Official Title of Study:

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTIPLE DOSE STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMIC EFFECTS OF BMS-986036 IN ADULTS WITH NONALCOHOLIC STEATOHEPATITIS

NCT Number: NCT02413372

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STATISTICAL ANALYSIS PLAN
FOR MB130045

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTIPLE DOSE STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMIC EFFECTS OF BMS-986036 IN ADULTS WITH NON-ALCOHOLIC STEATOHEPATITIS

VERSION # 2.0

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[redacted]

Research Hypothesis:

BMS-986036 administered daily or weekly for 16 weeks to obese adults with NASH will lower hepatic fat fraction (%) assessed by MRI to a greater extent than placebo.

Schedule of Analyses:

When approximately 60 subjects have completed 8 weeks of treatment, an interim analysis will be performed. Analyses will consist of summaries of the available data without revealing individual subjects' treatment assignments. The results of the interim analysis will be reviewed by a pre-specified panel of personnel.

Primary Analysis will be performed following the database lock after all subjects complete the end of treatment. Final analysis will be performed following the data base lock after all subjects have completed the study.

2 STUDY DESCRIPTION

2.1 Study Design

Study MB130045 is a randomized, double-blind, placebo-controlled, parallel-group, multiple dose design. Subjects will undergo screening evaluations to determine eligibility within 42 days prior to randomization. There will be a 7-day study skills training (Lead-In) period prior to randomization on Day 1. Eligible subjects will be randomized via Interaction Voice Response System (IVRS) on Day 1 to 1 of 3 parallel treatment groups. In total, approximately 90 randomized subjects (30 per group; ratio 1:1:1) will self-administer double-blind treatment, once daily for 16 weeks, in an outpatient setting. Subjects will be stratified using diagnosis of Type 2 diabetes mellitus (yes vs no) based on current American Diabetes Association criteria. Clinic visits are scheduled approximately every 2 weeks initially, and then monthly, to collect safety, PK and PD measures. The study design schematic is presented in Table 2.1-1:

For each subject, the total scheduled study duration from Screening to last Follow-up visit is approximately 12 months, comprised of screening (Day -42 to Day -8), placebo lead-in (approximately Day -7 to Day -1), on-treatment (Day 1 to Day 112) and a wash-out follow-up (Day 113 to Day 142) period, plus a scheduled follow-up visit that will be performed approximately 6 months (Day 292) after the last dose to perform DXA scanning and an additional immunogenicity measurement. Of note, subjects with a positive result in the ADA and/or anti-FGF21 antibody assays at the Day 142 and/or Day 292 follow-up visits, and who do not have evidence of decreasing or stable antibodies, will be followed for up to 12 months after the D142 visit until antibody levels resolve or demonstrate a consistent decreasing trend (these immunogenicity follow-up visits will be conducted approximately every 6-8 weeks).

The end of the study is defined as the date of the last scheduled follow-up visit, or immunogenicity follow-up visit, whichever is later, of the last subject in the study.

Table 2.1-1: Study Design Schematic

Visit Days									
D -42[a]	D -7	D 1	D 15	D 29	D 43	D 57	D 86[b]	D 112[c]	D 142	D 292[d]
Screening 5 weeks	Lead-in 1 week	On treatment 4 months							Follow-up	
	Placebo	Treatment A: 10 mg QD (daily) Treatment B: 20 mg QW (weekly) Treatment C: Placebo QD								

[a] MRI, MRE, and DXA baseline scans should be performed approximately 21 days prior to the Day 1 dose. Eligibility should be confirmed by central imaging lab prior to entry into the lead-in period (Day-7).

[b] The Day 86 visit is scheduled 4 weeks +1 day after the Day 57 visit, to tie in with a PK assessment.

[c] MRI, MRE and DXA end of treatment scans are conducted at Day 112 (+/- 1 week).

[d] DXA follow-up scan and immunognoicty sample collection are conducted 6 months (+/- 2 weeks) after the last dose.

D = Day

2.2 Treatment Assignment

During the Screening visit, the investigative site will call into the enrollment option of the IVRS designated by BMS for assignment of a 5-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, eg, 00001, 00002, 00003.... 00010. The patient identification number (PID) will ultimately be comprised of the site number and subject number. For example, the first subject screened (ie, enrolled) at site number 1, will have a PID of 0001 00001.Once it is determined that the subject meets the eligibility criteria following the Screening visit, the investigative site will call the IVRS to randomize the subject into the open dose panel.

At the time of entry into the lead-in period (Day -7 visit), the site will call IVRS in order for the lead-in medication to be assigned and dispensed. Subjects who successfully complete the lead-in period and meet the criteria for entry into the treatment period, will be randomly assigned by the IVRS to one of the following 3 double-blind treatment groups in a 1:1:1 ratio:

- BMS-986036 10 mg once daily (QD)
- BMS-986036 20 mg once weekly (QW)
- Placebo QD

Randomization will be stratified based upon diagnosis of Type 2 diabetes mellitus (yes vs. no).

The two strata for randomization are defined as follows:

- Strata 1: Diabetes Mellitus - Yes
- Strata 2: Diabetes Mellitus - No

Randomized subjects who discontinue will not be replaced.

Randomization schedules for both subject treatment and containers will be generated and kept by Bristol- Myers Squibb and stored in a secure location with restricted access.

At all study visits when study medication is dispensed, each subject will be assigned a kit number by the IVRS. Kit numbers will be assigned randomly and will correspond to the numbers printed on the packages and kits containing study drug. Kit numbers will be recorded on the appropriate eCRFs. The IVRS will be available 24 hours per day, 7 days per week.

2.3 Blinding and Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

In case of an emergency, the Investigator(s) has unrestricted access to randomization information via the IVRS and is capable of breaking the blind through the IVRS system without prior approval from sponsor. Following the unblinding the Investigator shall notify the Medical Monitor and/or Study Director.

Also, designated staff of BMS Research and Development can be unblinded at any time. The Bioanalytical Sciences section or its designate will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of samples from control group subjects. A single pharmacokineticist or designate in Clinical Pharmacology Pharmacometrics and a Biomarker scientist may be unblinded in order to prepare preliminary summaries of

pharmacokinetic, pharmacodynamic, and safety data, as needed before data are more generally unblinded. These summaries will not reveal individual subjects' treatment assignments. Except as noted above, other members of BMS Research and Development will remain blinded.

2.3.1 Interim Analysis Unblinding

In the event of an Interim Analysis, the interim analyses will be performed by unblinded individuals. The access to unblinded interim individual data will be limited to pre-specified personnel (e.g. statistician, programmer, PK scientist, pharmacometrician, and data integration programmer from Clinical Pharmacology and Pharmacometrics) as necessary to perform the interim analyses and data summaries Except as noted above, other members of BMS Research and Development will remain blinded to individual subjects' data.

Data summaries will not reveal individual subjects' treatment assignments and will be presented using masked treatment codes. Data summaries will be provided to the following BMS personnel: Early Development Team Lead, Exploratory Clinical and Translational Research Therapeutic Area (TA) Head, PK TA Head, Statistical TA Head and Biomarker TA Head. The study team other than the aforementioned personnel will be blinded to data summaries.

2.4 Protocol Amendments

This analysis plan reflects all protocol amendments including Amendment01 (dated 27-May-2015), Amendment02 (dated 29-Oct-2015) and Amendment 04 (03-Jun-2016).

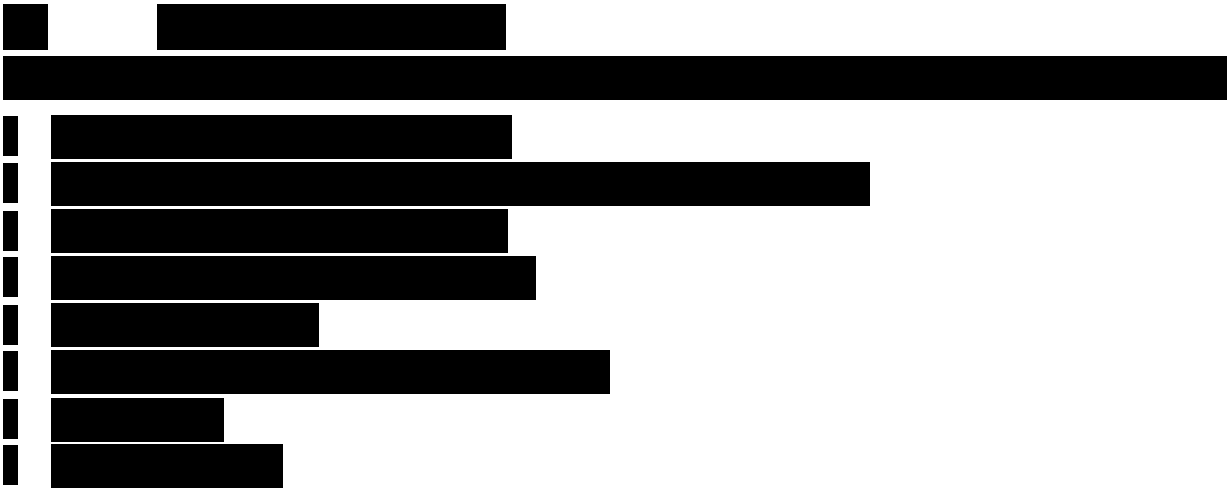
3 OBJECTIVES

3.1 Primary Objectives

The primary objective of this study is to assess the effect of 16 weeks of daily or weekly dose treatment of BMS-986036 on safety, tolerability and change in hepatic fat fraction (%) by MRI in patients with NASH.

3.2 Secondary Objectives

The secondary objectives are to assess the pharmacokinetics and immunogenicity of BMS-986036 in patients with NASH.



[redacted]

4 ENDPOINTS

4.1 Efficacy Endpoints

The primary efficacy endpoint is the change in hepatic fat fraction (%) by MRI from baseline to Week 16.

4.2 Safety Endpoints

The primary safety endpoints include incidence of AEs, serious AEs, and events of special interest including injection site assessment, AEs leading to discontinuation, and death as well as marked abnormalities in clinical laboratory tests, vital sign measurements, ECGs, physical examinations and bone mineral density (BMD) collected by DXA scan at specified time points in Table 5.1-1, Table 5.1-2 and Table 5.1-3 of the Protocol.

4.3 Pharmacokinetic Endpoints

The first secondary objective is to assess the pharmacokinetics of Total and C-Terminal intact BMS-986036 in NASH subjects. PK endpoints include Ctrough.

4.4 Immunogenicity Endpoints

The second secondary objective to assess the effect of daily or weekly doses of BMS-986036 on immunogenicity in NASH subjects will be measured by anti-BMS-986036 antibodies and anti-FGF21 antibodies at the specified time points in Table 5.5.1-1 of the Protocol.

[redacted]

[redacted].

5 SAMPLE SIZE AND POWER

The primary objective is to compare the change in hepatic fat fraction (%) from baseline to week 16 between each of 2 doses of BMS-986036 treatment group and placebo treatment group. With 27 subjects per treatment group with post-baseline measurements, there will be 82% power to detect a difference of 5% in mean change from baseline at Week 16 in hepatic fat fraction (%) between each of 2 doses of BMS-986036 treatment groups (10 mg daily and 20 mg weekly) and placebo at a significance level of 0.05 (one-sided). These calculations are based on an assumption that the hepatic fat fraction (%) change from baseline is normally distributed with a standard deviation of no greater than 7%, as estimated from data reported in a similar population[8,9]. No adjustment will be made for multiplicity.

To allow for dropouts, approximately 30 subjects per treatment group (total of 90 subjects) will need to be randomized, assuming up to 10% of the subjects do not complete post-baseline assessments.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

Screening: refers a period from the time the Informed Consent form is signed until initiation of the first lead-in placebo dose.

Lead in period: refers to a period from the first lead-in placebo dose until initiation of the first treatment dose.

On-Treatment period: refers to a period from the first treatment dose date to 14 days after the last treatment dose.

Follow-up period: refers to a period 15 days after the last treatment dose date.

6.2 Treatment Regimens

Approximately 30 subjects will be randomized to self-administer double-blinded study medication by subcutaneous injection at a dose of 10 mg BMS-986036 daily, 20 mg BMS-986036 weekly, or placebo daily for 16 weeks. The following table shows the total dose and number of subcutaneous injections per dose for each treatment group.

Table 6.2-1: Treatment Administration

Treatment		Solution Strength	Number and volume of subcutaneous injections	
			Day 1[a] of each treatment week	Days 2 - 7 of each treatment week
Lead-in phase	Placebo QD	N/A	2 x 1 mL	1 x 1 mL, daily
A	BMS-986036 10 mg QD	10 mg/ml	2 x 1 mL[b]	1 x 1 mL, daily
B	BMS-986036 20 mg QW	10 mg/ml	2 x 1 mL	1 x 1 mL, daily[c]
C	Placebo QD	N/A	2 x 1 mL	1 x 1 mL, daily

[a] For all treatments, on Day 1 of each treatment week, two injections are administered concurrently, in the morning.

[b] For treatment A, on Day 1 of each treatment week, the 2 injections consist of 1 active and 1 placebo, to maintain the blind between daily and weekly treatment arms.

[c] For treatment B, on Days 2-7 of each treatment week, the injection is placebo, to maintain the blind between daily and weekly treatment arms.

All analyses will be based on actual treatment regimens ("as treated"). Observations on safety parameters will be assigned to the most recent treatment regimen received.

6.3 Populations for Analyses

- All Enrolled Subjects, defined as all subjects who signed an informed consent;
- All lead-in subjects, defined as all subjects who have received at least one dose of placebo during the placebo lead-in period;
- All Randomized Subjects, defined as all subjects who are randomized to a treatment during the treatment period;
- All Treated Subjects, defined as all subjects who have received at least one dose of study treatment during the treatment period;
- Pharmacokinetic Population, defined as all subjects who receive any study medication and have any available concentration-time data. Additionally, the Evaluable PK Population is defined as subjects who have adequate PK profiles.

All available derived PK parameter values will be included in the PK data set and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.

7 STATISTICAL ANALYSES

SAS® version 8.2 or higher will be used for statistical analyses, tabulations and graphic presentations. S-Plus® may also be used for graphical presentations.

7.1 General Methods

Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Geometric mean and coefficient of variation (%CV) will also be presented for sample plasma concentration-time data and PK parameters. Descriptive summaries for categorical variables will utilize counts and percentages.

Adverse events and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA) version. Previous and concomitant medications will be coded using the most recent WHO Drug Dictionary version.

Longitudinal summaries of hepatic fat fraction (%), safety and biomarker endpoints use pre-defined visit windows (see Section 8.1.3).

7.2 Study Conduct

Relevant deviations from the study protocol, unscheduled corresponding unblinding events, protocol amendments and administrative changes will be documented and accounted for in presenting the data summaries, listings and descriptive statistical analyses. Relevant protocol deviations will be listed for all treated subjects. Any changes from planned protocol-specified analysis will be defined in the SAP and reported in the CSR. APPENDIX 1 describes the relevant protocol deviations that will be programmed from the database.

7.3 Study Population

7.3.1 Subject Disposition

Subject disposition will be listed. Summary tables reflecting the number of subjects who are enrolled, who enter lead-in period, reasons for not entering the lead-in period, who are randomized, and reasons for not being randomized will be presented as overall for all enrolled subjects.

The number of subjects who complete the treatment period, who do not complete the treatment period, who continue the follow up period, who do not continue the follow up period, who complete the study and reasons for discontinuation from the treatment period study, will also be summarized for all treated subjects, as overall and by treatment.

7.3.2 Demographic Characteristics

Demographic characteristics such as gender, age, race and ethnicity will be listed for all treated subjects. Demographic characteristics will also be summarized for all treated subjects, as overall and by treatment.

7.3.3 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for all treated subjects as overall and by treatment:

- Type 2 diabetes mellitus (yes, no);
- Hepatic fat fraction (%);
- NASH CRN fibrosis staging (1, 2, 3);
- NAS(NAFLD activity score);

- Fatty liver index
- ALT levels

7.3.4 Physical Measurements

Physical measurements such as body weight, height, waist circumference and body mass index (BMI) will be listed for all treated subjects. Measurements will also be summarized by nominal visit for all treated subjects, as overall and by treatment.

7.3.5 Medical History and Previous Medications

Medical history and previous medications taken prior to dosing will be listed for all treated subjects.

7.4 Extent of Exposure

Extent of exposure for 16-week double blinded treatment period will be summarized for all treated subjects, presenting the numbers and percentage of subjects with an extent of exposure within the following day ranges by treatment group: 1 to 15, 16 to 29, 30 to 43, 44 to 57, 58 to 86, 87 to 112 and > 112. Also the mean, SD, median and range of the extent of exposure to blinded treatment will be presented by treatment group. Study drug administration, randomization schedule will be documented as per subject listings. Any non-study medications taken by subjects, any conducted non-study medical treatment procedures, and any utilized non-study diagnostic procedures will also be listed.

7.5 Efficacy

To evaluate the effect of BMS-986036 on change in hepatic fat fraction (%) by MRI in subjects with biopsy-proven NASH after 16 weeks of treatment, a longitudinal repeated measures analysis will be used to analyze the change in hepatic fat fraction (%) from baseline to Week 16 in the treated population who have both a baseline and at least one post-baseline measurement. The model will include treatment group, week and treatment-by-week interactions as main effects and baseline hepatic fat fraction (%) and baseline diabetic status as covariates. An unstructured covariance matrix will be used to represent the correlation of the repeated measures within each subject. The model will provide point estimates, standard errors and 2-sided 90% confidence intervals for mean change from baseline at all time points within and between treatments. P-values will be calculated to compare the treatment effect in each of two BMS-986036 (10 mg daily and 20 mg weekly) treatment groups to that in the placebo treatment group at Week 16. Each treatment group comparison will be performed at a one-sided 0.05 significance level. No adjustment will be made for multiplicity.

Summary statistics will be tabulated for all treated subjects by treatment, study day for hepatic fat fraction (%) with corresponding change from baseline. Plot of mean profile over time will also be provided for hepatic fat fraction (%) by treatment. In addition, the descriptive statistics for hepatic fat fraction (%) will be summarized by baseline NASH CRN fibrosis staging (1, 2, 3), type 2 diabetes mellitus (yes, no), NAS (NAFLD activity score) and fatty liver index.

Two sensitivity analyses will be performed in the longitudinal repeated measure analysis.

- For patients without measurement at week 16 for hepatic fat fraction (%), last observation for hepatic fat fraction (%) measured on or after Day 86 will be carried forward to be the value at week 16.
- Baseline NASH CRN fibrosis staging and the treatment-by-baseline diabetic status interactions will be included in the model. The effect of BMS-986036 on the change in hepatic fat fraction (%) from baseline to week 16 within each stratum will be analyzed.

7.6 Safety

Analysis of all safety data will follow the BMS guideline of analysis of safety data.[10]

The evaluation of safety is based on clinical adverse events (AEs), vital signs, ECGs results, physical examinations, clinical laboratory results, the result of DXA scan for bone mineral density as well as injection assessment reported during the study.

All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment and overall. Any physical examination findings will be listed. ECG, vital signs and clinical laboratory test results and corresponding change from baseline will be listed and summarized by treatment group. Values for ECG, vital signs and clinical laboratory test results outside the pre-specified criteria will also be listed and summarized. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed. Bone mineral density (BMD) results will be tabulated.

Where appropriate, baseline is defined as the last non-missing result with a collection date-time less than the date-time of the first active dose of study medication, for laboratory results, vital signs, ECG and BMD results.

7.6.1 Deaths

All reported deaths after a subject is enrolled (i.e., has signed the informed consent) will be listed separately by subject for all enrolled subjects.

7.6.2 Serious Adverse Events

All reported serious adverse events (SAEs) will be listed for all enrolled subjects and may also be summarized for all treated subjects by treatment as needed.

7.6.3 Adverse Events

All AEs will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using current version of Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be summarized and listed by SOCs and PTs.

Adverse events which occur during the lead-in period will be tabulated for all lead-in subjects as overall. And adverse events which occur on or after the first active dose of study treatment will be tabulated for all treated subjects by treatment. Events will be assigned to the study treatment administered to the subject. The proportion of subject having an adverse event will be calculated

as the number of subjects experiencing the event, divided by the total number of subjects receiving study treatment.

All AE listings will indicate the unique subject identifier, age, gender, current treatment, the date of onset, the date of resolution, day of onset relative to the start of treatment, action taken, investigator's assessment of severity and relationship to study drug. Additional listings will be provided for adverse events leading to discontinuation and adverse events without recorded resolution. Summaries of adverse events will include adverse events, adverse events by intensity and adverse events by relationship. Adverse events leading to discontinuation may also be summarized as needed.

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in a single analysis period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

When a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event
- Onset date and time

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

Subjects will only be counted once in the 'Total' at their maximum intensity, regardless of SOC or PT.

In addition, a summary of exposure adjust AEs including multiple occurrences of unique events will be reported if there are at least 5% of treated subjects with multiple occurrences of unique events in any treatment group during double-blinded period. A by-subject listing of unique events will be provided.

Injection site reactions as a target physical examination will be monitored from Day -7 through the end of the out-patient follow-up period. The Draize Scale for erythema and edema will be used

as a guide for reporting AEs at the blinded study drug injection site, see Table 5.3.3-1 in the protocol. In addition, for injection site reaction will be summarized as a separate frequency table and listed.

7.6.4 Clinical Laboratory Evaluations

The results of all protocol-specified clinical laboratory tests, as well as laboratory results outside of the normal range, will be listed for all treated subjects. Scheduled laboratory measurements and corresponding change from baseline values will be summarized by treatment and nominal visit for each laboratory test. Laboratory abnormalities are determined from laboratory measurements analyzed at the central or local laboratory, and are graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.[11]

For each laboratory test, emergent laboratory abnormalities (not emergent, grade 1, grade 2, grade 3, grade 4, grade 1 to 4; grade 3 to 4) are summarized by treatment for all treated subjects. On-treatment emergent abnormalities are those with a higher toxicity grade than the baseline toxicity grade (including missing baseline). Laboratory abnormalities regardless of baseline toxicity grade are also summarized analogously by treatment. Commonly collected laboratory tests with DAIDS toxicity grades may include the following: hemoglobin, leukocytes, lymphocytes (absolute), neutrophils + bands (absolute), platelet, ALT, AST, total bilirubin, Direct bilirubin, alkaline phosphatase, GGT, albumin, INR, creatinine, calcium, phosphorus, magnesium, fasting glucose.

Laboratory abnormalities on treatment are also summarized by baseline toxicity grade (grade 0; grade 1, grade 2; grade 3, grade 4) and treatment regimen for the following laboratory tests: ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, calcium.

The laboratory value during the study period with the highest toxicity grade is reported for each test.

Laboratory results for subjects with any laboratory abnormality with grade 3 and grade 4 (scheduled and unscheduled) will be listed.

7.6.5 ECG

All recorded electrocardiograms will be listed.

If Fridericia's corrected QT (QTcF) is not available in the database, QTcF will be calculated using the reported uncorrected QT Interval and Heart Rate, and the following formula:

$$QTcF = \frac{QT}{(60/HEART\,RATE)^{1/3}}$$

If Bazzett's corrected QT(QTcB) is not available in the database, QTcB will not be calculated.

Summaries of ECG parameters (heart rate (HR), QT (QT, Bazett's corrected QT [QTcB], Fridericia's corrected QT [QTcF]), PR and QRS intervals) will be tabulated for all treated subjects by study day and treatment. Summaries of ECG parameters will include change from baseline at list of time points.

Subjects with ECG intervals outside of a pre-specified range will also be listed.

The following criteria (Table 7.6.5-1) will be used to determine ECG results that are outside of a pre-specified range:

Table 7.6.5-1: Criteria for ECG Results Outside of a Pre-specified Range

PR (msec):	Value > 200
QRS (msec):	Value > 120
QT (msec):	Value > 500 or change from baseline > 30
QTcB (msec):	Value > 450 or change from baseline > 30
QTcF (msec):	Value > 450 or change from baseline > 30

7.6.6 Vital Signs

Vital signs parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and body temperature) will be listed. Summaries of vital sign parameters will be provided for each vital sign parameter at corresponding visits for all treated subjects by treatment and respective changes from baseline.

Subjects with vital signs outside of a pre-specified range will also be listed.

The following criteria will be used to determine vital sign results that are outside of a pre-specified range, where changes from baseline are based on matched postural positions and are calculated as parameter value - baseline parameter value:

Table 7.6.6-1: Criteria for Vital Signs Results Outside of a Pre-specified Range

Heart Rate(bpm)	Value > 100 and change from baseline > 30, or Value < 55 and change from baseline < -15
Systolic BP(mmHg)	Value > 140 and change from baseline > 20, or Value < 90 and change from baseline < -20
Diastolic BP(mmHg)	Value > 90 and change from baseline > 10, or Value < 55 and change from baseline < -10
Respiration(breaths/min)	Value > 16 or change from baseline > 10
Temperature (°C)	Value > 38.3°C or change from baseline > 1.6°C

7.6.7 Physical Examination Findings

All physical examination abnormal findings will be listed for all treated subjects per subject and visit.

7.6.8 Bone Mineral Density

Bone mineral density (BMD) results will be summarized for all treated subjects by treatment group using descriptive statistics of values and percent change from baseline at each scheduled time point. The relationship between BMS-986036 (Total and C-Terminal intact) exposure and changes in bone mineral density may be explored.

7.7 Immunogenicity Analyses

Subjects on active drug will be tested for Anti-BMS-986036 and Anti-FGF21 antibody on Day 1, Day 29, Day 57, Day 86, Day 112, Day 142 and Day 292. Subjects testing positive ADA and/or anti-FGF21antibody results at the Day 142 and/or Day292 without evidence of decreasing or stable antibodies may be asked to return for antibody testing. These assessments may continue, approximately every 6-8 weeks, for up to 12 months following the Day 142 visit and will be discontinued when antibodies have resolved or are judged by Medical Monitor to be decreasing or stable.

A positive BMS-986036-induced immunogenicity response is defined as:

1) a missing baseline immunogenicity measurement and a positive laboratory reported immunogenicity response post-baseline
2) a negative laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline
3) a positive laboratory reported baseline immunogenicity response and a positive laboratory reported immunogenicity response post-baseline that has a titer value at least 4 fold greater than the baseline titer value

Immunogenicity results (anti-BMS-986036 antibody response, anti-FGF21 antibody response, and neutralizing antibody [NAB] response) will be summarized and listed. The relationship between immunogenicity and PK and/or PD may be explored for assessment of impact of immunogenicity. Post-dose positive results at 2 or more consecutive timepoints, where the first and last positive result are at least 16 weeks apart, is defined as persistently positive.

7.8 Pharmacokinetics

The Pharmacokinetic (PK) population will be used for all listings. Evaluable PK population will be used for summaries and statistical analyses. Analyses will include BMS-986036 (C-Terminal Intact) and BMS-986036 (Total) data in the PK dataset for BMS-986036.

Subject BMS-986036 serum concentration-time data will be listed for BMS-986036 (C-Terminal Intact) and BMS-986036 (Total). Summary statistics will be tabulated for observed serum Trough concentrations (C-terminal intact and Total) by treatment, study day and nominal time. Geometric means for Ctrougth will be plotted against study day or week by BMS-986036 dose.

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- [redacted]

[redacted]

[redacted]

7.10 Interim Analyses

Because data emerging from this study may be needed for a timely decision about adjustment to the development of the program, an interim analysis will be conducted after approximately 60 subjects have completed 8 weeks of treatment. Analyses will consist of summaries of the available data without revealing individual subjects' treatment assignments. Refer to section 2.3.1 for details regarding blinding/unblinding. The results of the interim analysis will be reviewed by a pre-specified panel of personnel. The following reports will be included for the interim analysis.

- Demographic Characteristics Summary
- Baseline Disease Characteristics Summary
- Summary Statistics for Hepatic Fat Fraction (%) and Change from Baseline Overtime
- Summary Statistics for Hepatic Fat Fraction (%) and Change from Baseline Overtime By Baseline Disease Characteristics
- [redacted]
- Summary Statistics for Physical Measurements: Body Weight and Waist Circumference
- [redacted]
- Summary Statistics for Fasting Lipids: Total Cholesterol, Triglyceride, LDL-C and HDLC

8 CONVENTIONS

EmBARC (Enhanced Biometric Analysis & Reporting Capability) standard time windowing, imputation rules, and counting rules will be applied.

8.1 Decimal Places

The number of decimal places displayed in efficacy, safety, and biomarker listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of confidence interval will be displayed to three decimal places.

8.1.1 Pharmacokinetic Summaries

In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%CV) will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places. Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations

For the summaries of serum concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, other than Ctrough, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

All available concentration-time data and derived pharmacokinetic parameter values will be included in the PK data set and listed accordingly.

Treatment of Outliers

Individual subject serum concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Certain concentrations at certain time points for a subject may be excluded in the population PK model following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

PK Exclusions[12]

PK Analysis, Reporting, and Exclusion criteria should following the BMS PK Harmonization document Version 2.0. Specific guideline for exclusionary criteria for half-life and how other PK parameters are affected for exclusion is under section 9.2 of the BMS PK Harmonization document.

Exclusion of one or more parameters or the entire dataset may be considered due to incomplete profile such as AUC(INF) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax. In addition, subjects may be excluded from the analysis if they missed doses or any other considerations which may impact drug absorption.

[redacted]

8.1.3 Visit Windows

All visit windowing are according to the visit number windowing defined in the EmBARC metadata workbook. Time is measured from the first active dose date of study therapy. For longitudinal summaries of data, windows around planned measurement times are based on the midpoint between planned study visits unless specified otherwise. If there are multiple records within the same visit window, then the value in the visit window closest to the day of the planned visit is selected.

The analysis visit window for imaging endpoints (MRI and MRE) are defined as follows: Screening Window: (-60d / +0d), D57 Window: (-14d / +40d) and D112 window: (-14d / +40d)

9 CONTENT OF REPORTS

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). Details of the tables, listings, and figures to be prepared for the final CSR will be included in a study-specific Data Presentation Plan (DPP).

APPENDIX 1 RELEVANT PROTOCOL DEVIATIONS

Relevant protocol deviations that can be programmed from the database are identified below. The list would be updated as appropriate if, in the course of monitoring the study, additional protocol deviations are found and considered relevant.

- No signed informed consent;
- Liver biopsy with documented results of NASH with NASH CRN fibrosis stage <1 or >3, or equivalent using a different scoring system.
- Body mass index (BMI) of < 25
- Hepatic fat fraction (%)< 10% by MRI performed during the Screening period
- Males and females, age< 21 or > 75 years
- Positive pregnancy test result during screening;
- Laboratory test values meeting any of the following criteria at screening:
  - ALT level ≥ 5xULN
  - Albumin <3.5 g/dL (35 g/L)
  - INR (International Normalized Ratio) >1.3
  - Total bilirubin ≥ 1.5 mg/dL (≥ 25.6 µmol/L)
  - Platelet count <100 x 10^9/L
  - Alpha fetoprotein (AFP) > 100 ng/mL (> 82.6 IU/mL)
  - [redacted]
  - Positive blood screen for hepatitis C antibody, hepatitis B surface antigen.
  - Subjects with a centrally read Screening DXA T-score at the total spine, total hip or femoral neck, less than or equal to -2.5 S.D.
  - Uncontrolled hypertension (systolic blood pressure [SBP] ≥160, and/or diastolic blood pressure [DBP] ≥ 95 mmHg).
  - QTcF > 480 msec on 12-lead electrocardiogram (ECG) during the Screening period, confirmed by repeat.
  - Impaired renal function defined as an estimated glomerular filtration rate (GFR) of <49 mL/min/1.73m^2 using Modification of Diet in Renal Disease (MDRD) equation.
- Use of oral, intravenous, subcutaneous or intra-articular glucocorticoids ≥ 5 days between randomization through to end of treatment.
- Randomized subjects who receive no study medication for ≥ 2 consecutive weeks during the double-blind treatment period.

[redacted]

[redacted]