Statistical Analysis Plan

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I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
C4	7 alpha hydroxy 4 cholesten 3 one
CFB	Change from Baseline
CI	Confidence Interval
CRF	Case Report Form
CRN	Clinical Research Network
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ELF	Enhanced Liver Fibrosis
EOS	End of Study
[redacted]	[redacted]
GLP-1	Glucagon-like peptide-1
GPP	Good Pharmacoepidemiology Practice
HbA1c	Hemoglobin A1c
HDL-C	High-density Lipoproteins-Cholesterol
HOMA-IR	Homeostasis Model Assessment-estimated Insulin Resistance
[redacted]	[redacted]
ICH	International Conference on Harmonization
INR	International Normalized Ratio (INR)
LISSAs	Local Injection Site Symptom Assessment
LDL-C	Low-density Lipoproteins-Cholesterol
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
Min	Minimum
[redacted]	[redacted]
MRI PDFF	Magnetic Resonance Imaging-proton Density Fat Fraction
N/A	Not Applicable
NA	Not Applicable
NASH	Nonalcoholic Steatohepatitis
PCFB	Percent Change from Baseline
PD	Disease Progression
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
T2D	Type 2 Diabetes
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. This SAP only describes the analysis to be conducted on the placebo-controlled 24-week histology cohorts of this trial. The analysis of pharmacokinetics (PK) data will be provided in a separate report and will not be included in this SAP.

The planned analysis for each phase of the study (double-blind, open-label, and placebo-controlled) will be detailed in separate analysis plans.

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

2.2. TIMINGS OF ANALYSES

An interim analysis is planned to be conducted after approximately 50% subjects per arm have completed 24 weeks of treatment. This will included review of safety and selected efficacy endpoints.

The final analysis of safety and efficacy is planned for all randomized subjects after the last randomized subject has completed the end of study visit at Week 30 or Early Termination visit in the placebo-controlled 24 week histology cohort.

For the purpose of delivery of topline results for the final analysis, a database snapshot will take place before the final database lock. The snapshot will include 24 weeks of selected efficacy and pharmacodynamics (PD) data and 30 weeks of safety data.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the treatment effect of NGM282 on absolute liver fat content as measured by magnetic resonance imaging protein density fat fraction (MRI-PDFF) in subjects with histologically confirmed Nonalcoholic Steatohepatitis (NASH).

3.2. SECONDARY OBJECTIVE(S)

- Assess the safety and tolerability of NGM282 in subjects with NASH with up to 24 weeks of treatment with NGM282.
- Evaluate the percent change from Baseline in absolute liver fat content at Weeks 6, 12, 24, 30 (End of Treatment, EOT).
- Evaluate the percentage of normalization for liver fat content at EOT.
- Evaluate the liver fat content response rate as defined by
    - a ≥ 5(%) decrease in absolute liver fat content
    - a ≥ 30% relative decrease in absolute liver fat content
- Evaluate the actual and percent changes from Baseline to EOT as well as the percentage of normalization of the following parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, bilirubin (total and direct), and gamma-glutamyl transferase (GGT). The percentage of normalization will be assessed for ALT and triglycerides. Percentage of normalization will also be investigated for a clinically meaningful threshold for triglycerides.
- Evaluate the actual and percent changes from Baseline to EOT for the following (if collected as part of the cohort):
    - Total cholesterol, high-density lipoproteins-cholesterol (HDL-C), low-density lipoproteins-cholesterol (LDL-C), triglycerides, and lipoprotein particles
    - [redacted]
    - Fasting blood glucose, insulin levels, [redacted], and homeostasis model assessment-estimated insulin resistance (HOMA-IR)
    - PRO-C3 and Enhanced Liver Fibrosis (ELF) Score
    - Body weight, body mass index (BMI), and waist circumference
    - 7-alpha-hydroxy-4-cholesten-3-one (C4) and serum bile acids

- Bile-mediated absorption as measured by vitamin D, International Normalized Ratio (INR), and fecal fat content

- Evaluate liver histologic response
  - Improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis
  - 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
- Evaluate the efficacy and safety of rosuvastatin administered in response to increases in total cholesterol and LDL-C from NGM282 treatment.

3.3. EXPLORATORY OBJECTIVE(S)

- [redacted]

3.4. STUDY DESIGN

Protocol 15-0105 is comprised of a double-blind placebo controlled parallel group study followed by additional open-label single blind and placebo-controlled 24-week histology cohorts studies. This analysis plan covers the placebo-controlled 24-week histology cohorts study designed to assess the efficacy and safety of NGM282. All subjects in the placebo-controlled 24-week histology cohort will be treated with NGM282 for 24 weeks once daily and will be followed for 6 weeks after completing final study-drug dose. No dose reductions will be allowed in this placebo-controlled 24-week histology cohort.

In the placebo-controlled 24-week histology cohort, approximately up to 75 subjects (50 NGM282 and 25 placebo) will be enrolled from ~10 U.S. sites and treated for 24 weeks with a 6-week safety follow-up. Subjects will be required to meet enrollment criteria similar to those of the open-label single-blind cohort as specifically defined in protocol Section 8.1.1 with the exception of the following: 1) only subjects with Stages 2 and 3 fibrosis at Screening will be enrolled. At Day 1 eligible subjects will be randomized into the study and stratified as either fibrosis stage 2 or 3.

The dose of NGM282 to be studied will be 1 mg [redacted] he active dose selection for this cohort will be blinded to the study site and subjects throughout the study period.

The first dose of NGM282 or placebo (Day 1) and doses at Weeks 2, 4, 6, 8, 12, 18, and 24 study visits will be self-administered in the clinic, with all other doses throughout the treatment period self-administered at home. Self-administration of NGM282 should occur as close as possible to the same time each day for every dose. Subjects will return to the clinic on Weeks 2, 4, 6, 8, 12, 18 and 24 for on-treatment assessments and to be dispensed NGM282 or placebo study-drug kits through Week 18. LDL-C will be evaluated at Weeks 2, 4, 8, and 12 in all subjects for possible increases in lipid levels associated with NGM282 administration.

Rosuvastatin will be started in subjects meeting specific LDL-C level criteria. The specific dosing and administration of Rosuvastatin will be based on whether the subject is statin naïve versus statin experienced and LDL-C levels at Weeks 2, 4, and 8 (LDL-direct may be used if LDL-C was not able to be analyzed). A decision about possible second-line lipid-lowering therapy with ezetimibe will be made on a case-by-case basis for subjects that have not achieved an adequate response or are unable to tolerate rosuvastatin. Bottles of Rosuvastatin tablets will be dispensed to all subjects initially and instructions to initiate dosing are dependent on observed lipid levels according to the dosing algorithm in (Appendix A). Week 24 will be the EOT clinic visit and subjects will return to the clinic at Week 30 (or 6 weeks after last dose of NGM282 or placebo) for an EOS follow-up visit. Subjects are required to undergo MRI performed during Screening and at Weeks 6, 12, 24 (EOT)/Early Withdrawal, and 30 (EOS) visits.

This cohort will have two other assessments performed to assess liver histology in addition to MRI-PDFF. [redacted] where available at the local radiology center. [redacted]

3.5. DETERMINATION OF SAMPLE SIZE

[redacted]

[redacted] the assumptions of calculated sample-size estimates for 24-week efficacy used an NGM282 response of 50% versus 15% for placebo utilizing 80% power and alpha=0.05 with a 2:1 randomization scheme. Assuming a 15% drop-out rate, the planned sample size of 50 NGM282-treated subjects and 25 placebo subjects is sufficient to evaluate efficacy and support powering estimates for late-stage clinical trials.

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

- The primary efficacy endpoint for this study will be the actual change in liver fat content as measured by MRI PDFF in subjects with histologically confirmed NASH after 24 weeks of treatment.

4.2. SECONDARY EFFICACY ENDPOINTS

- The actual and percentage change from Baseline in liver fat content by MRI-PDFF at Weeks 6, 12, 24, and 30.
- The percentage of normalization in liver fat content at EOT.
- The percentage of responders
  - a liver fat content decrease >= 5(%)
  - a liver fat content relative decrease by >= 30%
- The actual and percentage changes from Baseline to EOT as well as the percentage of normalization of AST, ALT, bilirubin (total, direct), triglycerides and GGT. Percentage of normalization by Week 24 will be investigated for these parameters (including clinically meaningful normalization of Triglycerides)
- The actual and percentage changes from Baseline to EOT of the following parameters: Total cholesterol, HDL-cholesterol, LDL-cholesterol, and lipoprotein particles.
- The actual and percentage changes from Baseline to EOT of the following parameters: [redacted], Pro-C3, ELF Score, Fasting blood glucose, insulin levels, HbA1c, [redacted], and HOMA-IR, Body weight, BMI, and waist circumference, C4 and serum bile acids, Bile-mediated absorption as measured by fat-soluble vitamins and fecal fat content.
- The percentage of liver histologic responders
  - Improvement in liver fibrosis by ≥ 1 stage by NASH Clinical Research Network (CRN) criteria with no worsening of steatohepatitis
  - 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.

4.3. EXPLORATORY ENDPOINTS

- [redacted]

- [redacted]

4.4. SAFETY ENDPOINTS

The safety and tolerability endpoints will consist of incidence of adverse events (AEs) and local injection site reactions, as well as changes in clinical laboratory tests (hematology, biochemistry and urinalysis), vital signs, electrocardiogram (ECG) and physical examinations.

5. ANALYSIS POPULATIONS

5.1. INTENT-TO-TREAT POPULATION

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

5.2. SAFETY POPULATION

The Safety Population will include all enrolled subjects who receive at least one dose of NGM282 (full or partial) and have at least one post-dose safety evaluation.

All safety endpoints will be summarized using the Safety population and will be based on actual treatment received if this differs from the enrolled treatment.

5.3. EFFICACY POPULATION

The Efficacy Population will include all enrolled subjects who receive at least one dose (full or partial) of NGM282 and have at least one valid, non-missing post-dose efficacy/PD parameter value.

All efficacy and PD endpoints will be summarized and analyzed using the Efficacy population. This will be the main population for the analysis of efficacy and PD endpoints. The Efficacy population will be based on enrolled treatment if this differs from actual treatment received.

5.4. PER PROTOCOL (PP) POPULATION

[redacted]

5.5. LIVER HISTOLOGY POPULATION

[redacted]

5.6. PROTOCOL DEVIATIONS

Subject data will be examined prior to database lock for evidence of protocol deviations in order to identify subjects with major protocol violations which would exclude such subjects from the Per Protocol Population. Possible protocol deviations will be independently reviewed and approved by NGM Biopharmaceuticals Australia Pty Ltd. All protocol deviations will be detailed in a listing by subject and treatment group for the ITT Population. Deviations will be categorized as minor or major based of predefined criteria and assigned by the study team prior to database lock.

Protocol deviations are defined as follows:

- Not meeting all inclusion and exclusion criteria, as detailed in Sections 3.5 of the SAP
- Intake of any prohibited medications, as detailed in Section 6.5 of the protocol
- Failure to follow the conduct of the study

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

Unless otherwise specified, for numeric data, descriptive statistics will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). The same number of decimal places as used in the raw data will be presented when reporting min and max, 1 decimal place more than in the raw data will be presented when reporting mean and median, and SD. If the raw data have 3 decimals or more, 3 decimals will be presented for the mean, median, min and max, and SD.

All categorical/qualitative data will be presented using frequency counts and percentages. All percentages will be rounded to 1 decimal point, with the denominator being the number of subjects in the relevant population, unless otherwise stated. Percentages equal to 100 will be presented as 100%; percentages will not be presented for zero frequencies but the categories whose counts are zero will be displayed for the sake of completeness.

Unless otherwise specified, all the tables will be summarized by treatment group (and overall, if applicable). All the listings will be sorted by treatment group, subject number and assessment date/time.

All confidence intervals (CIs) will be two-sided and will use 95% confidence levels. Any analyses requiring significance testing will use a two-sided test at the 5% significance level, unless otherwise specified.

In general, only data from nominal scheduled visits will be presented in the summary tables and figures unless otherwise specified. Data from unscheduled visits will not be summarized but will be presented in the data listings.

All analyses and outputs will be generated using SAS® version 9.4 (or higher).

6.2. KEY DEFINITIONS

6.2.1. Baseline

Unless otherwise specified, baseline will be defined for each subject and will be defined as the last available, valid, non-missing assessment reported on or before the start of first study drug administration.

6.2.2. Study Day

The date of first dose of study drug is designated as Day 1. Study days for screening visits are negative numbers and there will be no study day 0.

Study day will be calculated relative to first study drug administration. If the date of interest occurs on or after the first study drug administration date, study day will be

calculated as (date of interest - first study drug administration date) + 1. If the date of interest occurs prior to the first study drug administration date, study day will be calculated as (date of interest - first study drug administration date).

A subject's treatment end date is defined by the subject's last dose date in the study. A subject's study end date is defined by the date of the subject's last assessment in the study.

6.2.3. Change from Baseline /Percent Change

CFB (Change from baseline) = Post-baseline assessment - baseline assessment

PCFB (Percent Change from baseline) = (Post-baseline assessment - baseline assessment)/baseline assessment

6.3. MISSING DATA

Subjects who discontinue the study prematurely will not be replaced. No imputation will be made for missing data. All analyses will be based on available data, unless otherwise stated. Subjects Incomplete or missing data will be presented in the listings as they were reported on the CRFs.

Missing or incomplete dates for AEs and concomitant medications will be imputed as needed only to determine treatment emergence or distinguish between prior and concomitant medications.

If an AE has a missing onset date, then the AE will be considered a TEAE unless a non-missing stop date indicates otherwise. A medication with a completely missing start date will be considered a prior medication. A medication with a missing stop date will be considered a concomitant medication.

If an AE or a medication has a partial start or stop date, the following rules will be used to determine whether it is an AE or a TEAE, a prior or a concomitant medication.

Date imputation rules for medications and adverse events are summarized in Table 1.

Table 1 Imputation of Missing Dates

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month and day but the year is present	January 1 of that year or first dose date if the year is the same as the first dose date	December 31 of that year
Missing day but the year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date.	Last day of that month

Note: If the imputed start date is after the stop date, then the start date will be set to equal the stop date.

6.4. VISIT WINDOWS

No visit windowing will be applied to assessments—the nominal visit name/time point will be used in statistical summaries.

6.5. POOLING OF CENTRES

Data from all investigational centers will be pooled for summaries and analyses.

6.6. SUBGROUPS

Not applicable for this study.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

The total number of subjects entered into the study and included in each analysis population will be summarized by actual treatment group and overall. The number of subjects prematurely discontinuing from treatment and study, along with the reason for early termination will be summarized.

Individual data listings for subject disposition will be presented for each subject, including enrollment date, treatment start date, treatment discontinuation date, study discontinuation date, discontinuation reason, and population flags.

Subject disposition will be summarized using the ITT population.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

[redacted]

Demography (age, sex, race, ethnicity, type 2 diabetic status, cirrhosis status, cardiovascular event status, statin status, height, body weight, BMI and waist circumference at screening), will be summarized, by Steatosis score [Overall, 0 (< 5%), 1 (5%–33%), 2 (34%–66%) and 3 (> 66%)] and treatment group.

Individual data listings for demographic and baseline characteristics will be presented for each subject.

Age = (date signed informed consent - date of birth + 1) / 365.25 and truncated to complete years.

Height (cm) = height (inches) * 2.54

Weight (kg) = weight (lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

Previous Diagnoses including cirrhosis, diabetes, cardiovascular events/diseases, …, etc. will also be summarized descriptively by presenting the number and percent of subjects reporting a history of each condition.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history including any past and/or concomitant diseases or past surgeries will be collected at baseline. All terms will be coded using MedDRA Version 18.0 and summarized by System Organ Class (SOC), preferred term, and treatment group. Medical history data will also be listed. Medical history data will be summarized using the Efficacy and Safety Populations.

7.4. PRIOR AND CONCOMITANT MEDICATION

Medications will be classified using the current version of the World Health Organization Drug Dictionary Enhanced, B2 Format (March, 2015). Individual data listings will be presented for each subject, with separate listings for prior medications and concomitant medications. In addition, concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classes and PT using frequency counts and percentages. For the summaries of concomitant medications, subjects who take the same medication (in terms of the preferred term) more than once will be counted only once for that medication. Prior medications will be summarized separately in a fashion similar to concomitant meds.

Prior and concomitant medication data will be summarized using the Efficacy and Safety Populations.

7.4.1. Prior Medication

Prior medications are medications that were stopped ≥28 days prior to screening visit.

7.4.2. Concomitant Medication

Concomitant medications are any medications started between 28 days prior to Screening through the End of Study visit.

8. EFFICACY AND PHARMACODYNAMIC (PD) ENDPOINTS

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSES

The primary efficacy endpoint for this study will be the change in liver fat content as measured by MRI PDFF in subjects with histologically confirmed NASH after 24 weeks of treatment. The analyses for this primary endpoint are detailed in the previous SAP for double-blind phase.

8.2. SECONDARY EFFICACY/PD ENDPOINT(S) AND ANALYSES

The main analysis population for secondary efficacy endpoints is the Efficacy Population. The analysis will also be repeated for the Per Protocol population and for subjects who completed their Week 24 assessment (completers) only.

8.2.1. The actual and percentage change from baseline in liver fat content by Magnetic Resonance Imaging-proton Density Fat Fraction. MRI-PDFF at Weeks 6, 12, 24, and 30

The observed values and changes from baseline will be summarized at Weeks 6, 12, 24, and 30, by NGM282 treatment group and fibrosis stage. The actual change and percentage change in absolute liver fat content from baseline to Week 6, Week 12, Week 24 and Week 30 will be compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment group and fibrosis stage at baseline as cofactors and baseline endpoint and baseline ALT as covariates. Least square means with standard errors (SE), differences in least square means with SE, 95% CIs for the difference in least square means, and corresponding p-values will be presented.

The assumptions of normality will be evaluated. If the assumptions of normality are not satisfied, a rank ANCOVA method will be performed in addition to the parametric model.

The rank ANCOVA is a non-parametric statistical method described in Stokes, Davis, and Koch, 2000. It can be considered as an extension to the Wilcoxon rank-sum test with the ability to adjust for covariates and cofactors in the model. The mean, median and p-value for the actual change will be presented.

8.2.2. The percentage of normalization in absolute liver fat content at Week 24

Normal liver fat content normalization will be defined as <= 5.0(%). Percent of subjects with normalized liver fat content will be presented by treatment group and fibrosis stage and will be analyzed through a chi-square test. The difference between proportions observed in each treatment group, along with 95% CIs for the difference between proportions, will be presented for all pairwise comparisons of treatment

groups. Fisher exact test will be used if 50% of the cells have expected counts less than 5.

8.2.3. The percentage of responders (based on a liver fat content decrease >= 5%, and relative decrease >=30%)

The percentage of responders will be analyzed through a chi-square test. The difference between proportions observed in each treatment group, along with 95% CIs for the difference between proportions, will be presented for all pairwise comparisons of treatment groups. Fisher exact test will be used if 50% of the cells have expected counts less than 5.

[redacted]

8.2.4. The actual and percentage changes from baseline by Week 24 of AST, ALT, bilirubin (total, direct), triglycerides and GGT.

The actual and percentage changes from baseline will be summarized by treatment group. An ANCOVA model as stated in 8.2.1 will be used to compare between treatment groups.

In addition, the percentage of subjects with AST, ALT, Total Bilirubin, Direct Bilirubin, Triglycerides, and GGT lab measurements within the normal range will be summarized by lab parameter, treatment group and visit. All pairwise treatment group comparisons of the proportion of subjects within the normal range will be tested using a chi-square test. Fisher exact test will be used if 50% of the cells have expected counts less than 5.

[redacted]

8.2.5. The actual and percentage changes from baseline at Week 24 and EOS of the following parameters: Total cholesterol, HDL-cholesterol, LDL-cholesterol, and lipoprotein particles.

The actual and percentage changes from baseline will be summarized by treatment group and fibrosis stage. ANCOVA model as stated in 8.2.1 will be used to compare between treatment groups. The ANCOVA model as stated in 8.2.1 will be used to compare the two treatment groups.

8.2.6. The percentage of liver histologic responders

Responders:

- The subjects who have an improvement in liver fibrosis by ≥ 1 stage with no worsening of steatohepatitis (no worsening of lobular inflammation or hepatocyte ballooning or steatosis grade) from baseline to Week 24.
- The subjects who have complete resolution of NASH (defined as an NAS score of 0 or 1 for inflammation and 0 for ballooning) with no worsening of fibrosis (i.e., no progression of NASH CRN fibrosis stage) from baseline to Week 24.

The difference between proportions observed in each treatment group, along with 95% CIs for the difference between proportions, will be presented. The percentage of responders in each treatment group will be compared using a chi-square test. Fisher exact test will be used if 50% of the cells have expected counts less than 5.

8.2.7. Other Secondary Endpoints

The actual and percentage changes from Baseline at Week 24 of the following parameters: [redacted], PRO-C3, ELF score, Fasting blood glucose, insulin levels, HbA1c, [redacted], and HOMA-IR, Body weight, BMI, and waist circumference, C4 and serum bile acids, Bile-mediated absorption as measured by vitamin D, INR, and fecal fat content.

The actual and percentage changes from baseline will be summarized by NGM282 treatment group. ANCOVA model as stated in 8.2.1 will be used to compare between treatment groups.

8.3. EXPLORATORY EFFICACY/PD ENDPOINT(S) AND ANALYSES

[redacted]

9. SAFETY

9.1. EXTENT OF EXPOSURE

Treatment exposure will be based on the Safety Population. Individual data listings for treatment exposure will be presented for each subject. Treatment exposure will be summarized by assessing the duration of exposure and compliance. Treatment compliance is defined as the number doses administered/number of doses prescribed per protocol during the time the subject was on study.

9.2. ADVERSE EVENTS

AEs, including serious AEs, will be coded using the MedDRA Version 18.0. The number and percentage of subjects experiencing an AE will be summarized for each system organ class (SOC) and preferred term (PT) by treatment group. In addition, AEs will be tabulated according to severity, causality, and relation to the study drug (both NGM and Rosuvastatin).

All AE summaries will be restricted to Treatment Emergent Adverse Events (TEAEs) only. TEAEs are defined as AEs that commence on or after the date of first study drug administration. AEs without an onset date or time will be defined as treatment emergent, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to the start of first administration of study drug or if the AE stop date indicates that the event started or stopped prior to the start of first administration of study drug. Please refer to Section 6.3 for determination of TEAEs for completely or partially missing dates.

The intensity of AEs is rated by CTCAE v4.03. For both NGM282 and Rosuvastatin, adverse events might be not related, possibly related, probably related and definitely related to these study drugs.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA preferred term) more than once will be counted only once for that event. Separate summaries will be provided for AEs by intensity, causality, and relationship to study drug. For summaries by SOC, PT, and maximum intensity, a subject is counted once at the highest intensity level for which the event occurred at the SOC level and the highest intensity level for each unique PT within that SOC level. Therefore, subjects may only contribute once to each PT and once to each SOC level. Summaries by relatedness would be handled similar to the summaries by intensity.

The summaries presenting frequency of AE by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following tables will be summarized for adverse events.

- An overall summary of the number and percentage of subjects reporting any TEAEs, serious TEAEs, NGM282-related TEAEs, Rosuvastatin-related TEAEs, TEAEs leading to withdrawal and TEAEs leading to death.
- TEAEs overall and by system organ class and preferred term
- TEAEs by CTCAE grade, overall and by system organ class and preferred term.
- TEAEs of CTCAE grade 3 or higher, overall and by system organ class and preferred term.
- TEAEs leading to withdrawal, overall and by system organ class and preferred term
- Serious TEAEs, overall and by system organ class and preferred term NGM282-related
- NGM282-related TEAEs overall and by system organ class and preferred term
- TEAEs by maximum relationship to NGM282, overall and by system organ class and preferred term
- NGM282-related TEAEs leading to withdrawal, overall and by system organ class and preferred term
- NGM282-related Serious TEAEs, overall and by system organ class and preferred term Rosuvastain-related
- Rosuvastatin-related TEAEs overall and by system organ class and preferred term
- TEAEs by maximum relationship to Rosuvastatin, overall and by system organ class and preferred term
- Rosuvastatin-related Serious TEAEs, overall and by system organ class and preferred term
- Rosuvastatin-related TEAEs leading to withdraw, overall and system organ class and preferred term

For the rosuvastatin-related summary tables, only subjects who received rosuvastatin will be included. All AEs will be provided in listings regardless of TEAEs or not. All Serious AEs and AEs leading to study drug withdrawal and death will be provided in separate listings.

9.3. LABORATORY EVALUATIONS

Laboratory data (hematology, biochemistry, and urinalysis) will be summarized by treatment group, fibrosis stage and time point. Actual values and change from baseline will be presented for lab parameters with continuous measures. In addition, frequency tabulations of categorical urinalysis lab parameters will also be presented by treatment

group and time point. Shift tables from baseline clinical grade (low/normal/high) will also be presented for chemistry and hematology laboratory parameters.

Individual data listings of laboratory results will be presented for each subject. Laboratory values will be compared to normal ranges; out of range and clinically significant laboratory values will be identified in the listings (low, high).

Anti-drug antibodies, neutralizing antibodies and urine microscopy evaluation will be listed only.

9.4. VITAL SIGNS

Observed values as well as changes from Baseline will be summarized descriptively for all vital sign parameters (pulse, systolic/diastolic blood pressure, oral temperature, respiratory rate, weight and waist circumference), by treatment group and time point. All vital signs data will be presented in data listings.

9.5. ECG

Observed values as well as changes from Baseline will be summarized descriptively for all ECG parameters (QT interval, QTc interval, P-R interval, R-R interval and QRS duration), by treatment group and time point.

In addition, frequency tabulations of overall ECG interpretation results (Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant) will be presented by actual treatment group at each time point.

All ECG data will be presented by subject in data listings.

9.6. INJECTION-SITE REACTIONS

Injection site reactions will be evaluated using a local injection-site symptom assessment (LISSA). Frequency tabulations of the severity of each pre-specified symptom (pain, tenderness, erythema/redness and induration/swelling) will be presented by actual treatment group at each time point.

9.7. PHYSICAL EXAMINATION

Individual data listings for physical examination results will be presented for each subject.

9.8. PREGNANCY

Individual listings for urine and serum pregnancy test data will be presented for each subject.

10. INTERIM ANALYSES

[redacted]

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

NA

12. REFERENCE LIST

1. Categorical Data Analysis Using SAS System. Maura E. Stokes, Charles S. Davis, Gary G, Koch 2000.

13. APPENDIX A

[redacted]

[redacted]

[redacted]

[redacted]

Table 2 Schedule of Study Procedures for Placebo-Controlled 24 Week Histology Cohort

Study Procedure	D –28 to –1 (Screening) [a]	D 1	W 2	W 4	W 6	W 8	W 12	W 18	W 24/ EW (EOT)	W 30 (EOS)
Visit Window (Days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Informed consent	X									
Demographics	X									
Medical history	X									
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X								
Height	X									
Body weight, BMI, waist circumference	X	X					X		X	X
Physical exam	X	X		X		X	X	X	X	X
12-lead ECG	X	X					X		X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Adverse events (AEs) [k]	X	X	X	X	X	X	X	X	X	X
Chemistry [fasted ≥ 10 hrs]	X	X [j]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]
Complete blood count (CBC)	X	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 (INR)	X	X					X		X	X
Alpha fetoprotein (AFP)	X									
Pregnancy test [f]	X	X							X	X
Hepatitis and HIV screen	X									
Urinalysis (UA)	X	X					X		X	X
Urine drug screen	X									
Fasting lipid panel	X	X	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]
Lipoprotein particles		X		X		X	X		X	X
Lipase		X		X		X	X		X	X
C4 and serum bile acids		X	X	X	X	X	X	X	X	X

Vitamin D		X					X		X	X
PK blood samples [g]		X	X	X	X	X	X	X	X	X
Anti-drug antibodies (ADAs)		X	X	X	X	X	X	X	X	X
Neutralizing antibodies (NAbs)		X	X	X	X	X	X	X	X	X
ELF Panel		X			X		X		X	X
[redacted]		[redacted]								

ADA = anti-drug antibody; AE = adverse event; AFP = alpha fetoprotein; BMI = body mass index; C4 = 7-alpha-hydroxy-4-cholesten-3-one; CBC = complete blood count; 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] INR = International Normalized Ratio; IWRS = Interactive Web Response System; LISSA = local injection-site symptom assessment; [redacted] MRI = magnetic resonance imaging; NAb = neutralizing antibody; PK = pharmacokinetic; UA = urinalysis; W = week.

[a] There should be a minimum of 14 days between Screening and Day 1 visits for adequate separation of the repeated Chemistry (liver function tests) and International Normalized Ratio assessments.

[b] Screening MRI will serve as baseline for efficacy endpoint analysis. Adiposity assessments will be collected as part of the standard MRI procedure at all sites.

[c] [redacted]

[d] 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 historical biopsy available within 3 months of Screening.

[e] Lab results for ALT, AST, Total Cholesterol, LDL, HDL and triglycerides are blinded to site from Week 2 onward.

[f] A serum pregnancy test will be performed on all female subjects at Screening, Week 24, and Week 30. A urine pregnancy test will be performed on all female subjects at Day 1 (pre-dose).

[g] PK blood samples will be collected in all subjects before dosing themselves in the clinic (pre-dose) and at 2 hours post-dose at Day 1, Week 12, and Week 24.

[h] 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 be dispensed additional rosuvastatin at Week 24 and continue through Week 30.

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

[j] Baseline ALT reported result based on the following calculation: Elevation of ALT > 2x above subject-specific baseline value (calculated using the median of the Screening and Day 1 value) and total bilirubin > 2x ULN

[k] Adverse events will be monitored and recorded from patient signing informed consent through follow-up.[l] Subjects will be instructed to self-inject NGM282 each morning in the abdomen and to skip the dose if it is past 12:00 noon and administer the next dose the following morning. Subjects will not self-inject NGM282 at home on clinic visit days.

14. PROGRAMMING CONSIDERATIONS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

15. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted] provide an overview of the development of such SAS programs.

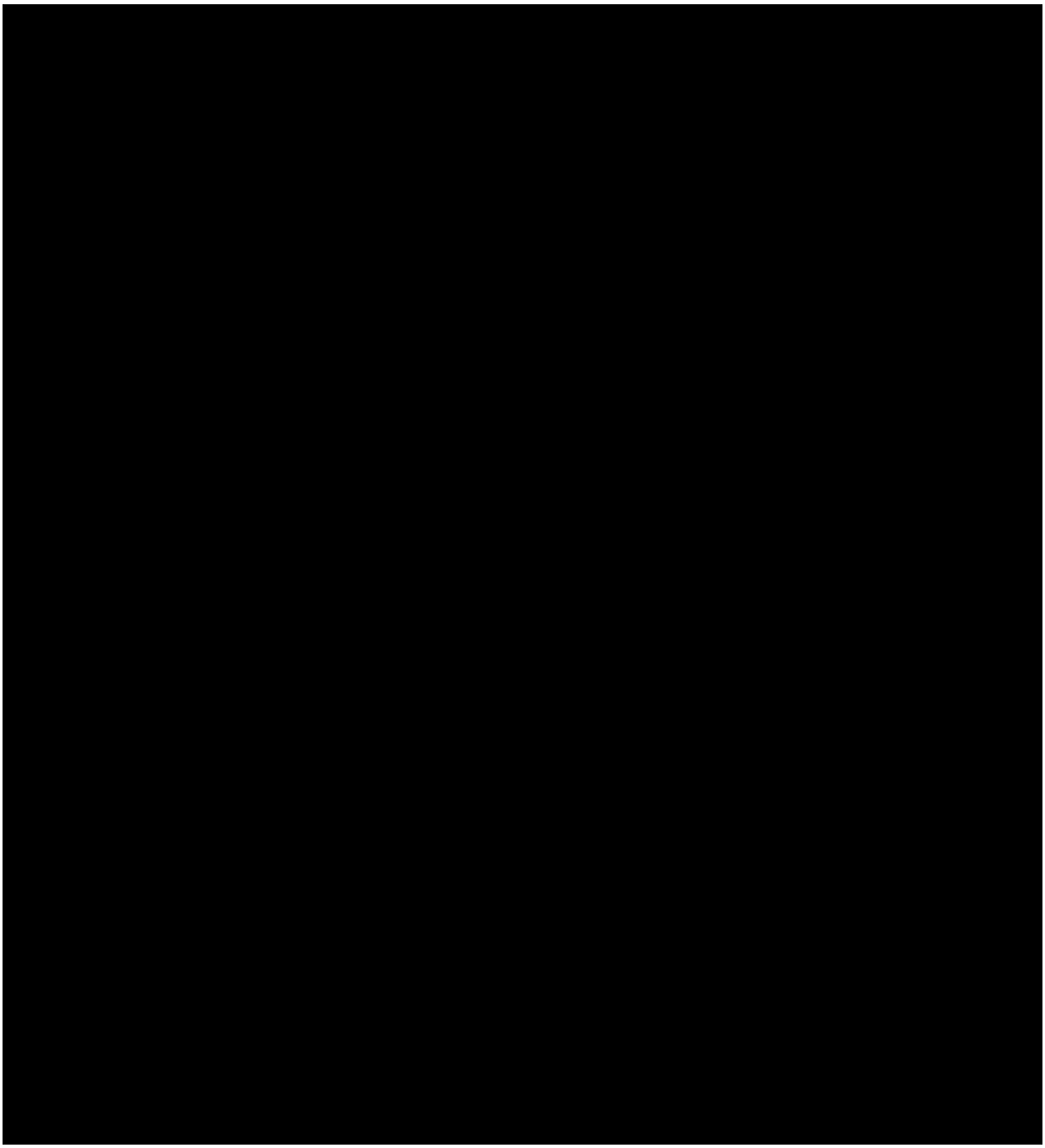
[redacted] describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output."

16. INDEX OF TABLES

[redacted]

[redacted]

[redacted]



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19. MOCK-UPS

19.1. TABLE MOCK-UPS (A SEPARATE DOCUMENT)

19.2. FIGURE MOCK-UPS (A SEPARATE DOCUMENT)

19.3. LISTING MOCK-UPS (A SEPARATE DOCUMENT)