may be included in the study:

1. Males and females 18 to 75 years of age (inclusive) who are able to comprehend and willing to sign an Informed Consent Form (ICF)

2. Histologically confirmed NASH diagnosis as defined by the NIH NASH CRN (see Appendix 1, Kleiner 2005) and liver biopsy criteria outlined below. A historical biopsy is acceptable if performed within the required 6-months of Screening and tissue slides are available for a qualified central pathologist reader:

   - NAS ≥ 4 with a minimum of 1 point in each component
   - Histologic evidence of Stage 2 or Stage 3 fibrosis without cirrhosis

3. Total liver fat content of ≥ 8% as measured by MRI-PDFF

4. Subjects with T2D or insulin resistance are permitted as long as diabetic medications are stable as outlined in Section 9.3 Concomitant Medications and subject attempts to maintain a stable regimen during the study period.

5. Other concomitant medications/therapies for NAFLD or NASH: requires a stable regimen for at least 3 months prior to the Screening biopsy of record and throughout the study (Refer to Section 9.3 Concomitant Medications).

6. Statin use based on the following criteria for statin-naïve or statin-experienced at Screening:

   - **Statin naïve** is defined as no administration of statins within 3 months prior to Screening.
   - **Statin experienced** is defined as administration of the following stable daily doses of approved statin therapies taken for at least 3 months prior to Screening through Week 2
     - Atorvastatin: ≤ 40 mg/day
     - Fluvastatin: ≤ 40 mg/day
     - Lovastatin: ≤ 40 mg/day (immediate release), ≤ 30 mg/day (extended release)
     - Pitavastatin: ≤ 2 mg/day
     - Pravastatin: ≤ 40 mg/day
     - Simvastatin: ≤ 40 mg/day
     - Rosuvastatin: ≤ 20 mg/day

7. The following laboratory parameters must be met at Screening:

   - Total bilirubin ≤ULN (Upper Limit of Normal) based on the Day -42 value or average of at least 2 Screening values obtained during the Screening Period, except for subjects with an established diagnosis of Gilbert's Syndrome provided the direct bilirubin level is ≤ULN and hemoglobin and reticulocyte count are normal.

   - Aspartate aminotransferase (AST) ≥ 30 IU/L and ≤ 250 IU/L in all subjects, based on the Day -42 value or average of at least 2 screening values obtained during the Screening Period

     i. Exception: subjects with an average AST ≥ 20 and < 30 IU/L will be permitted provided that at least one of the following criteria are met:

        1. Local historical biopsy within 6 months with a NAS of 4 with at least 1 point in each component and fibrosis Stage 2 or 3. Subjects with a historical biopsy will have their slides evaluated by the central reader prior to undergoing MRI-PDFF.

        2. Vibration-controlled transient elastography (VCTE® by Fibroscan) ≥ 9.5 kPa within 6 months of Screening. If no historical Fibroscan is available, it may be conducted and evaluated as per local "standard-of-care" prior to Day -28.

   - Hemoglobin A1c (HbA1c) ≤ 9.5%
   - Platelet count ≥ Lower Limit of Normal (LLN) (i.e., 140,000/mm^3)
   - Creatinine clearance ≥ 60 mL/min as calculated by Cockcroft-Gault equation
   - Alpha fetoprotein (AFP) < 100 ng/mL

8. Female subjects who are of non-childbearing potential must have had a hysterectomy, bilateral oophorectomy, medically documented ovarian failure, are documented postmenopausal, OR a follicle stimulating hormone > 40 mIU/mL

9. Female subjects of child-bearing potential must not be pregnant or nursing. Female subjects of childbearing potential are defined as women < 55 years of age with ≤ 2 years of amenorrhea and who meet both of the following criteria:

   i. A negative serum pregnancy test at Screening and urine pregnancy test prior to randomization

   ii. Correct and consistent use of one of the following methods of birth control in addition to a male partner using a condom from Screening to 30 days after the last dose of study drug:

      1. hormone containing contraceptive
      2. intrauterine device with a failure rate < 1% per year
      3. cervical cap or diaphragm with spermicidal agent
      4. tubal sterilization
      5. vasectomy in male partner

6. complete abstinence of sexual intercourse

10. Male subjects are eligible for the study if they meet the following criteria:

a. Male subjects must agree to consistently and correctly use a condom in combination with one of the following from the date of consent to 30 days after the last dose of study drug:

i. Condom with spermicide
ii. Vasectomy
iii. Complete abstinence of sexual intercourse.

AND

b. Female partner(s) must use any of the approved methods of birth control in inclusion criterion #9.

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

12. BMI ≥25 kg/m^2 for subjects self-identified of Asian descent only

8.2 Exclusion Criteria

The following will exclude potential subjects from the study:

1. Clinically significant acute or chronic liver disease of an etiology other than NASH

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

3. History or presence of cirrhosis (compensated or decompensated) as determined by histology and/or relevant medical complications and/or laboratory parameters

4. Prior or pending liver transplantation

5. Model of end-stage liver disease (MELD) score ≥ 12 (except for subjects with established Gilbert's syndrome)

6. Evidence of worsening liver disease (defined below) between Screening visits (i.e., Day -42 and Day -28) including measures of AST, ALT, TBL, and ALP:

- For subjects with AST, ALT, TBL, or ALP baseline levels > ULN on Day -28, the Day -28 assessment should not exceed an increase of 35% over the Day -42 assessment.
- For subjects with Gilbert's syndrome and a total bilirubin > ULN at the Day -42 assessment, the total bilirubin assessment at Day -28 should not exceed an increase of 50% over the Day -42 assessment.

Note: For AST, ALT, TBL, and ALP, if the percent increase in laboratory values between Day -42 and Day -28 is > 35%, repeat blood samples will be

collected at an unscheduled visit at a minimum of two weeks from the Day -28 visit. The average of Day -42 and Day -28 values will be compared to the 3rd value to determine if eligibility ranges (i.e., % agreement ≤ 35%) are met.

7. 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 (except for uncomplicated elective pacemaker procedure, 3 months post procedure will be allowed).

8. History of gastric bypass or bariatric surgery or planned procedure during the study period. Removal of a gastric balloon or lap band is permitted if surgery performed within 6 months prior to Day 1.

9. Type 1 diabetes

10. History of clinically significant unstable or untreated illness or any other major medical disorder that may interfere with patient treatment, assessment, or compliance with the protocol

11. Any contraindication or inability to obtain an MRI

12. Inability to obtain or any contraindication to liver biopsy (if a historical biopsy with viable tissue slides are not available within the required time period)

13. Screening ECG with clinically significant abnormalities or unexplained findings that the investigator feels needs further evaluation and treatment

14. Positive for HBsAg, anti-HIV, or anti-HCV plus HCV-RNA. Subjects who are anti-HCV- 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

15. History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to Screening); subjects under evaluation for malignancy are not eligible

16. Clinically-relevant drug use within 12 months of Screening. A positive drug screen 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 Sponsor Medical Monitor or designee. Marijuana is not part of the drug screen.

17. Significant alcohol intake as measured by a phosphatidylethanol (PEth) level ≥ 200 ng/mL AND positive results from AUDIT-C alcohol consumption questionnaire (Appendix 8)

18. *Criterion eliminated per protocol amendment 3*

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

20. Use of any prohibited concomitant medications as described in Section 9.3 from Day -42 to the end of the study including:

    - Investigational agents, other than aldafermin, or devices for any indication. These agents must also have been discontinued prior to Screening
    - Combination preparations of statins and other lipid-lowering agents (other than approved statin therapies listed in inclusion criterion #6)
    - Weight loss medications
    - Any medication that is contraindicated according to the rosuvastatin package insert (Appendix 6) or if subject has a known hypersensitivity to rosuvastatin product components (Section 10.1.3).
    - Any medication that is contraindicated according to the ezetimibe package insert (Appendix 7) or if subject has a known hypersensitivity to ezetimibe product components.
    - Hepatotoxic medications (Appendix 9). For subjects who have been on stable therapy with no related hepatotoxicity, the MM may be contacted to assess the medical context and eligibility of the subject. Allopurinol to treat gout is permitted provided there is no prior history of intolerability.
    - Anabolic steroids; Low levels of estrogen or testosterone as replacement therapy are allowed per Medical Monitor approval.

21. History of statin intolerance as evidenced by presence of ALT elevations, adverse event(s), or other significant side effects attributed to statins

22. Prior participation in a clinical trial of aldafermin is excluded **unless** previously enrolled into a placebo treatment group of the trial.

23. Subject with severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies

24. Participation in a study of another investigational agent:

    - NASH investigational agents: < 3 months prior to Screening if treated with active study drug or < 28 days if treated with placebo
    - All other investigational agents: within 28 days or five half-lives of the drug (whichever is longer) prior to Screening

25. Any acute or chronic condition that, in the opinion of the Investigator or the Sponsor Medical Monitor, would limit the subject's ability to complete and/or participate in this clinical study

26. Pregnancy or lactation

27. *Criterion eliminated per protocol amendment 4*

8.3 Study Treatment Discontinuation, Interruption, or Dose Reduction for an Individual Subject

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

i. Treatment emergent adverse event (TEAE) of grade 3 or 4 (CTCAE V5.0) severity
ii. Any suspected statin-related adverse event related to muscle symptoms (Appendix 5)
iii. Adverse event of muscle symptoms (e.g., myalgia, pain, or weakness) or elevated creatine kinase
iv. Laboratory value(s) indicative of drug induced liver disease (DILI)

Specific actions taken will be as follows:

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

- Any possibly or probably related Grade 3 TEAE
- Any Grade 4 or higher TEAE

Aldafermin and statin will be discontinued

ii. Any suspected statin-related adverse event (other than muscle symptoms):

Subjects will be allowed a one-time rosuvastatin dose adjustment if the subject experiences a statin-related adverse event (as determined by the PI) which would compromise the subject continuing in the study. 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 and forwarded to the Sponsor Medical Monitor or designee for approval of the rosuvastatin/placebo dose reduction. 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 and dispense 2 bottles (10 mg and placebo). If the AE resolves, rosuvastatin may be restarted. Subjects on rosuvastatin 20 mg or 40 mg will be restarted on rosuvastatin 10 mg. If the AE reoccurs following administration of the new dose of rosuvastatin, rosuvastatin/placebo should not be restarted and second-line lipid-lowering therapy (ezetimibe) will be considered with third party unblinded Medical Monitor approval. Aldafermin dosing will not be interrupted. Rosuvastatin Dose Reduction Algorithm also presented in Appendix 4.

iii. Adverse event of muscle symptoms (e.g., myalgia, pain, or weakness) or elevated creatine kinase:

A sample will be collected for assessment of CK within 48-72 hours, and CK assessment will be repeated if needed (refer to Appendix 5). At Weeks 12 and 24, the creatine kinase (CK) level will be compared to the subject's baseline level.

- If CK level is ≤ 3x baseline, subject will continue on aldafermin and over-encapsulated rosuvastatin.
- If CK level is > 3x baseline, CK will be repeated within 48 - 72 hours and aldafermin and rosuvastatin will be held:
  - If CK is ≤ 3x baseline, subject can re-start on aldafermin and rosuvastatin based on the investigator's judgement.
  - If CK is > 3x and < 5x baseline, repeat CK levels within 48 - 72 hours while aldafermin and rosuvastatin on hold.
  - If CK is ≥ 5x baseline, aldafermin and rosuvastatin will be discontinued.

Upon repeat testing for subjects previously with CK > 3x but < 5x baseline:

- If CK is ≤ 3x baseline, subject can re-start on aldafermin and rosuvastatin based on the investigator's judgement.
- If CK level is > 3x baseline, subject will discontinue aldafermin and rosuvastatin.

iv. Laboratory value(s) indicative of DILI:

a) Elevation of AST or ALT > 2x above subject-specific baseline value (calculated using the average of the Day -42, Day -28 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 > 2x baseline or TBL > 1.5x 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 b below).

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 upper limit of normal (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 < 2x ULN, discontinue if ALT or AST increases to > 5x BLM
- If BLM ≥ 2x ULN but < 5x ULN, discontinue if ALT or AST increases to > 3x BLM

- If BLM ≥ 5x ULN, discontinue if ALT or AST increases to > 2x BLM
- Discontinue if ALT or AST increase > 2x BLM AND the increase is accompanied by a concomitant increase in TBL to > 2x BLM OR the INR concomitantly increases by > 0.2
- 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 the subject lives 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.

8.4 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 Principal Investigator (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. 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.

9 Study Methods

9.1 Schedule of Study Procedures

The Schedule of Study Procedures is shown in Table 4. The visits should occur as close to the intended dates as possible. However, Weeks 2 and 4 will have a visit window of ±3 days. Weeks 8, 12, 18, and 24 will have a visit window of ±7 days. Week 25 will have a visit window of +3 days, and Week 30 will have a visit window of ±7 days. Subjects attending any visits out of windows from Day 1 to Week 24/Early Withdrawal (EOT) visit should be brought back into compliance with the overall study-visit schedule as soon as possible thereafter. Subjects will return to the clinic at Week 25 and Week 30 (1 and 6 weeks after last dose) for a post-treatment response and EOS follow-up visits, respectively.

Subjects who have an LDL-C value of > 100 mg/dL and > 15 mg/dL above their Day 1 value at Week 25 will need to be re-assessed at Week 30. Subjects who have an LDL-C value of > 100 mg/dL and > 15 mg/dL above their Day 1 value at Week 30 will have am additional 4- week follow up visit to confirm their LDL-C value is ≤ 100 mg/dL or ≤ 15 mg/dL above their Day 1 value. Subjects will continue to be followed until their LDL-C value is ≤ 100 mg/dL or ≤ 15 mg/dL above their Day 1 value. Subjects whose LDL-C values are not adequately managed by their maximum tolerated rosuvastatin dose plus ezetimibe will be discontinued from study and an early withdrawal study visit will be completed. The follow up/EOS visit should be scheduled for 6 weeks after the early withdrawal study visit.

Table 4. Schedule of Study Procedures

Study Procedure	(Screening) [b] D –42	D -28 to -1	D1	W2	W4	W8	W12	W18	W 24/EW (EOT)	W25 (Post-Tx)	W30 (EOS)
Visit Window (Days) [a]				± 3	± 3	± 7	± 7	± 7	± 7	+3	± 7
Informed consent	X										
Demographics	X										
Medical history	X										
Smoking History	X										
Inclusion/exclusion criteria	X		X								
Height	X										
Body weight, BMI, waist circumference	X		X				X		X		X
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alcohol Consumption [c]	X										
12-lead ECG	X		X				X		X		X
Vital signs	X		X	X	X	X	X	X	X		X
Central read of locally performed historical biopsy slides, if available	X										
MRI-PDFF [d]		X					X		X		X
Liver biopsy [e]		X							X		
[redacted]	X										
[redacted]			X								
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events [f]	X	X	X	X	X	X	X	X	X	X	X
LISSA evaluations			X	X	X	X	X	X	X		
Chemistry (fasted ≥ 10 hrs)	X [h]	X [h]	X [g h]	X [g]	X [g]	X [g]	X [g h]	X [g]	X [g h]	X [g]	X [g]
Complete blood count	X		X	X	X	X	X	X	X		X
HbA1c	X		X				X		X		X
Insulin level and HOMA-IR	X		X				X		X		X
[redacted]			[redacted]				[redacted]		[redacted]		[redacted]
International Normalized Ratio	X		X	X	X	X	X	X	X	X	X
Alpha fetoprotein	X										
Pregnancy test [i]	X	X	X		X		X		X		X
Hepatitis and HIV screen	X										
Urinalysis	X		X				X		X		X
Urine drug screen [j]	X		X				X		X		

PEth alcohol screen	X										
Fasting lipid panel	X		X [g]	X [g]	X [g]	X [g]	X [g]	X [g]	X [g]	X [g]	X [g]
Lipoprotein particles [redacted]			X	X	X	X	X	X	X		X
Lipase			X	X	X	X	X	X	X	X	X
C4 and serum bile acids [k]			X [k]	X	X	X	X	X	X [k]	X	X
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-drug antibodies & NAb			X	X	X	X	X	X	X	X	X
ELF Panel/ PRO-C3			X				X		X	X	X
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic biomarker sample, including PNPLA3 [n]			X								
aldafermin /matched placebo in-clinic self-administration [o]			X	X	X	X	X	X	X		
Dispense aldafermin /matched placebo			X	X	X	X	X	X			
Dispense rosuvastatin [p]				X	X	X	X	X	X		
Medication compliance				X	X	X	X	X	X		X [q]
Lipid-Lowering Therapy Assessment				X	X	X	X	X	X	X [q]	X [r]

BMI = body mass index; C4 = 7-alpha-hydroxy-4-cholesten-3-one; D = Day; ECG = electrocardiogram; ELF = enhanced liver fibrosis; EOS = End of Study; EOT = End of Treatment; EW = Early Withdrawal; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment–estimated insulin resistance; hr. = hour; [redacted]; LISSA = local injection-site symptom assessment; MRI = magnetic resonance imaging; PEth = phosphatidylethanol, PRO-C3 = N-terminal Type III collagen; PK = pharmacokinetic; [redacted]; Tx = treatment; W = week

[a] Weeks 2 and 4 will have a visit window of ±3 days. Weeks 8, 12, 18, and 24 will have a visit window of ±7 days. Week 25 will have a visit window of +3 days. Week 30 will have a visit window of ±7 days.

[b] There must be a minimum of 14 days (2 weeks) between Day -42 and Day -28 Screening Visits to allow for adequate separation of baseline liver function tests. If baseline 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 -28 visit and the repeat liver function tests, and Screening Day -28 to -1 will be extended an additional 14 days (2 weeks). Subjects who have completed all Screening assessments, including liver biopsy, and are eligible to participate in the study may have their Screening window extended with Sponsor approval for up to 2 additional weeks if the delay is due to scheduling conflicts.

[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 (refer to exclusion criterion #19)

[d] Screening Day -28 MRI-PDFF (includes [redacted]) will serve as baseline for efficacy endpoint analysis. The Screening MRI result is valid for up to 8 weeks and may be used for a subject who is re-screened within that time frame. [redacted]

[e] All subjects are required to have a liver biopsy result at Screening and additional liver biopsy at Week 24. A Screening liver biopsy will be performed only in subjects who do not have a historical biopsy available within 6 months of Screening.

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

[g] Serum chemistry will include ALT, AST, ALP, bicarbonate, bilirubin (direct and total), BUN, calcium, chloride, creatinine, CK, GGT, glucose, HDL, LDL, lipase, 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.

[h] Creatine Kinase will be collected at Day -42, Day 1 and Week 12, and Week 24.

[i] A serum pregnancy test will be performed on all female subjects of childbearing potential at Day -42, -28 Screening visits and Day 1 (pre-dose), A urine pregnancy test will be performed on all female subjects of childbearing potential at Weeks 4, 12, 24, and 30. If the urine pregnancy test is positive, a serum pregnancy test will be performed to confirm

results.

[j] Urine drug and alcohol screens may be repeated during treatment for subjects suspected of excessive alcohol intake or to rule out association with a safety event

[k] C4 and bile acid testing will be collected at Day 1 and Weeks 2, 4, 8, 12, 18, 24, 25 and 30. In addition, for subjects participating in the optional PK sub-study, additional C4 will be tested at the same timepoints as the PK blood sample collections: Day 1 and Week 24 at pre-dose, and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours.

[l] PK blood samples will be collected in all subjects before dosing themselves in the clinic (pre-dose) on Day 1, and Weeks 2, 4, 8, 12, 18, 24, and 25. On Day 1, and Week 24, a 2-hour post-dose sample will be collected. Week 24 PK testing should be done at the 2-hour post time point after the subject has injected their last dose of aldafermin /matched placebo.

[m] 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 24 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 8-hour time points is ±5 minutes. The window for sample collection for the 12- through 24-hour time points is ±30 minutes

[n] A blood sample for genetic biomarker testing will be collected predose on Day 1

[o] Subjects will be instructed to self-inject aldafermin daily at the same time each day in the abdomen. Subjects will not self-inject aldafermin at home on clinic visit.

[p] Rosuvastatin will be dispensed at Weeks 2, 4, 8, 12, and 18 visits and subjects will be provided further dosing instruction based on their LDL-C levels and whether they are statin-naïve versus statin experienced. Subjects on a statin at screening will switch from their current statin to 5 mg (Asian subjects) or 10 mg (non-Asian subjects) rosuvastatin at Week 2 and will be dispensed additional rosuvastatin at Week 24 and continue through Week 30.

[q] Medication compliance will be assessed at Week 30 only in subjects who were statin experienced at Baseline.

[r] Subjects who have an LDL-C value of > 100 mg/dL and > 15 mg/dL above their Day 1 value at Week 25 will need to be re-assessed at Week 30. Subjects who have an LDL-C value of > 100 mg/dL and > 15 mg/dL above their Day 1 value at Week 30 will have a 4-week follow-up visit to confirm their LDL-C value is ≤ 100 mg/dL or ≤ 15 mg/dL above their Day 1 value.

9.2 Study Visit Procedures

9.2.1 Day –42 (Screening) Procedures

Subjects will report to clinic fasted. The Screening procedures should be all be completed within 42 days from consent in order to randomize the subject.

- Obtain informed consent
- Collect demographic data
- Ascertain medical history
- Collect smoking history
- Assess inclusion/exclusion criteria
- Measure height
- Measure body weight, BMI, waist circumference
- [redacted]
- Complete AUDIT-C alcohol consumption questionnaire
- 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)
- Register screened subject [redacted]
- 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
    - CBC
    - HbA1c
    - Insulin level
    - HOMA-IR calculation
    - INR
    - Alfa fetoprotein (AFP)
    - Serum pregnancy test (all female subjects of childbearing potential)
    - Hepatitis and HIV screen
    - PEth alcohol screen
    - Lipid panel
- Obtain urine for 10-hour fasted laboratory sample collection for:
    - Urinalysis
    - Urine drug screen

- Subjects with a local historical biopsy will have their slides evaluated and read by the central pathologists to ensure eligibility prior to undergoing MRI-PDFF

9.2.2 Day –28 to Day -1 (Screening) Procedures

Subjects will report to clinic fasted. Day -28 Screening procedures must be completed no sooner than 14 days (2 weeks) +3 days after the Day -42 Screening visit to allow for adequate separation of liver function tests.

- Obtain blood for 10-hour fasted laboratory sample collection for:
  - Chemistry
- Obtain urine for 10-hour fasted laboratory sample collection for:
  - Pre-dose serum pregnancy in all females of childbearing potential
- Obtain an MRI-PDFF assessment (preferably prior to any histologic evaluation unless a historical biopsy is available)
- Obtain viable tissue slides from eligible historical liver biopsy or undergo a liver biopsy procedure to obtain new tissue
- Record concomitant medications
- Record AEs

9.2.3 Day 1 Procedures

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

<u>Pre-dose:</u>

- Reassess inclusion/exclusion criteria
- Measure body weight, BMI, and waist circumference
- [redacted]
- 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)
- Randomize subject [redacted] for aldafermin/matched placebo study-drug kit assignment
- 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
  - C4 and serum bile acids
  - PK (pre-dose)
  - Anti-drug antibodies (ADAs)
  - Neutralizing antibodies (NAbs)
  - ELF panel
  - Pro-C3
  - [redacted]
  - [redacted]
  - [redacted]
  - Blood sample (pre-dose) for genetic biomarker testing
  - pre-dose serum pregnancy in all females of childbearing potential
- Obtain urine for 10-hour fasted laboratory sample collection for:
  - urinalysis
  - urine drug screen

In-clinic dosing and assessments:

- Dispense initial aldafermin/matched placebo study-drug kit and home diary
- Provide aldafermin/matched placebo study-drug self-administration training.
- Oversee subject's aldafermin/matched placebo study-drug self-administration.
- Perform local injection-site symptom assessment (LISSA) evaluation.

Before clinic discharge:

- Obtain 2-hour post-dose PK sample

- Remind subject to bring study-drug kit/diary and to not self-inject aldafermin/matched placebo on clinic visit days
- Schedule Week 2 visit

For Optional PK Sub-study Subjects:

For those subjects participating in the optional PK sub-study, PK samples will be collected before subjects dose themselves in the clinic and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. The 24-hour post-dose sample will be collected prior to dosing themselves with aldafermin/matched placebo on Day 2. Additional samples will be collected for C4 testing at the same timepoints as the PK blood sample collections. The window for sample collection for the pre-dose through 8-hour time points is ±5 minutes. The window for sample collection for the 12- through 24-hour time points is ±30 minutes.

9.2.4 Week 2 Procedures

Subjects will report to clinic fasted and not dosed with aldafermin/matched placebo. 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
  - CBC
  - INR
  - Lipid panel
  - Lipoprotein particles
  - Lipase
  - C4 and serum bile acids
  - PK (pre-dose)
  - ADAs
  - NAbs
- [redacted]
- [redacted]
- [redacted]

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

In-clinic dosing and dispensing:

- Collect old aldafermin/matched placebo study-drug kit/diary and conduct reconciliation
- Dispense new aldafermin/matched placebo study-drug kit/diary
- Dispense rosuvastatin medication/diary
- Oversee subject's aldafermin/matched placebo study-drug self-administration (from new kit).
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study-drug kit/diary and to not self-inject aldafermin/matched placebo on clinic visit days
- Schedule Week 4 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 9.4.14).

9.2.5 Week 4 Procedures

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

Pre-dose:

- [redacted]
- 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
    - CBC
    - INR
    - Lipid panel
    - Lipoprotein particles

- Lipase
- C4 and serum bile acids
- PK (pre-dose)
- ADAs
- NAbs
- [redacted]
- [redacted]
- [redacted]

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

- Obtain urine for 10-hour fasted laboratory sample collection for:
  - Pre-dose urine pregnancy in all females of childbearing potential

In-clinic dosing and dispensing:

- Collect old aldafermin/matched placebo study-drug kit/diary and conduct reconciliation
- Dispense new aldafermin/matched placebo study-drug kit/diary
- Dispense rosuvastatin medication/diary
- Oversee subject's aldafermin/matched placebo study-drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study-drug kit/diary and to not self-inject aldafermin/matched placebo on clinic visit days
- Schedule Week 8 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 9.4.14).

9.2.6 Week 8 Procedures

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

Pre-dose:

- [redacted]

- 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
    - CBC
    - INR
    - Lipid panel
    - Lipoprotein particles
    - Lipase
    - C4 and serum bile acids
    - PK (pre-dose)
    - ADAs
    - NAbs
    - [redacted]
    - [redacted]
    - [redacted]

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

<u>In-clinic dosing and dispensing:</u>

- Collect old aldafermin/matched placebo study-drug kit/diary and conduct reconciliation.
- Dispense new aldafermin/matched placebo study-drug kit/diary
- Dispense rosuvastatin medication/diary
- Oversee subject's aldafermin/matched placebo study-drug self-administration (from new kit)
- Perform LISSA evaluation

<u>Before clinic discharge</u>:

- Remind subject to bring study-drug kit/diary and to not self-inject aldafermin/matched placebo 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 9.4.14).

9.2.7 Week 12 Procedures

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

Pre-dose:

- Measure body weight, BMI, and waist circumference
- [redacted]
- 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)
- Obtain an MRI-PDFF assessment
- 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
    - CBC
    - HbA1c
    - Insulin level
    - HOMA-IR calculation
    - [redacted]
    - INR
    - Lipid panel
    - Lipoprotein particles
    - Lipase
    - C4 and serum bile acids
    - PK (pre-dose)
    - ADAs
    - NAbs

- ELF panel
- Pro-C3
- [redacted]
- [redacted]
- [redacted]

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

- Obtain urine for 10-hour fasted laboratory sample collection for:
  - Pre-dose urine pregnancy in all females of childbearing potential
  - Urinalysis
  - Urine drug screen

In-clinic dosing and dispensing:

- Collect old aldafermin/matched placebo study-drug kit/diary and conduct reconciliation
- Dispense new aldafermin/matched placebo study-drug kit/diary
- Dispense rosuvastatin medication/diary
- Oversee subject's aldafermin/matched placebo study-drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- Remind subject to bring study-drug kit/diary and to not self-inject aldafermin/matched placebo 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 9.4.14).

9.2.8 Week 18 Procedures

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

Pre-dose:

- [redacted]
- 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 and serum bile acids
    - PK (pre-dose)
    - ADAs
    - NAbs
    - [redacted]
    - [redacted]
    - [redacted]

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

<u>In-clinic dosing and dispensing:</u>

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

- Dispense new rosuvastatin medication/diary
- Oversee subject's aldafermin/matched placebo study-drug self-administration (from new kit)
- Perform LISSA evaluation

Before clinic discharge:

- If subject is taking statins, evaluate tolerability and continue therapy to Week 24 for statin naïve or Week 30 for statin experienced
- Record new and/or changes to AEs after aldafermin/matched placebo dosing
- Remind subject to bring study-drug kit/diary and to not self-inject aldafermin/matched placebo on clinic visit days
- Schedule Week 24 (End of Treatment) 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 9.4.14).

9.2.9 Week 24 / Early Withdrawal (End of Treatment) Procedures

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

The following procedures will be performed at the Week 24/Early Withdrawal visit:

Pre-dose:

- Measure body weight, BMI, and waist circumference
- [redacted]
- 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)
- Obtain an MRI-PDFF assessment.
- 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
    - Insulin level
    - HOMA-IR calculation

- [redacted]
- INR
- Lipid panel
- Lipoprotein particles
- Lipase
- C4 and serum bile acids
- PK (pre-dose) collect for all subjects other than those participating in the Optional PK sub-study
- ADAs
- NAbs
- ELF panel
- Pro-C3

- [redacted]
- [redacted]
- [redacted]

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

Obtain 10-hour fasted clinical laboratory samples for the following:

- Urine pregnancy test (all female subjects of childbearing potential)
- Urinalysis
- Urine drug screen

In-clinic dosing:

- Collect old aldafermin/matched placebo study-drug kit/diary and conduct reconciliation
- Collect old rosuvastatin bottle and conduct reconciliation
- Dispense new rosuvastatin study-drug/diary (only for subjects who were statin experienced at Baseline)
- Oversee subject's aldafermin/matched placebo study-drug self-administration (from old kit) (not applicable for Early Withdrawal subjects)
- Perform LISSA evaluation

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.)

- Obtain 2-hour post-dose PK blood sample
- Schedule subject for Week 25 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 9.4.14).

For Optional PK Sub-study Subjects:

For those subjects participating in the optional PK sub-study, PK samples will be collected pre-dose before subjects dose themselves in the clinic and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours. The 24-hour post-dose sample will be collected prior to dosing themselves with aldafermin/matched placebo on Day 2. Additional samples will be collected for C4 testing at the same timepoints as the PK blood sample collections. The window for sample collection for the pre-dose through 8-hour time points is ±5 minutes. The window for sample collection for the 12- through 24-hour time points is ±30 minutes.

9.2.10 Week 25 (Post-Treatment Response) Procedures

Subjects will report to this visit fasted. The following procedures will be performed at the Week 25 visit:

- [redacted]
- Record concomitant medications
- Record new and/or changes to AEs
- Obtain 10-hour fasted clinical laboratory samples for the following:
  - Chemistry
  - INR
  - Lipid panel
  - Lipase
  - C4 and serum bile acids
  - PK sample
  - ADAs
  - NAbs
  - ELF panel

- Pro-C3
- [redacted]
- [redacted]
- [redacted]

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

Before clinic discharge:

- Schedule Week 30 (End of Study) visit

Lipid-Monitoring Assessment:

The third-party Medical Monitor will evaluate LDL-C (refer to Section 9.4.14). Subjects who have an LDL-C value of > 100 mg/dL, and > 15 mg/dL above their Day 1 value at Week 25 will be re-assessed at Week 30.

9.2.11 Week 30 (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
- [redacted]
- 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)
- Obtain an MRI-PDFF assessment
- 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

- PK Sample
- Lipid panel
- Lipoprotein particles
- Lipase
- C4 and serum bile acids
- ADAs
- NAbs
- ELF panel
- Pro-C3
- [redacted]
- [redacted]
- [redacted]

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

- Urine pregnancy test (all female subjects of childbearing potential).
- Obtain urine sample for urinalysis
- 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)***

Lipid-Monitoring Assessment:

For subjects who were identified at Week 25 as needing re-assessment of LDL-C at Week 30, 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 to confirm their LDL-C value has returned ≤ 100 mg/dL or ≤ 15 mg/dL above their Day 1 value (refer to Section 9.4.14).

9.2.12 Lipid Monitoring Assessment 4 Week Follow up Visit Procedures

This visit will be performed 4 weeks after the EOS 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:
    - Chemistry
    - Lipid panel

9.2.13 Monitoring of Anti-Drug Antibody Response

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

9.3 Concomitant Medications

Any medication taken at least once within 42 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 period.

9.3.1 Prohibited Medications

- Investigational agents, other than aldafermin/matched placebo, or devices for any indication. These agents must also have been discontinued prior to Screening per exclusion criterion #24.
- Any other lipid lowering agents or combination preparation of statins (other than ezetimibe when used as a second-line lipid management therapy per Section 9.4.14, or one of the approved statin therapies listed in inclusion criterion #6) including:
    - Cholestyramine, colesevelam, PCSK9 inhibitors (evolocumab or alirocumab), colestid, niacin, fibrates, fenofibrates, fish oil from Day -42 onward through the end of the study.
- Agents used for the treatment of any condition listed in the exclusionary enrollment criteria (see Section 8.2) from Day -42 onward through the end of the study.
- Weight loss medications, including orlistat, phentermine, topiramate, qsymia, lorcaserin hydrochloride, naltrexone hydrochloride, liraglutide, benzphentamine, diethylpropion, phendimetrazine from Day -42 onward through the end of the study.
- Contraindicated medications according to the rosuvastatin package insert, Appendix 6 including; cyclosporine, gemfibrozil, protease inhibitors (atazanavir, ritonavir, lopinavir, simeprevir), coumarin anticoagulants, fenofibrates, niacin, colchicine, from Day -42 onward through the end of the study.

- Contraindicated medications according to the ezetimibe package insert, Appendix 7 including; cyclosporine, fenofibrate, cholestyramine, coumarin anticoagulants, from Day -42 onward through the end of the study.
- Known hepatotoxic agents (refer to Appendix 9) For subjects who have been on stable therapy with no related hepatotoxicity, the MM may be contacted to assess the medical context and eligibility of the subject, from Day -42 onward through the end of the study.
- This list of prohibited medications along with Appendix 6, Appendix 7, and Appendix 9 are not an inclusive list. Investigator judgement must be used to justify initiating any study medication during the study. Use of allopurinol to treat gout is allowed if there is no history of intolerance.

9.3.2 Restricted Concomitant Medications/Treatments:

- Statin Therapies: For statin experienced subjects only, the following daily dose of approved statin therapies are allowed if dosing is stable at least 3 months prior to Screening through Week 2:
  - Atorvastatin: ≤ 40 mg/day
  - Fluvastatin: ≤ 40 mg/day
  - Lovastatin: ≤ 40 mg/day (immediate release), ≤ 30 mg/day (extended release)
  - Pitavastatin: ≤ 2 mg/day
  - Pravastatin: ≤ 40 mg/day
  - Simvastatin: ≤ 40 mg/day
  - Rosuvastatin: ≤ 20 mg/day
- Other therapies for NAFLD or NASH require a stable regimen for at least 3 months prior to the Screening biopsy of record and throughout the study including:
  - Standard vitamin supplements
  - Vitamin E (>400 IU)
  - Pentoxifylline
- Diabetic medications:
  - Insulin: require stable dosing, defined as reasonable dose adjustments to maintain glucose control, for at least 3 months prior to Day 1
  - All other diabetic medications (except liraglutide which is prohibited): require a stable dose for at least 3 months prior to Day 1. The investigator may adjust diabetic medications as warranted based on clinical response/glucose control parameters throughout the study.

- Antibiotics (not listed in Appendix 9) use will be at the discretion of the principal investigator
- Procedural Medications including anti-anxiety medication for MRI scan, anesthetic or sedation (e.g., a benzodiazepine) for liver biopsy or for other minor (outpatient) procedures will be used at the discretion of the principal investigator
- Anabolic steroids; low levels of estrogen or testosterone as replacement therapies are allowed.

9.4 Clinical Evaluations

9.4.1 Alcohol Consumption

9.4.1.1 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 (see Appendix 8). 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.

9.4.1.2 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 enrollment 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.

9.4.1.3 PEth Screen

Subjects that present with a significant alcohol intake as measured by a phosphatidylethanol (PEth) level ≥ 200 ng/mL AND also have a positive AUDIT-C score (Section 9.4.1.1) will be excluded from the study at Screening.

9.4.2 Liver Biopsy

Subjects who meet the Screening criteria of an available liver biopsy tissue specimen within 6 months of Screening will not be required to undergo a new liver biopsy. For subjects who have participated in a prior study involving an investigational agent for NASH, the prior liver biopsy obtained within 6 months may be used only if the subject was treated with placebo. All other subjects will be required to undergo a liver biopsy per the study site's local standard-of-care procedure during the Screening period and prior to randomization.
Sites should not perform a local reporting of the NAS or fibrosis score at either Screening or

Week 24 to the site in order to maintain the blinding of the primary endpoint. Tissue from all subjects will be collected, prepped and sent to the Central Study Pathologist for review for the absence/presence of NASH as defined in the Biopsy Manual. Liver biopsies with histologically confirmed NASH will be further assessed using the NAS established and validated by the NASH CRN (see Appendix 1). Liver biopsies will be assessed for degree of steatosis (0 – 3), lobular inflammation (0 – 3), hepatocellular ballooning (0 – 2), and fibrosis (0 – 4). The first three components will be added together to determine the NAS that ranges from 0 to 8. Liver biopsies with an NAS of < 4 will be considered exclusionary. Subjects with liver biopsies with Stage 4 fibrosis, consistent with cirrhosis, will be excluded from this study. The Week 24 biopsy should be obtained ≤ 7 days before last dose of aldafermin/matched placebo.

9.4.3 Magnetic Resonance Imaging (MRI)

All enrolled subjects will have a Baseline (from the Screening result) and EOT MRI of the liver to evaluate [redacted] liver fat. Subjects will have an MRI performed at Screening Day -28 and at Weeks 12, 24 (EOT), and 30 (EOS). MRI-PDFF will be reported on all MRI imaging scans. Scans should be performed at high field strength (3T preferred, 1.5T acceptable), without the administration of oral or intravenous contrast material. MRI examinations will include a six-echo gradient recalled [redacted]

The initial study MRI examination will be performed during the Screening period prior to randomization. An MRI-PDFF value of ≥ 8% at Screening as assessed by the central radiology core is one of the inclusion criteria for the study. Therefore, for subjects who require a liver biopsy as part of the trial (for whom no recent liver biopsy is available), it is recommended that the liver biopsy be scheduled no sooner than 7 business days after (electronic) transmission of the screening MRI examination to the central radiology core to allow adequate time for processing and reporting of the result. The screening MRI-PDFF results will be reported to the individual site no more than 5 business days after the MRI examination is received. The Screening MRI result is valid for up to 8 weeks and may be used for a subject who is re-screened within that time frame. None of the on treatment or post treatment MRI results (other than incidental findings) will be provided to the sites. Week 24/EW/EOT MRI-PDFF should be performed before the last dose of aldafermin/matched placebo.

For both Screening and EOT/Early Withdrawal MRI examinations, subjects should consume nothing by mouth (NPO) for 4 hours prior to their MRI appointment. Medications and small amounts of water are acceptable.

Prior to MRI, all subjects should undergo safety assessment per institutional protocols and per the guidelines of the local Institutional Review Board. Subjects should be questioned regarding claustrophobia, pregnancy or potential pregnancy, size or weight exceeding the capabilities of the MRI system, metal implants, and other potential safety issues.

Detailed instructions for MRI procedures and provision of examination to a central reader will be presented in a separate MRI Manual.

9.4.4 Pharmacokinetic Blood Sample Collection and Processing

In all subjects, blood samples for PK analysis of aldafermin levels will be collected before dosing at study visits at [redacted]

The [redacted]

The window for sample collection for the pre-dose and 2-hour time points is ±5 minutes.

[redacted] at the Day 1 and Week 24 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 0.5-hr through 8-hour time points is ±5 minutes. The window for sample collection for the 12- through 24-hour time points is ±30 minutes.

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

9.4.5 C4 and Bile Acid Testing

C4 and bile acid testing will be collected at Day 1 and Weeks 2, 4, 8, 12, 18, 24, 25, and 30. In addition, for subjects participating in the optional PK sub-study, additional C4 will be tested at the same timepoints as the PK blood sample collections: Day 1 and Week 24 at pre-dose, and post-dose at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours.

9.4.6 Biomarkers

Blood samples will be collected for ELF score, Pro-C3, [redacted] genetic biomarker including PNPLA3 will be collected as outlined in Table 4.

9.4.7 Insulin/HOMA-IR

Insulin level and HOMA-IR will be evaluated at Day -42 (Screening), Day 1, Week 12, Week 24 and Week 30. Subjects will have fasted 10 hours.

9.4.8 Lipoprotein Particles

Lipoprotein particles, [redacted] will be tested on scheduled visits on Day 1 through Week 24 and on Week 30. Subjects will have fasted 10 hours (Table 4).

9.4.9 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be collected as outlined in Table 4. 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.

Serum chemistry will include ALT, AST, ALP, bicarbonate, bilirubin (direct and total), BUN, calcium, chloride, creatinine, CK, GGT, glucose, HDL, LDL, lipase, phosphate, potassium, proteins (albumin, total protein), sodium, total cholesterol, and TG. Creatine Kinase will be collected at Day -42, Day 1, Weeks 12 and 24. Samples for analysis of ADAs, NAbs, and exploratory biomarkers will be collected. A blood sample for genetic biomarker testing will be collected pre-dose on Day 1. 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 -42 and Day -28 to assess whether there is worsening of liver disease during screening according to exclusion criterion #6. An unscheduled visit may be necessary to confirm eligibility if the difference exceeds 35%. If performed, unscheduled visit results will be compared to the average of Day -42 and Day -28 results to determine if eligibility ranges (i.e., % agreement $\leq$ 35%) are met.

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

9.4.10 12-Lead Electrocardiograms

12-lead ECGs will be performed after the subject has been supine for at least 5 minutes, and as outlined in Table 4.

9.4.11 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 Table 4. Seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes.

9.4.12 Physical Examinations and RUQ Pain Assessment

[redacted]

Subjects will be weighed, BMI calculated, and waist circumference measured at Screening Day -42, Day 1, and Weeks 12, 24, and 30. Formal instructions for recording weight and measuring waist circumference will be provided to sites.

9.4.13 Local Injection-Site Symptom Assessments (LISSA)

Injection-site evaluation will be made and documented by the PI or clinic staff using a LISSA (Appendix 2).

LISSA evaluations are to be performed at each clinic visit from Day 1 through Week 24.

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 2007 FDA Toxicity Grading Scale (Appendix 2) 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.

9.4.14 Lipid-Lowering Therapy Assessment

LDL-C will be evaluated at all study visits for possible increases in lipid levels associated with aldafermin administration. Rosuvastatin will be started in subjects meeting specific LDL-C level criteria at Week 2. Rosuvastatin and matched placebo are over-encapsulated in bottles of 35 capsules (Section 10.4.2). Initiation and ongoing dose adjustments of rosuvastatin will be managed by an unblinded third-party Medical Monitor and through the [redacted]. Lipid levels will be blinded to the sponsor and site. Initiation and dose adjustments will be determined by the lipid levels collected at Weeks 2, 4, 8, 12, and 18. LDL-C samples will be analyzed and reported to the third-party Medical Monitor. Bottles of rosuvastatin and/or matching placebo will be dispensed at each study visit through Week 18 (statin naïve) or Week 24 (statin experienced) as instructed through [redacted]. The subject will be sent home from their clinic visit with the IVRS assigned bottle(s) and instructed to refrain from dosing until told from which bottle or bottles to dose by the study site. The third-party Medical Monitor will review the LDL-C level and assign the dose of rosuvastatin [redacted] based on the dosing algorithm (Appendix 3). The site will subsequently communicate to the subject the assigned bottle(s) and dosing should be immediately initiated.

Subjects who have not responded adequately to rosuvastatin (defined as >100 mg/dL and > 15 mg/dL above their Day1 LDL-C level), and who are currently receiving their maximum tolerated rosuvastatin dose, will be considered for additional lipid-lowering therapy (ezetimibe). The third-party Medical Monitor will contact the site regarding any subject meeting this criterion. Ezetimibe will be prescribed and taken as second-line treatment per investigator judgement and approval from the Sponsor Medical Monitor or designee. Rosuvastatin therapy should be continued as assigned. Ezetimibe should be used in accordance with the FDA-approved package insert (Appendix 7).The subjects should also continue aldafermin/matched placebo through EOT as assigned.

Subjects whose LDL-C values are still not adequately managed, (defined as > 100 mg/dL and > 15 mg/dL above their Day 1 LDL-C value) and are currently receiving their maximum tolerated rosuvastatin dose plus ezetimibe, will be discontinued from the study and an early withdrawal study visit completed. The follow up/EOS visit should be scheduled for 6 weeks after the early withdrawal study visit. Refer to Appendix 4, Rosuvastatin Dose Reduction Algorithm and Appendix 5, Adverse Event of Statin-Related Muscle Pain or Creatine Kinase (CK) Algorithm.

9.4.15 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.

10 Study Drug

10.1 Clinical Supplies

10.1.1 Aldafermin

Aldafermin is formulated in [redacted]

Aldafermin is provided as a sterile solution for injection in a single-use pre-filled syringe for SC administration at doses of 0.3 mg, 1 mg, and 3 mg. The drug product is manufactured for NGM under current Good Manufacturing Practice regulations at [redacted]

10.1.2 Aldafermin-matched Placebo

Aldafermin placebo is formulated in aqueous isosmotic buffer solution [redacted]

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 current Good Manufacturing Practice regulations [redacted]

10.1.3 Rosuvastatin

Commercial rosuvastatin tablets will be over-encapsulated and will be supplied as 5 mg, 10 mg, 20 mg (2 x 10 mg tablets over-encapsulated into 1 capsule), or 40 mg strengths in 35-count bottles. Inactive ingredient microcrystalline cellulose will be used to backfill overencapsulated rosuvastatin calcium tablets. Placebo capsules for rosuvastatin calcium contains only microcrystalline cellulose and will be supplied in 35- 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 the study pharmacy manual for details.

10.2 Study-Drug Accountability

The PI is responsible for ensuring that a current record of inventory/drug accountability (aldafermin/matched 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.

10.3 Study-Drug Storage

Aldafermin/matched 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/matched 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., their 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 take care in keeping both study drugs out of the reach of children and other family members who may have access to the storage location.

10.4 Dose Preparation and Administration

10.4.1 Aldafermin

Subjects will be instructed to dose with aldafermin/matched placebo at home at a similar time each day. Study-drug/placebo syringes will be equilibrated to room temperature prior to use. Study-drug/placebo 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 on-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.

10.4.2 Rosuvastatin

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.

10.5 Removal of Study Blind

Breaking of any blind will be available to the PI through [redacted]. The subject's treatment assignment will be available to the PI in the event of a medical emergency or an AE that necessitated 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] and an automated notification will be sent to the Sponsor.

11 Adverse Events

11.1 Definition and Grading Intensity of Adverse Events

An AE is defined as any untoward medical occurrence in a subject of clinical investigational participation administered a pharmaceutical product, whether or not considered drug related. A TEAE is an AE that is reported after a dose of study drug.

AEs include the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant diseases or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a subject 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, regardless of how identified (e.g., volunteered, elicited, noted on physical examination), will be recorded throughout the study (i.e., from Screening until Follow-up).

Subjects will be followed for resolution of AEs, by querying the subjects for an ongoing AE until resolved 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 on the subject's CRF.

Any pregnancy diagnosed during the study must be reported immediately to the PI 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 medication may have interfered with the effectiveness of a contraceptive medication or method.

The PI will rate the severity of AEs using the CTCAE v5 to grade the severity. Each CTCAE v5 term is a Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT). The CTCAE displays Grades 1–5 with unique clinical descriptions of severity for each AE. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and, therefore, is not an option.

11.2 Criteria for Determining Relationship to Study Drug

The PI will make a blinded determination of the relationship of the AE to aldafermin/matched placebo, rosuvastatin/matched placebo or ezetimibe (as applicable). All determinations of relationship will be made using a four-category system (not related, possible, probable, or definite) according to the following guidelines:

- **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

11.3 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., places the subject, in the view of the PI, at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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 Principal Investigator. These subjects will be managed as outlined in Section 9.4.14 of the protocol.

11.4 Cardiovascular Adjudication

An external independent Cardiovascular Adjudication Committee (CAC) will adjudicate serious adverse events (SAEs). The CAC members will be independent of the Sponsor, and the clinical study sites and Investigators. The blinded medical review of known or suspected cardiac events will primarily focus on CV death, myocardial infarction, cerebrovascular accident (stroke), and hospitalization for heart failure. The event definitions and adjudication process are described in a CAC Charter.

Sites may be asked to provide additional source documentation relevant to any event reported to the CAC.

12 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 (min), and maximum (max) will be presented for continuous variables, frequency and percentage distribution for categorical variables, and Kaplan–Meier estimates for time-to-event variables.

12.1 Sample Size Determination

The sample size for this study is determined based on power simulations for the primary efficacy analysis (Pinheiro 2014). Assuming a histologic response rate of 15% for placebo and 50% for aldafermin 3 mg and a 15% subject drop-out rate at Week 24, it is demonstrated that a sample size of 152 subjects (38 subjects per treatment group) can provide at least 84% power to detect an upward dose-response trend at the 5% significance level under 6 different possible dose-response scenarios (Table 5).

Table 5. Power Simulations for the Primary Efficacy Analysis

Response Rate		
Aldafermin 0.3 mg	**Aldafermin 1 mg**	**Power**
16% (Low)	19% (Low)	93%
18% (Low)	30% (Medium)	91%
20% (Low)	42% (High)	92%
32% (Medium)	39% (Medium)	84%
36% (Medium)	45% (High)	86%
43% (High)	48% (High)	86%

12.2 Randomization

Eligible subjects will be randomized into one of the four treatment groups (0.3 mg aldafermin, 1 mg aldafermin, 3 mg aldafermin, or matched placebo) in a 1:1:1:1 ratio using a permuted block randomization schedule. Randomization will be stratified by baseline stage of fibrosis [redacted]

[redacted]

As such, the protocol will require a minimum of approximately 35% of subjects with F3 on biopsy. Depending on the overall enrollment rate and the proportion of subjects enrolled with F2 or F3, the sponsor may limit the enrollment of F2 subjects to be no greater than approximately 65% (99/152 subjects).

12.3 Analysis Populations

Subjects will be analyzed using the following analysis populations:

- **Intent-to-Treat Population**

All randomized subjects will be included in the Intent-to-Treat (ITT) population. The ITT population will be based on randomized treatment if this differs from actual treatment received.

- **Safety Population**

All subjects who receive at least one dose (full or partial) of study drug will be included in the Safety population. All safety endpoints will be summarized using the Safety population and will be based on actual treatment received if this differs from the randomized/enrolled treatment.

- **Full Analysis Population**

All randomized/enrolled 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 will be included in the Full Analysis population. The Full Analysis population will be based on randomized/enrolled treatment if this differs from actual treatment received.

- **Per Protocol (PP) Population**

The Per Protocol (PP) population will constitute a subset of the Full Analysis population and will include subjects that have at least one valid, non-missing baseline and post-dose liver biopsy results and do not have protocol deviations that impact the liver biopsy assessments.

- **Pharmacokinetic Population**

All randomized/enrolled subjects who receive at least one dose (full or partial) of drug and have quantifiable PK measurements will be included in the PK population. Subjects with protocol violations will be assessed by the medical monitor or designee for inclusion in the PK population. PK summaries and analyses will be conducted using the PK population. The PK population will be based on actual treatment received if it differs from that to which the subject was randomized/enrolled.

12.4 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.

12.5 Efficacy Analyses

12.5.1 Primary Efficacy Analysis

The primary efficacy endpoint for this study is the histologic response at Week 24, defined as a subject achieving an improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) with no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis) after 24 weeks of treatment.

Subjects with two biopsies (baseline and post-baseline) will be considered for this analysis only if the second biopsy is taken after at least 12 weeks (i.e., 50% of the intended 24-week treatment period) of treatment on study drug. For the primary efficacy analysis, missing histologic responses at Week 24 will be imputed using a multiple imputation (MI) method under the assumption of missing at random. The details of the MI method will be provided in the SAP.

The primary efficacy endpoint will be analyzed using the MCP-Mod (Multiple Comparison Procedure – Modelling) 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 against the alternative hypothesis that there is a dose-response. The details of the MCP-Mod approach will be provided in the SAP.

Sensitivity analyses will include imputations with missing histologic responses as both responders and non-responders, and analysis with the assumption of missing not at random (e.g., pattern mixture models).

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

12.5.2 Secondary Efficacy Analyses

Secondary efficacy analyses include the analyses of the primary efficacy endpoint (i.e., histologic response at Week 24) based on pair-wise comparisons between treatment groups and the analyses of the secondary efficacy endpoints.

All binary efficacy endpoints (i.e., responders) will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline fibrosis stage.

All continuous efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model with effects for treatment, baseline fibrosis stage and 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.

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.

12.5.3 Other Efficacy/Pharmacodynamic Analyses

The details of these analyses will be provided in the SAP.

12.6 Safety

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.

13 Administrative Aspects

13.1 Protocol Adherence

The PI 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 EC.
No alterations in the protocol will occur without agreement between the Sponsor and the PI.
No alterations in the protocol affecting subject safety will occur without the express written approvals of the Sponsor, PI, and EC.

13.2 Disclosure

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 PI 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 PI 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.

13.3 Monitoring

The Sponsor's or designee's 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 PI will grant access to all documents (related to the study and the individual subjects) at any time these are requested. In turn, the CRA will adhere to all requirements for patient confidentiality as outlined in the ICF. The PI and PI'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.

13.4 Institutional Review Board/Ethics Committee

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/EC for approval. The 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.

13.5 Informed Consent

This study will be conducted in compliance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidelines 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 and PI, or designee, 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.

13.6 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.

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.

13.7 Financing and Insurance

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

13.8 Publication Policy

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

Investigator Protocol Review and Signature Form

Protocol Number: **18-0108, Protocol Amendment 4.0**

Protocol Title: **A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy, Safety, and Tolerability of Three Doses of Aldafermin Administered for 24 Weeks for the Treatment of Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)**

I have read the above-mentioned Protocol dated: **15 January 2020**

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.

Name of Principal Investigator
(Please PRINT)

Principal Investigator
(Signature)

Date

Name of Investigational Site
(Please PRINT)

Sponsor Protocol Approval and Signature Page

Protocol Number: **18-0108, Protocol Amendment 4.0**

Protocol Title: **A Phase 2b, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy, Safety, and Tolerability of Three Doses of Aldafermin Administered for 24 Weeks for the Treatment of Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)**

I have read the above-mentioned Protocol dated: **15 January 2020**

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.

[redacted] 15-January-2020

Date

Sr. Director, Clinical Development
NGM Biopharmaceuticals, Inc.

14 References

14.1 Clinical Study References

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
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
15-0105	2a	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multiple-Center Study with Additional Open-Label Single-Blind and Placebo-Controlled 24-Week Histology Cohorts to Evaluate the Safety, Tolerability, and Efficacy of NGM282 Administered for Up to 24 Weeks in Patients with Histologically Confirmed Nonalcoholic Steatohepatitis (NASH)	NASH

14.2 Nonclinical Study References

Study No	Study Title
Study 13-PD-NGM282-1007	A 24-Week Study of Ectopic NGM282 Expression following Intravenous Adeno-Associated Viral Delivery in FXR-deficient Mice

14.3 Literature References

Abdelmalek MF, Trotter JF, Bashir MR, et al. NGM282 rapidly and significantly improves steatosis and inflammation in 6 weeks with a continued on-treatment and persistent off-drug treatment effect. Oral presentation at: NASH-TAG Conference; 2018 Jan 4-6; Park City, UT.

Afzali A, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. Liver Transpl 2012;18:29–37.

Alisi A, Ceccarelli S, Panera N, et al. Association between serum atypical fibroblast growth factors 21 and 19 and pediatric nonalcoholic fatty liver disease. PLoS One 2013;8:e67160.

Aranha MM, Cortez Pinto H, Costa A, et al. Bile acid levels are increased in the liver of patients with steatohepatitis. Eur J Gastroenterol Hepatol 2008;20:519–25.

Argo CK, Caldwell SH. Epidemiology and natural history of non alcoholic steatohepatitis. Clin Liver Dis 2009;13:511–31.

Bannerjee R, Pavlides M, Tunnicliffe EM, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatol 2014 Jan;60:69–77.

Bechmann LP, Kocabayoglu P, Sowa JP, et al. Free fatty acids repress small heterodimer partner (SHP) activation and adiponectin counteracts bile acid induced liver injury in superobese patients with nonalcoholic steatohepatitis. Hepatology 2013;57:1394–406.

Belfort R, Harrison SA, Brown K, et al. A placebo controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–307.

Bhala N, Jouness RI, Bugianesi E. Epidemiology and natural history of patients with NAFLD. Curr Pharm Des 2013;19:5169–76.

Brunt EM, Kleiner DE, Wilson LA, et al. Portal chronic inflammation in nonalcoholic fatty liver disease (NAFLD): a histologic marker of advanced NAFLD clinicopathologic correlations from the nonalcoholic steatohepatitis clinical research network. Hepatology 2009;49:809–20.

Caldwell SH, Chang CY, Nakamoto RK, et al. Mitochondria in nonalcoholic fatty liver disease. Clin Liver Dis 2004;8:595–617.

Cazzo E, Jimenez LS, Pareja JC, et al. Effect of Roux-en-Y gastric bypass on nonalcoholic fatty liver disease evaluated through NAFLD fibrosis score: a prospective study. Obes Surg. 2015 Jun;25(6):982-5.

Centers for Disease Control US Obesity Trends http://www.cdc.gov/obesity/data/index.html (Accessed 12 December 2014).

Charlton MR, Burns JM, Pedersen RA, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology 2011;141:1249–53.

Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology 2012;142:711–25.

DePaoli AM, Zhou M, Kaplan DD, et al. FGF19 Analog as a Surgical Factor Mimetic That Contributes to Metabolic Effects Beyond Glucose Homeostasis. Diabetes 2019 Jun; 68(6): 1315-1328.

Eren F, Kurt R, Ermis F, et al. Preliminary evidence of a reduced serum level of fibroblast growth factor 19 in patients with biopsy proven nonalcoholic fatty liver disease. Clin Biochem 2012;45:655–8.

Faubion WA, Guicciardi ME, Miyoshi H, et al. Toxic bile salts induce rodent hepatocyte apoptosis via direct activation of Fas. J Clin Invest. 1999 Jan;103:137–45.

Filozof C, Chow SC, Dimick-Santos L, et al. Clinical endpoints and adaptive clinical trials in precirrhotic nonalcoholic steatohepatitis: Facilitating development approaches for an emerging epidemic. Hepatol Commun. 2017 Aug 1;1:577–85.

Friedman SL, Ratziu V, Harrison SA, et al. A randomized, placebo-controlled trial of cenicriviroc for treatment of nonalcoholic steatohepatitis with fibrosis. Hepatology 2018 May;67:1754–67.

Glass LM, Dickson RC, Anderson JC, et al. Total body weight loss of ≥10 % is associated with improved hepatic fibrosis in patients with nonalcoholic steatohepatitis. Dig Dis Sci 2015;60:1024–30.

Harrison SA, Torgerson S, Hayashi P, et al. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2003;98:2485–90.

Harrison SA, Rinella ME, Abdelmalek MF, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2018a Mar 24;391(10126):1174–85.

Harrison SA, Rossi SJ, Bashir MR, et al. NGM282 improves fibrosis and NASH-related histology in 12 weeks in patients with biopsy-confirmed NASH, which is preceded by significant decreases in hepatic steatosis, liver transaminases and fibrosis markers at 6 weeks. Oral presentation at: EASL 2018 - The International Liver Congress 2018 - The 53rd Annual Meeting of the European Association for the Study of Liver Diseases; 2018 Apr 11–15; Paris, France.

Higuchi H, Gores GJ. Bile acid regulation of hepatic physiology: IV. Bile acids and death receptors. Am J Physiol Gastrointest Liver Physiol. 2003 May;284:G734–8.

Kim D, Kim WR, Kim HJ, et al. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology 2013;57:1357–65.

Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313–21.

Klingenberg B. Proof of concept and dose estimation with binary responses under model uncertainty. Statistics in Medicine 2009; 28:274-292.

Lake AD, Novak P, Shipkova P, et al. Decreased hepatotoxic bile acid composition and altered synthesis in progressive human nonalcoholic fatty liver disease. Toxicol Appl Pharmacol 2013;268:132–40.

Loomba R, Lawitz E, Mantry PS, et al. The ASK1 inhibitor selonsertib in patients with nonalcoholic steatohepatitis: a randomized, phase 2 trial. Hepatology. 2017e Sep 11. doi: 10.1002/hep.29514. [Epub ahead of print].

Luo J, Ko B, To C, et al. Hepatoprotective effects of NGM282 compared to obeticholic acid and bezafibrate in mouse models of cholestasis. International Liver Congress 49th Annual Meeting, Late Breaker Poster # 1308. April 10th 2014, London UK.

Luo J, Ko B, Elliott M, et al. A nontumorigenic variant of FGF19 treats cholestatic liver diseases. Sci Transl Med. 2014 Jul 30;6(247):247ra100.

Luo J, Ko B, Ding X, et al. Serum cholesterol changes associated with NGM282 treatment in obese insulin resistant cynomolgus monkeys are reversed with either a statin or a PCSK9 inhibitor. J Hepatol. 2017;66(1):S430

Mehta R, Birerdinc A, Younossi ZM. Host genetic variants in obesity related nonalcoholic fatty liver disease. Clin Liver Dis 2014;18:249–67.

Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012 Apr 26;366:1577–85.

Neuschwander Tetri BA, Brunt EM, Wehmeier KR, et al. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR gamma ligand rosiglitazone. Hepatology 2003;38:1008–17.

Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015 Mar 14;385:956–65.

Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. World J Hepatol 2014;6:274–83.

Paradis V, Zalinski S, Chelbi E, et al. Hepatocellular carcinomas in patients with metabolic syndrome often develop without significant liver fibrosis: a pathological analysis. Hepatology 2009;49:851–9.

Patel J, Bettencourt R, Cui J, et al. Association of noninvasive quantitative decline in liver fat content on MRI with histologic response in nonalcoholic steatohepatitis. Therap Adv Gastroenterol 2016;9:692–701.

Pavlides M, Banerjee R, Sellwood J, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. J Hepatol. 2016 Feb;64(2):308-315.

Pinheiro J, Bornkamp B, Glimm E, et al. Model-based dose finding under model uncertainty using general parametric models. Stat Med. 2014 May 10;33(10):1646-61.

Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010;51:121–9.

Ratziu V, Harrison SA, Francque S, et al. Elafibranor, an agonist of the peroxisome proliferator-activated receptor-α and -δ, induces resolution of nonalcoholic steatohepatitis without fibrosis worsening. Gastroenterology. 2016 May;150:1147–59.e5.

Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675–85.

Schreuder TC, Marsman HA, Lenicek M, et al. The hepatic response to FGF19 is impaired in patients with nonalcoholic fatty liver disease and insulin resistance. Am J Physiol Gastrointest Liver Physiol 2010;298:G440–5.

Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015 Apr;13:643–54.e1-9; quiz e39–40.

Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378:804–14.

Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2012;10:837–58.

Tsochatzis EA, Papatheodoridis GV, Archimandritis AJ. Adipokines in nonalcoholic steatohepatitis: from pathogenesis to implications in diagnosis and therapy. Mediators Inflamm 2009;2009:831670.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September 2007.

Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011;140:124–31.

Wojcik M, Janus D, Dolezal Oltarzewska K, et al. A decrease in fasting FGF19 levels is associated with the development of non alcoholic fatty liver disease in obese adolescents. J Pediatr Endocrinol Metab 2012;25:1089–93.

World Health Organization Uppsala Monitoring Centre. Drug dictionary enhanced. March 2018. http://who-umc.org/DynPage.aspx?id=98105&mn1=7347&mn2=7252&mn3=7254&mn4=7338

Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018 Jan;15:11–20.

Zhou M, Wang X, Phung V, et al. Separating tumorigenicity from bile acid regulatory activity for endocrine hormone FGF19. Cancer Res 2014 Jun 15;74:3306–16.

Zhou M, Learned RM, Rossi SJ, et al. Engineered FGF19 eliminates bile acid toxicity and lipotoxicity leading to resolution of steatohepatitis and fibrosis in mice. Hepatol Commun. 2017;1(10):1024-1042.

15 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

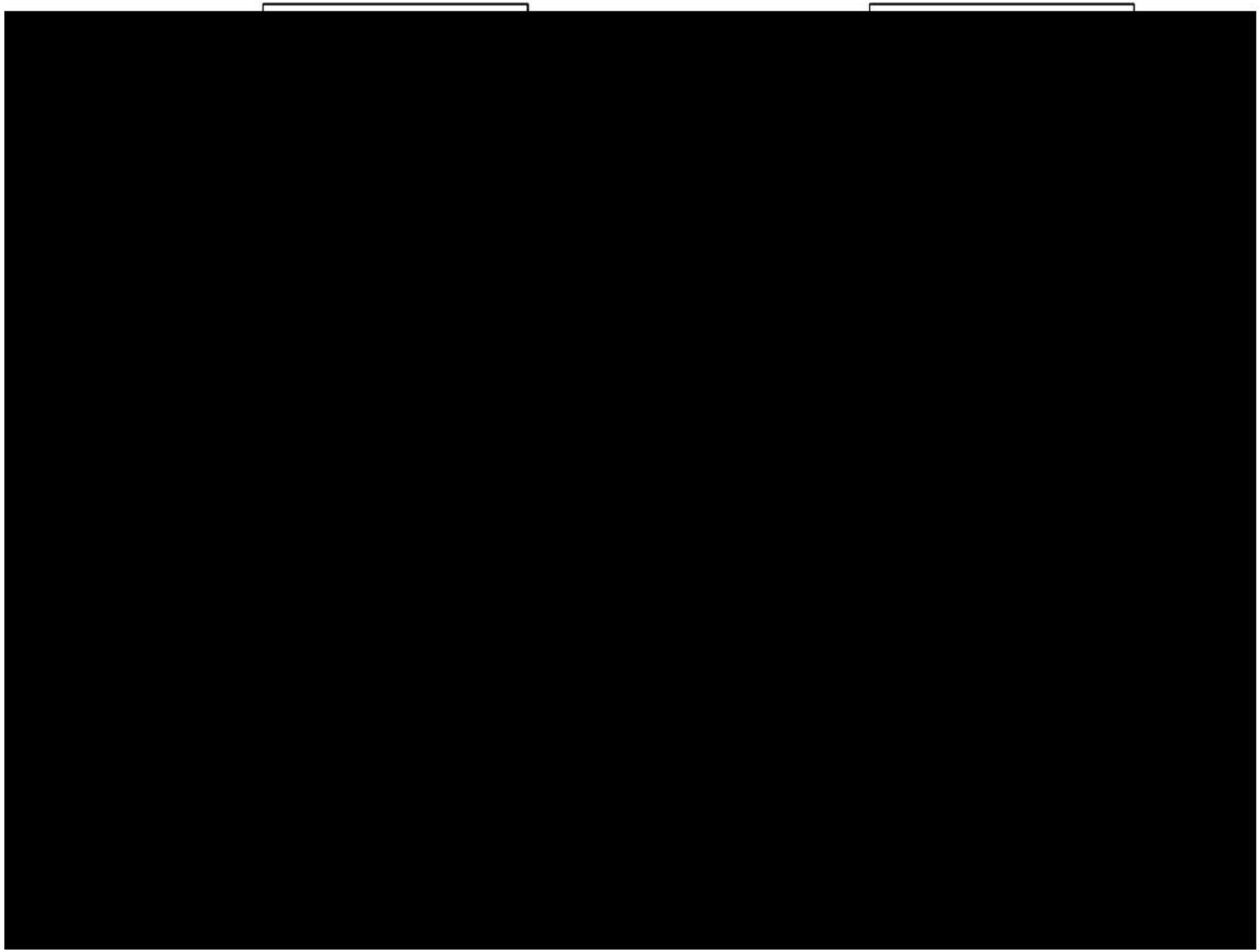
Local Reaction to Injection Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily 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]	2.5–5 cm	5.1–10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling [b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	> 10 cm 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.

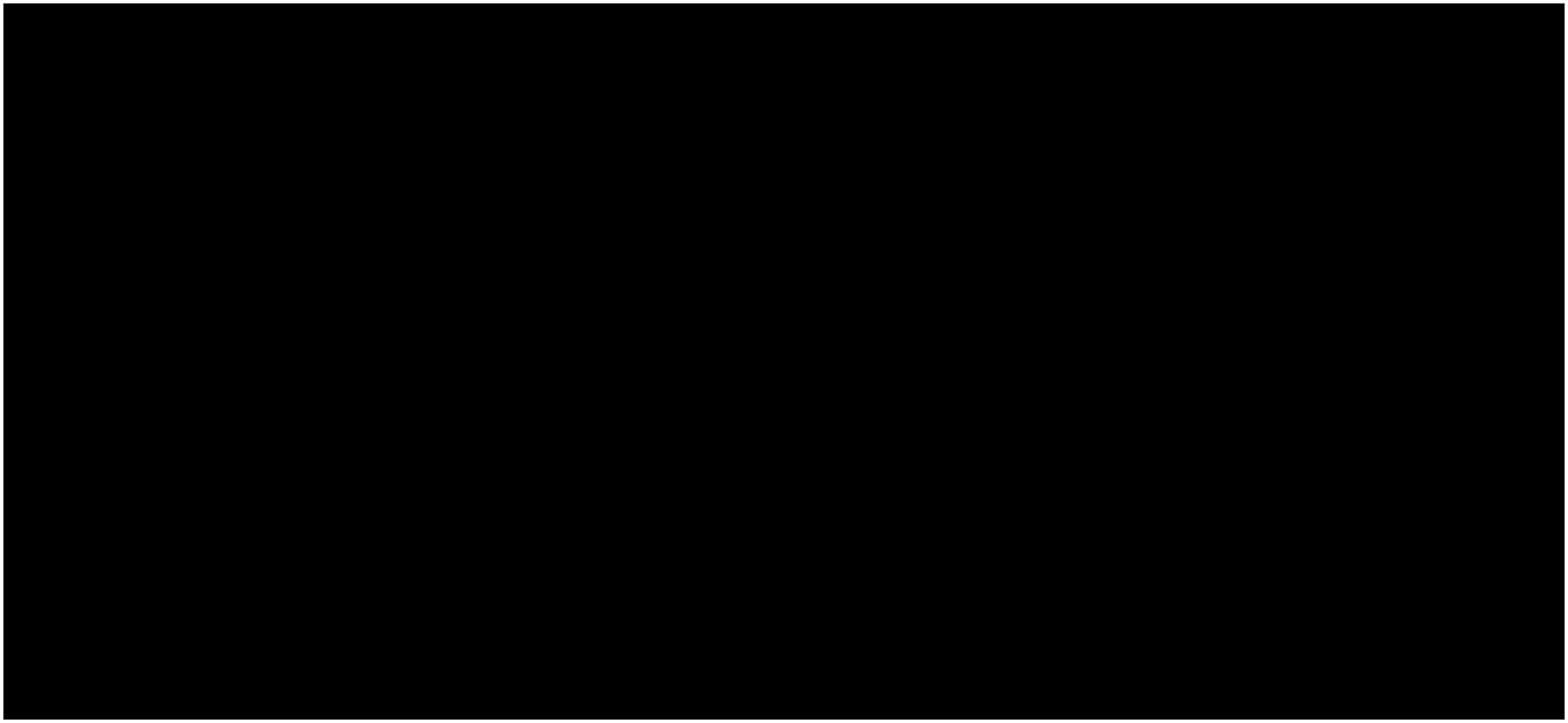
[b] Induration or Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Appendix 3. Lipid Lowering Algorithm



Appendix 4. Rosuvastatin Dose Reduction Algorithm

Appendix 5. Statin-Related Muscle Symptoms or Creatine Kinase (CK) Elevation



Appendix 6. Rosuvastatin Package Insert

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

https://www.accord-healthcare.com/ie/products/accord/rosuvastatin

https://glenmarkpharma-us.com/rosuvastatin-calcium-tablets

Appendix 7. Ezetimibe Package Insert

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

https://www.merck.com/product/usa/pi_circulars/z/zetia/zetia_pi.pdf

Appendix 8. 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 9. Prohibited Hepatotoxic Agents

All other hepatotoxic agents will be left to the discretion of the PI. There should be clear documentation in the subject records of Investigator approval of use. For subjects who have been on stable therapy with no related hepatotoxicity, the MM may be contacted to assess the medical context and eligibility of the subject.

***Prohibited Hepatotoxic Concomitant Medications**	
Generic Name	Drug Class/Common Use
Acetaminophen > 3000 mg/day	Analgesic/Antipyretic
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
Nitrofurantoin	Anti-infective, urinary (antibiotic)
Norethisterone	For menstrual issues
Phenytoin	anticonvulsant
Pirfenidone	Pulmonary fibrosis
Propylthiouracil	Antithyroid
Pyrazinamide	Anti TB
Quinidine	Antiarrhythmic
Rifampin	Anti TB
Sulfasalazine	Anti-infective (DMARD, antibiotic)
Suramin	Injectable – antiprotozoal agent
Thioguanine	Antineoplastic/Antirheumatic,
Ticlopidine	Antithrombotic, platelet inhibitor
Valproate	Anticonvulsant (epilepsy), mood stabilizer (Bipolar)