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# Clinical Protocol 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

**Revised Protocol: 03**
**Incorporates Amendments 01, 02 & 04 and Administrative Letter 01**

**Study Director**
[redacted]

**Medical Monitor**
Edgar Charles, MD
[redacted]

[redacted]

**protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).**

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

# DOCUMENT HISTORY

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Amendment 04 | 03-Jun-2016 | Adjusts the number of subjects needed to support the interim analysis and clarifies the unblinded BMS personnel. |
| Revised Protocol 03 | 03-Jun-2016 | Incorporates Amendment 04 |
| Amendment 02 | 29-Oct-2015 | **Amendment Rationale:**<br>(i) Addition of immunogenicity testing and endogenous FGF21 assessments at the Day 292 follow up visit [redacted].<br>(ii) Extension of follow-up immunogenicity testing and endogenous FGF21 assessments (for subjects with positive immunogenicity testing) to up to 12 months post-Day 142 . This provides a longer follow-up (12 months instead of 6 [redacted].<br>(iii) Changes to protocol inclusion criteria and concomitant medication allowance as follows:<br>• Adjustment of BMI inclusion criterion from $\geq$ 30 to $\geq$ 25 kg/m$^2$<br>• Removal of Fatty Liver Index inclusion criterion<br>• Adjustment of restriction of Vitamin E from > 60 IU/day to > 120 IU/day<br>[redacted]<br>(iv) Clarification of imaging procedure schedule and assessments throughout the protocol to support internal consistency<br>(v) General clarifications related to pregnancy testing and follow-up schedule assessments to better support internal consistency<br>(vi) Correction of typographical errors<br>(vii) Update of Medical monitor assignment on title page consistent with administrative letter 01 |
| Revised Protocol 02 | 29-Oct-2015 | Incorporates Amendment 02 items |
| Administrative letter 01 | 28-Jul-2015 | Updated medical monitor assignment |
| Revised Protocol 01 | 27-May-2015 | Incorporates Amendment 01 items. |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Amendment 01 | 27-May-2015 | (i) Addition of a Data Monitoring Committee by independent reviewers to support safety data review for all treated subjects (ii) Revision for discontinuation criteria (iii) Addition of a reference for the Common Terminology Criteria for Adverse Events (CTCAE) grading (iv) Addition of an immunogenicity sample collection at Day 15 (v) [redacted] The interim analysis is corrected to reflect 'summaries', instead of 'summaries and graphs'. (viii) [redacted] (ix) Correction of typographical errors |
| Original Protocol | 03-Feb-2015 | Not applicable |

# SYNOPSIS

## Clinical Protocol MB130045

### PEG-FGF21

**Protocol Title:** 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

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):** Each eligible subject will be randomized to self administer BMS-986036 by subcutaneous injection at a dose of 10 mg daily, or 20 mg weekly or a daily placebo injection, for 16 weeks.

**Study Phase:** 2A

**Research Hypothesis:** BMS-986036 administered daily or weekly for 16 weeks to adults with Non-alcoholic Steatohepatitis (NASH) will lower the percent of hepatic fat content to a greater extent than placebo.

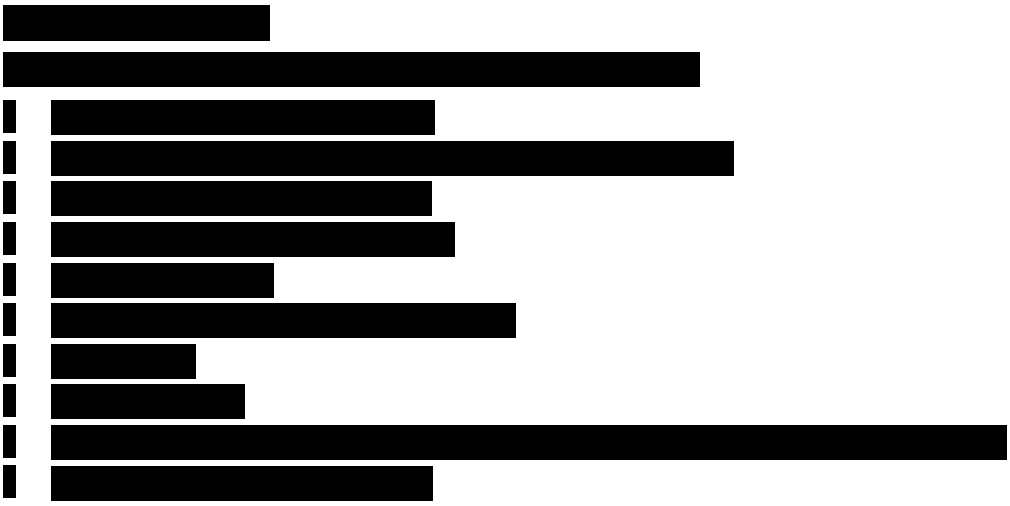
**Objectives:**

**Primary Objectives**

To assess the effect of 16 weeks of daily or weekly doses of BMS-986036 on safety, tolerability and change in hepatic fat fraction (%) by MRI in patients with NASH.

**Secondary Objectives**

To assess the pharmacokinetics and immunogenicity of BMS-986036 in patients with NASH.



**Study Design:**

**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 daily<br>Treatment B: 20 mg weekly<br>Treatment C: Placebo daily | | | | | | | |

[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 immunogenicity sample collection are conducted 6 months (+/- 2 weeks) after the last dose.

D = Day

**Study Population:** Approximately 90 male and female subjects aged 21 to 75 years with a BMI of $\geq$ 25 inclusive with a liver biopsy performed within 1 year of Screening (or between Screening and Lead-in) with documented results of NASH with NASH CRN fibrosis stage 1-3 and a hepatic fat fraction (%) $\geq$ 10% by MRI.

Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception for at least 4 weeks before dosing.

**Study Drug:** includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

**Study Drug for MB130045**

| Medication | Potency | IP/Non-IP |
|---|---|---|
| Placebo for BMS-986036-01 Injection | N/A | IP (8 vials/Kit) |
| BMS-986036-01 Injection, 10mg/vial | 10 mg/mL | IP (8 vials/Kit) |

**Study Assessments:**

- Safety Outcome Measures: Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.
- Pharmacokinetic Measures: serum concentration of BMS-986036 (Total and C-terminal intact).

- [redacted]

**Statistical Considerations:**

**Sample Size:**

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 in a similar population. 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.

**Endpoints:**

Baseline is defined as the last non-missing pre-dose measurement for all the endpoints.

**Primary Endpoints**:

- Change in hepatic fat fraction (%) from baseline to Week 16.
- 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.

**Secondary Endpoints**:

- Pharmacokinetic endpoint: Assess the pharmacokinetics of C-terminal and total BMS-986036 in NASH subjects to be assessed by the following endpoint: Ctrough
- Immunogenicity endpoints: anti- BMS-986036 antibodies and anti-FGF21 antibodies

[redacted]

**Analyses:**

**Primary Analysis:**

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 (%) at Week 16 from baseline 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 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 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.

**Safety Analysis:**

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment group. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed. BMD results will be tabulated.

**Pharmacokinetic analyses:**

Summary statistics will be tabulated for observed BMS-986036 serum concentrations (Total and C-Terminal intact).

**Immunogenicity analyses:**

Responses of anti-BMS-986036 antibodies and anti-FGF21 antibodies will be listed and tabulated by treatment and study day. The relationship between immunogenicity and PK and/or PD may be explored.

[redacted]

**Interim Analyses:**

Because data emerging from this study may be needed for 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. The results of the interim analysis will be reviewed by a pre-specified panel of personnel.

## TABLE OF CONTENTS

[redacted]

## 1.2 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.

## 1.3 Objectives(s)

### *1.3.1 Primary Objectives*

To assess the effect of 16 weeks of daily or weekly doses of BMS-986036 on safety, tolerability and change in hepatic fat fraction (%) by MRI in patients with NASH.

### *1.3.2 Secondary Objectives*

To assess the pharmacokinetics and immunogenicity of BMS-986036 in patients with NASH.

[redacted]

## 1.5 Overall Risk/Benefit Assessment

This is the first study in which BMS-986036 will be administered to patients with NASH; two previous studies have been conducted or are ongoing including the completed first-in-human study in obese, but otherwise healthy volunteers and an ongoing study in obese diabetic subjects. The preclinical data in diabetic NASH animal models, and clinical data in non-diabetic and diabetic subjects, demonstrate beneficial metabolic effects with short term administration of BMS-986036 (up to 12 weeks). These benefits included weight loss, reduction of hepatic fat and improved insulin sensitivity; however, it is not known whether study subjects with obesity and NASH in this proof of concept study will benefit in these or other ways from BMS-986036. In addition, immunogenicity, bone effects and injection site reactions will be explored as potential risks of BMS-986036. Data from this phase 2a study will be used to guide future clinical development of BMS-986036.

### *1.5.1 Risk Mitigation Strategy*

Immunogenicity

BMS-986036 is a PEGylated recombinant variant of human FGF21 and has the potential to be immunogenic, however, the potential safety liability of antibody formation in humans is considered to be low. Most human protein therapeutics can induce a rapid and strong ADA response in animals but the presence of ADA in these species does not necessarily predict immunogenicity in humans.[34] Following daily dosing, BMS-986036 ADA were detected in rats and monkeys in 1-month (up to 59% and 20%, respectively) and 4-month (up to 87% and 30%, respectively) toxicology studies at all doses tested. However, the presence of ADAs in these species had no substantial or meaningful impact on the overall toxicokinetic results of total and C-terminal intact BMS-986036, pharmacodynamic, toxicology, clinical pathology or histopathology endpoints on these studies.

In the first in human study, three of 72 subjects (4%) dosed with BMS-986036 had positive results in the ADA and anti-FGF21 antibody assays at the end of study time point. Additional post-study follow-up immunogenicity testing for these three subjects showed progressively decreasing assay titers at subsequent visits over a six month time period. One of these three

subjects tested neutralizing in the neutralizing antibody assay at two out of three follow up visits. At the end of this follow up period, all 3 subjects were reported in good health with no adverse events reported.

There is a theoretical risk of neutralizing antibody formation to BMS-986036 that could cross react with endogenous FGF21. FGF21 knockout mice are known to be viable, are able to reproduce and have a generally normal phenotype.[35] The clinical consequences of a neutralizing anti-drug antibody (ADA) response to endogenous FGF21 are unknown, as FGF21 deficiency has not been reported in humans. Subject safety will be closely guarded in early clinical studies. All subjects administered BMS-986036 will be closely monitored for possible immunogenicity related adverse events (AEs), such as rash, fever and severe injection site reactions. Clinically relevant immune reactions (e.g. hypersensitivity reactions) considered related to BMS-986036 will be reported as AEs and treated according to current standard of care medical practice.

All subjects will be monitored for occurrence of ADA and anti-FGF21 antibodies during dosing, at approximately 4 weeks following the last dose (D142 follow-up visit), and at approximately 6 months following the last dose (D292 follow-up visit). If present, antibodies will be assessed for neutralizing activity. Subjects with a positive result in the ADA and/or anti-FGF21 antibody assays at the Day 142 or Day 292 follow-up visits, without evidence of decreasing or stable antibodies, will be followed afterwards with immunogenicity assessments 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.

In addition, endogenous FGF21 will be measured at all follow up visits, including the D142 and D292 follow up visits and the immunogenicity follow up visits (for subjects with positive ADA and/or anti-FGF21 antibodies at D142 and/or D292, without evidence of decreasing or stable antibodies).

Bone effects

No bone resorption marker change has been observed in subjects in the first in human study (MB130001). Bone formation markers were slightly reduced in all subjects in the MAD, including those treated with placebo, and only in subjects treated with the highest daily dose (30 mg daily) were bone markers reduced to an extent greater than placebo. A BMS-986036-related bone risk to adult humans is considered low; unlike thiazolidinediones (TZDs), bone resorption markers were not increased. To minimize the potential risk to subjects in whom a reduction of bone formation markers could impact skeletal healing, those with recent fracture or orthopedic surgery will be excluded.

To assess whether chronic dosing of BMS-986036 has the potential to modulate bone turnover and vitamin D and mineral metabolism, bone turnover markers (BSAP, P1NP and CTX-1), PTH and 1,25 dihydroxy vitamin D along with calcium, magnesium, phosphorus are being assessed in the ongoing MB130002 study in T2DM subjects. .

In this study, we will continue to monitor bone turnover markers, calcium, magnesium and phosphorus before and after the dosing period. Samples for PTH and 1,25 dihydroxy vitamin D will be collected, and may be assayed if a perturbation is observed in the MB130002 study.

Additionally, bone mineral density (BMD) will be measured by DXA at baseline, end of treatment and six months following end of dosing to determine whether daily or weekly administration of BMS-986036 for up to 16 weeks has any acute or sustained effect on BMD.

# 2 ETHICAL CONSIDERATIONS

## 2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

## 2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

## 2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form(s) and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form(s) and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
- If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form(s) must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

# 3 INVESTIGATIONAL PLAN

## 3.1 Study Design and Duration

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 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 a diagnosis of Type 2 diabetes mellitus (yes vs no) based on current American Diabetes Association (ADA) 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 3.1-1.

**Table 3.1-1: 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)<br>Treatment B: 20 mg QW (weekly)<br>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 immunogenicity sample collection are conducted 6 months (+/- 2 weeks) after the last dose.

D = Day

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), clinical laboratory evaluations, MRI, MRE and DXA scans will be performed at selected times throughout the study. Subjects will be closely monitored for adverse events throughout the study. Blood will be collected for pharmacokinetic (PK) and pharmacodynamic (PD) analysis. Approximately 500 mL of blood will be drawn from each subject during the study.

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 (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.

## 3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

## 3.3 Study Population

For entry into the study, the following criteria MUST be met at Screening. No exceptions will be granted.

### *3.3.1 Inclusion Criteria*

1. **Signed Written Informed Consent**
   a. Signed informed consent form.
2. **Target Population**
   a. Liver biopsy performed within 1 year of Screening or may be performed between Screening and Lead-in (Day -7) with documented results of NASH with NASH CRN fibrosis stage 1-3, or equivalent using a different scoring system.
   b. Body mass index (BMI) of ≥ 25. Note: BMI = weight (kg)/[height (m)] $^2$
   c. Hepatic fat fraction (%) ≥ 10% by MRI performed during the Screening period.
   d. Subject is able to medically tolerate the performance of the MRI or DXA scans and has suitable weight and circumference. See Section 3.4.3 for further details.
   e. Subject agrees not to initiate a weight loss program and agrees to maintain consistent dietary habits and exercise regimen for the duration of the study.
   f. Subject re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented and will receive a new subject number.
3. **Age and Reproductive Status**
   a. Males and females, ages 21 to 75 years, inclusive
   b. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
   c. Women must not be breastfeeding.

d. WOCBP must agree to follow instructions for method(s) of contraception for at least 4 weeks before dosing, for the duration of treatment with study drug (s) 16 weeks plus 5 half-lives of study drug (30 days) plus 30 days (duration of ovulatory cycle) for a total of 2 months post-treatment completion.

e. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (16 weeks) plus 5 half-lives of the study drug (30 days) plus 90 days (duration of sperm turnover) for a total of 4 months post-treatment completion.

f. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one highly effective method of contraception.

**HIGHLY EFFECTIVE METHODS OF CONTRACEPTION**

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

### *3.3.2 Exclusion Criteria*

**1. Medical History and Concurrent Diseases**

a. Evidence of a medical condition contributing to chronic liver disease other than NASH (such as, but not limited to, hemochromatosis, autoimmune hepatitis, Wilson disease, alpha-1 antitrypsin deficiency, drug or alcohol-induced liver disease, toxin exposures, viral hepatitis).

b. Evidence of cirrhosis.

c. Decompensated liver disease including, but not limited to, a history or presence of bleeding varices, ascites, or hepatic encephalopathy.

d. Uncontrolled diabetes defined as HbA1c of 9.5% or higher within 8 weeks prior to screening, or symptoms of poorly controlled diabetes, such as marked polyuria and polydipsia with greater than 10% weight loss, within 12 weeks of screening.
e. Subjects who have experienced 5% or more weight loss due to participation in a weight loss program or use of weight loss medication within 8 weeks of screening.
f. Any bone trauma, fracture or bone surgery (i.e., hardware placement, joint replacement, bone grafting or amputation) within 8 weeks of screening.
g. Known immunocompromised status, including but not limited to, individuals who have undergone organ transplantation or who are positive for the human immunodeficiency virus.
h. Subjects receiving regular oral or injectable glucocorticoid medication. Inhaled, nasal or topical steroids used at the registered dose strengths are permitted.
i. Any bariatric surgery or biliary diversion (e.g. gastric bypass, gastric banding, Roux-en-Y, etc.).
j. Subjects with a history of cancer within the last 5 years (other than treated basal or squamous cell carcinoma) are excluded.
k. Any major surgery within 6 weeks of screening.
l. Donation of blood to a blood bank or in a clinical study (except a screening visit) within 6 weeks of screening (within 4 weeks for plasma only).
m. Blood transfusion within 6 weeks of screening.
n. Any significant acute or chronic medical illness, other than the underlying condition being studied, including, but not limited to coronary artery disease, congestive heart failure, cerebrovascular disease, renal failure, serious psychiatric disease.
o. Recent (within 1 year of study drug administration) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 1) or significant alcohol consumption (average > 20 g/ day females or > 30 g/day males).
p. Inability to self-administer subcutaneous injections.
q. Inability to be venipunctured and/or tolerate venous access.
r. Inability to comply with all protocol assessments including the follow-up visits.
s. Any other sound medical, psychiatric and/or social reason as determined by the investigator.

**2. Physical and Laboratory Test Findings**

a. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population.
b. ALT level ≥ 5xULN
c. Albumin <3.5 g/dL (35 g/L)
d. INR (International Normalized Ratio) >1.3
e. Total bilirubin ≥ 1.5 mg/dL (≥ 25.6 µmol/L)
f. Platelet count <100 x $10^9$/L
g. Alpha fetoprotein (AFP):

- AFP > 100 ng/mL (> 82.6 IU/mL), OR
- AFP ≥ 50 and ≤ 100 ng/mL (≥ 41.3 IU/mL and ≤ 82.6 IU/mL) requires a liver ultrasound. Subjects with findings suspicious for HCC are excluded.

h. HbA1c ≥ 9.5%

i. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen (via Screening lab).

j. 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. (a worse score would be -3.0 S.D., for example).

k. Uncontrolled hypertension (systolic blood pressure [SBP] >= 160, and/or diastolic blood pressure [DBP] >= 95 mmHg). Anti-hypertensive medications are permitted if the dose has been stable for >2 weeks before Screening.

l. QTcF > 480 msec on 12-lead electrocardiogram (ECG) during the Screening period, confirmed by repeat.

m. 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. A repeat measurement of screening serum creatinine is permitted when the investigator suspects that initial screening results may have been affected by volume contraction (e.g., prolonged fasting, diuretic use) or other transient conditions. Note: GFR (mL/min/1.73 m$^2$) = 175 × (Serum creatinine)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American).

**3. Allergies and Adverse Drug Reaction**

a. History of allergy to PEGylated compounds or FGF21-related compounds.

b. History of hypersensitivity to protein-based therapeutics.

c. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

**4. Other Exclusion Criteria**

a. Prisoners or subjects who are involuntarily incarcerated.

b. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

c. Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4.

d. Subjects in whom MRI, MRE and DXA procedures cannot be performed. Section 3.4.3 provides a list of some common conditions that may preclude the subject from having MRI, MRE and DXA. However, this should not be used as a substitute for local clinical standards of care. The ultimate decision to perform any of these procedures in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local ethics committee/institutional review board.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

### *3.3.3 Women of Childbearing Potential*

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is >40 mlU/ml at any time during the washout period, the woman can considered postmenopausal.

- 1 week minimum for vaginal hormonal products, (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

## 3.4 Concomitant Treatments

### *3.4.1 Prohibited and/or Restricted Treatments*

Prohibited and/or restricted medications are described below:

1) Use of drugs (systemic administration) historically associated with NAFLD for more than 2 weeks in the year prior to randomization and through to end of treatment (including, but not limited to amiodarone, selective estrogen receptor modulators [such as tamoxifen, raloxifene], methotrexate, valproic acid, phenothiazines, sulfonamides, tetracycline, isoniazid, antithyroid drugs, phenytoin and high-dose estrogens [such as clomiphene]).
2) Use of glucagon-like peptide-1 receptor (GLP-1) agonists (including, but not limited to exenatide, liraglutide, lixisenatide, albiglutide) for more than 2 weeks in the year prior to randomization and through to end of treatment.
3) Use of thiazolidinediones within 6 months prior to randomization and through to end of treatment.
4) Use of vitamin E (>120 IU/day) from screening and through to end of treatment, unless the subject had taken vitamin E consistently for 3 months or more prior to liver biopsy for this study.
5) Use of anti-obesity agents (including but not limited to orlistat) within 8 weeks prior to screening and through to end of treatment.
6) Use of oral, intravenous, subcutaneous or intra-articular glucocorticoids within 8 weeks of screening or acute, short-term glucocorticoid use more than once within one year prior to Screening. If systemic glucocorticoids are administered between Screening and Day 1, the subject may be rescreened after discontinuing glucocorticoids and stabilization of metabolic parameters has occurred.

7) Use of oral, intravenous, subcutaneous or intra-articular glucocorticoids ≥5 days between randomization through to end of treatment.
8) Initiation of anti-hyperglycemic therapies within 8 weeks prior to screening. Anti-hyperglycemic therapies may be adjusted for enrolled subjects to meet treatment goals from Screening and through to end of treatment.
9) Initiation of anti-hypertensive therapies within 8 weeks prior to screening. Antihypertensives may be adjusted for enrolled subjects to meet blood pressure treatment goals from Screening and through to end of treatment.
10) Initiation of lipid lowering therapies within 8 weeks prior to screening. Adjustment of the same class of lipid lowering therapies from screening and through to end of treatment is allowed to meet lipid treatment goals.
11) Exposure to any investigational drug or placebo within 8 weeks of Screening.
12) Prior exposure to BMS-986036 or other investigational drugs that contain recombinant versions of FGF21.
13) Prior or current exposure to prescription or investigational systemic PEGylated drug(s).

No concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed by the investigator for treatment of specific clinical events.

Medications taken within 4 weeks prior to study drug administration must be recorded on the CRF. Any concomitant therapies must be recorded on the CRF.

### *3.4.2 Other Restrictions and Precautions*

All subjects will be instructed in the technique of withdrawing investigational product from a vial into a syringe and self-administering study drug or placebo by subcutaneous injection. All subjects will be instructed in the safe handling and disposal of needles and syringes.

### *3.4.3 Imaging Contraindications (MRI, MRE and DXA)*

The imaging specialist at the study site's imaging facility is responsible for determining if a subject is contraindicated from having this procedure. The following is a list of some common conditions that may preclude the subject from scans. However, this should not be used as a substitute for local clinical standards of care. The ultimate decision to perform any scan should rest with the site radiologist, the investigator, and the standard set by the local Ethics Committee:

1. Subjects who have a history of claustrophobia.
2. Subjects who have a physical limitation related to fitting in the bore of the magnet or weight greater than that allowable by the imaging instrument.
3. Subjects with a pacemaker, epicardial pacemaker wires, MRI-incompatible cardiac valve prostheses, and MRI-incompatible vascular clips less than two-months old, or MRI-incompatible aneurysm clips of any age.
4. Subjects with MRI-incompatible cochlear implants.
5. Subjects with spinal nerve stimulators.
6. Subjects with an infusion pump.
7. Subjects with known metallic fragments in the body.

8. Subjects with an employment history, which involves exposure to welding.
9. Subjects who have shrapnel at any place in their body.

## 3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Per the subjects request to stop study treatment and/or retract willingness to provide consent to continue participation in the study
- Any clinical adverse event (AE) determined as a Grade 3 or Grade 4 or higher - (based upon the current version of Common Terminology Criteria for Adverse Events (CTCAE)[36] criteria) will be handled as follows:
  a. Any subject(s) experiencing Grade 3 and/or a Grade 4 ADR (AE or laboratory abnormality considered study drug related as determined by the investigator must discontinue investigational product.
  b. Clinical data from subjects experiencing a Grade 3 AE or above which is determined to be unrelated to study drug will be reviewed by the BMS medical monitor/study director in conjunction with the investigator, to determine the risk/benefit for a subject to continue or discontinue in the study. The investigator will provide documented justification of the decision for filing purposes.
- Any clinical adverse event (AE) laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)
- Pregnancy
- Laboratory or Clinical Criteria: If any of the following laboratory or clinical criteria is obtained for any subject, the result must be repeated/confirmed within 72 hours and the BMS central medical monitor/study director should be informed. If the results are confirmed, the subject must discontinue treatment. Clinical criteria must have the Principal Investigator or sub-investigator assessment prior to discontinuation.
  - Evidence of confirmed hepatic decompensation (Child-Pugh Class B or C, Score >6);
  - ALT > 2 x baseline and > 5 x ULN, and either total bilirubin > 2 x ULN or INR > 2.
  - Any Grade 3 or above AE or clinically significant laboratory abnormality considered study drug-related (as described above and reported according to the current version of the CTCAE grade criteria)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue investigational product should comply with protocol specified follow-up as outlined in Table 5.1-2, Table 5.1-3. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

## 3.6 Post Study Drug Follow up

Subjects who discontinue study drug may continue to be followed.

### *3.6.1 Withdrawal of Consent*

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### *3.6.2 Lost to Follow-Up*

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

# 4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (e.g., background therapy, rescue medications)
- Diagnostic agents: given as part of the protocol requirements must also be included in the dosing data collection.

BMS-986036 will be provided as a blinded solution for subcutaneous injection. Randomized subjects will self-administer double-blind treatment, once daily for 16 weeks, in an outpatient setting. Blinded treatment is supplied in Kits. Each Kit contains 8 vials, to support 1 week of treatment. 2 vials are provided for use on Day 1 of each week, and 1 vial is provided for use each day, on Days 2-7.

Once-daily treatment will consist of subcutaneous injection(s) administered in the abdomen. Subjects will be trained to rotate injection sites relative to the umbilicus. The time of dose administration will be called "0" hour, with regard to pre- and postdose clinical planned events. On clinic visit days, the morning injections are administered at the clinic, at a time determined by the Investigator to coordinate with the pre- and post-dose protocol specified clinical events scheduled for that clinic visit day. Treatment administration is described in Table 4-1.

**Table 4-1: 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.

Product description and storage information is described in Table 4-2.

**Table 4-2: Study Drugs for MB130045**

| Product Description Class and Dosage Form | Potency | IP/Non-IMP | Blinded or Open Label | Packaging/Appearance | Storage Conditions (per label) |
|---|---|---|---|---|---|
| Placebo for BMS-986036-01 Injection | N/A | IP (8 vials/Kit) | Blinded | A clear colorless or a light yellow solution in a vial essentially free of particulate matter by visual inspection | Store Refrigerated, 2-8 degree Celsius (36-46 degree Fahrenheit), Protect from light |
| BMS-986036-01 Injection, 10mg/vial | 10 mg/mL | IP (8 vials/Kit) | Blinded | A clear colorless or a light yellow solution in a vial essentially free of particulate matter by visual inspection | Store Refrigerated, 2-8 degree Celsius (36-46 degree Fahrenheit), Protect from light |

## 4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) are:

- Placebo solution for subcutaneous injection
- BMS-986036-01 Injection, 10mg/ml (10mg/vial)

## 4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

## 4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

## 4.4 Method of Assigning Subject Identification

During the Screening visit, the investigative site will call into the enrollment option of the Interactive Voice Response System (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.

## 4.5 Selection and Timing of Dose for Each Subject

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 (see Section 3.3), 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.

## 4.6 Blinding/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/ 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.

### *4.6.1 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.

## 4.7 Treatment Compliance

During the on-treatment phase, there will be a compliance check at each scheduled visit. The kit containing vials of study drug should be returned at each visit, and compliance will be assessed based upon an interview with the subject and a count of the vials. The Investigator (or designee) will record the amount of study drug dispensed and returned at each visit and the dates of any study drug interruption. During the double-blind treatment period, if the subject is $\leq$ 80% compliant with study drug (BMS-986036/matching placebo) the period of noncompliance should be noted as a protocol deviation and the sponsor should be notified. The subject should be educated/properly instructed by designated site personnel on taking the study medication in accordance with the protocol.

## 4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for the return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

# 5 STUDY ASSESSMENTS AND PROCEDURES

## 5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1, Table 5.1-2 and Table 5.1-3.

**Table 5.1-1: Screening Procedural Outline (MB130045)**

| Procedure | Screening<br>D-42 to D-8 | Lead-in<br>D-7 | Notes |
|---|---|---|---|
| **Visit Window (days)** | | +/- 2 | |
| **Eligibility Assessments** | | | |
| Informed Consent | X | | A subject is considered part of the study only when a protocol specific informed consent is signed. |
| Inclusion/Exclusion Criteria | X | X | |
| Medical History | X | | Include any toxicities or allergy related to previous treatments. |
| Liver biopsy | X | | Performed within 1 year of screening or between Screening and Lead-in. Must be NASH CRN fibrosis stage 1 to 3, or equivalent. |
| Patient education: subcutaneous injection and diary usage | | X | Patients will be educated on the techniques/use of subcutaneous injection and patient diary. Subjects may return for additional visits during the Lead-in phase, if the subject or the site feels additional education/instruction is required. The Investigator will review subject diary, placebo compliance, and assess self-injection skills on Day 1 BEFORE randomizing the subject in IVRS. |
| Practice at Home | | X (D-7 to D-1) | Subcutaneous placebo injection and diary use (once per day) from Day -7 to Day -1. |
| **Imaging Facility Assessments** | | | |
| Dual-emission X-ray Absorptiometry (DXA) | X | | Performed approximately 21 days prior to the Day 1 dose.<br>Eligibility should be confirmed by central imaging lab prior to entry into the lead-in period (Day -7).<br>Bone imaging (hip and lumbar spine) performed at all imaging facilities.<br>Body composition (whole body), an exploratory measure, will be additionally carried out at imaging facilities with the appropriate hardware/software. |
| Magnetic Resonance Imaging (MRI) | X | | Performed approximately 21 days prior to the Day 1 dose.<br>Eligibility should be confirmed by central imaging lab prior to entry into the lead-in period (Day -7). |
| [redacted] | [redacted] | | [redacted] |
| **Safety Assessments** | | | |
| Physical Examination (PE) | X | | To include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, and extremities, neurological, skin, and musculoskeletal. |
| Targeted PE | | X | A targeted physical exam should be performed by the investigator or qualified professional. It includes assessment of heart, lung, abdomen and injection site reactions (as measured by the Draize Scale for erythema and edema (see Section 5.3.3) and should also be guided by the examiner's observations and/or patient complaints on new or changed conditions, |

**Table 5.1-1: Screening Procedural Outline (MB130045)**

| Procedure | Screening<br>D-42 to D-8 | Lead-in<br>D-7 | Notes |
|---|---|---|---|
| | | | symptoms or concerns. |
| Physical Measurements | X | X | Weight, BMI and waist circumference measurement. See Section 5.9<br>Height at screening only. |
| Vital Signs | X | | Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes. |
| Electrocardiogram (ECGs) | X | | ECGs should be recorded after the subject has been supine for at least 5 minutes. ECG parameters including QTcF will be collected on the CRF. |
| IVRS Call | X | X | IVRS call to be conducted on the day of each subject visit where indicated |
| Laboratory Tests (hematology, clinical chemistry, urinalysis, INR) | X | | Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests. |
| Pregnancy Testing | X | | Female subjects of child bearing potential. Serum pregnancy testing performed at screening |
| [redacted] | [redacted] | | |
| Lipid panel | X | | Triglycerides, total cholesterol, LDL and HDL |
| FSH | X | | In women <55 years, to confirm menopause. |
| **Clinical Drug Supplies** | | | |
| Dispense Lead-in supply | | X | |
| Review injection technique | | X | |
| **Adverse Event Reporting** | | | |
| Monitor for Non-Serious Adverse Events | | X | All non-serious AEs will be collected from the start of the Lead-In phase until 30 days after discontinuation of dosing. AEs should be followed to resolution or stabilization. |
| Monitor for Serious Adverse Events | X | X | All SAEs must be collected from the date of subject's written consent until 30 days after discontinuation of dosing. In addition, the investigator should report any SAE that occurs after 30 days post-dosing that is believed to be related to study drug or protocol-specified procedure |

Abbreviations: D = Day

**Table 5.1-2: On Treatment Procedural Outline (MB130045)**

| Procedure | D 1 | D 15 | D 29 | D 43 | D 57 | D 86 | End of Treatment D 112 | Early Termination Visit[a] | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Clinic Visit Window (days)** | 0 | +3 | +3 | +3 | +3 | +3 | -3 | | |
| Patient education: subcutaneous injection and diary usage | X | | | | | | | | The Investigator will review subject diary, placebo compliance, and assess self-injection skills on Day 1 BEFORE randomizing the subject. |
| IVRS call | X | X | X | X | X | X | X | X | IVRS call to be conducted on the day of each subject visit |
| Randomize | X | | | | | | | | Predose on Day 1. |
| **Safety Assessments** | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | Predose on Day 1. |
| Physical Examination (PE) | X | | | | | | X | X | Predose on Day 1. Injection site reactions (as measured by the Draize Scale for erythema and edema (see Section 5.3.3) |
| Targeted PE | | X | X | X | X | X | | | See note in screening procedures. |
| Physical Measurements | X | X | X | X | X | X | X | X | Weight, BMI and waist circumference measurement. Weight must be recorded using a calibrated scale. Predose on Day 1. |
| Vital Signs | X | X | X | X | X | X | X | X | See note in screening procedures. |
| Electrocardiogram (ECGs) | X | | | | | | X | X | See note in screening procedures, or as clinically indicated. |
| Laboratory Tests (hematology, clinical chemistry, urinalysis, INR) | X | X | X | X | X | X | X | X | Pre-dose on Day 1. See note in screening procedures and Section 5.3.2. . |
| Pregnancy Testing | X | | X | | X | X | X | X | Female subjects of child bearing potential. Urine pregnancy testing performed at all specified visits, with a reflex to serum pregnancy testing if urine pregnancy testing is positive. |
| Dual-emission X-ray Absorptiometry (DXA) | | | | | | | X | X | Window +/- 1 week<br>Bone imaging (hip and lumbar spine) at all imaging facilities. |
| **Adverse Event Reporting** | | | | | | | | | |
| Monitor for Non-Serious Adverse Events | X | X | X | X | X | X | X | X | Day 1 assessment occurs after study drug administration. |
| Monitor for Serious Adverse Events | X | X | X | X | X | X | X | X | See note in screening procedures. |
| **Efficacy Assessments** | | | | | | | | | |
| MRI | | | | | X | | X | X | MRI should be conducted within +/- 1 week. At early termination, MRI conducted only if subject received ≥ 6 weeks of study drug and was ≥1 month from previous MRI. |

**Table 5.1-2: On Treatment Procedural Outline (MB130045)**

| Procedure | D 1 | D 15 | D 29 | D 43 | D 57 | D 86 | End of Treatment D 112 | Early Termination Visit[a] | Notes |
|---|---|---|---|---|---|---|---|---|---|
| **Pharmacokinetic (PK) Assessments** | | | | | | | | | |
| PK Sampling | See Table 5.5.1-1 | | | | | | | | |
| Immunogenicity testing | See Table 5.5.1-1 | | | | | | | | Refer to Section 5.7 |
| [redacted] | | | | | | | | | |
| [redacted] | | | | | | | [redacted] | [redacted] | [redacted] |
| [redacted] | | | | | [redacted] | | | | |
| **Clinical Drug Supplies** | | | | | | | | | |
| Review injection technique | X | | | | | | | | |
| Dispense Study Drug | X | X | X | X | X | X | | | Supplied by BMS. |
| Blinded drug administration | X | X | X | X | X | X | X | | Blinded treatment will be administered at the site on clinic visit days. |
| Patient diary review | X | X | X | X | X | X | X | X | |

[a] Early Termination is not a scheduled visit. For early termination PK and PD assessments, refer to Table 5.5.1-1

Abbreviations: D = Day

**Table 5.1-3: Post Treatment Follow-up Procedural Outline (MB130045)**

| Procedure | D 142 (30 days after last dose) | D 292 (6 mo after last dose) | Follow-up for immunogenicity[a] (up to 12 months post Day 142) | Early Termination Visit[b] | Notes |
|---|---|---|---|---|---|
| **Visit Window** | +/- 3 days | +/-2 wk | n/a | | |
| IVRS Call | X | | | X | |
| **Safety Assessments** | | | | | |
| Physical Examination | X | | | X | |
| Targeted Physical Examination | | | | | Injection site reactions (as measured by the Draize Scale for erythema and edema (see Section 5.3.3), others as clinically indicated. See note in Screening procedures. |
| Physical Measurements | X | | | X | Weight (using calibrated scale), BMI and waist circumference measurement. |
| Vital Signs | X | | | X | See note in screening procedures. |
| Electrocardiograms (ECGs) | X | | | X | See note in screening procedures. |
| Laboratory Tests (hematology, clinical chemistry, urinalysis, INR) | X | | | X | See note in screening procedures. |
| Pregnancy Testing | X | | | X | Female subjects of child-bearing potential. Urine pregnancy testing to be performed at post treatment specified visits with reflex to serum if urine pregnancy testing is positive. |
| Dual-emission X-ray Absorptiometry (DXA) | | X | | | Bone imaging (hip and lumbar spine) at all imaging facilities. |
| **Adverse Event Reporting** | | | | | |
| Monitor for Adverse Events | X | | | X | Up to 30 days after the last dose. |
| Monitor for Serious Adverse Events | X | | | X | See note in screening procedures. |
| **Pharmacokinetic (PK) Assessments** | | | | | |
| PK Sampling | X | X | | | Refer to Table 5.5.1-1 |
| Immunogenicity testing | X | X | X | X | Refer to Table 5.5.1-1 and Section 5.7 |
| [redacted] | [redacted] | | | | |

[a] Applies only to subjects with positive immunogenicity at D142 and/or D292. (Refer to Section 5.7). These immunogenicity follow-up visits will commence after D142 or D292, if immunogenicity results are positive at D142 or D292, respectively, without evidence of decreasing or stable antibodies.

[b] Early Termination is not a scheduled visit. For early termination PK and PD assessments, refer to Table 5.5.1-1

Abbreviations: D = Day

### *5.1.1 Retesting During Screening or Lead-in Period*

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (i.e., the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

## 5.2 Study Materials

Supplied by the site:

The site will provide all required materials for the tests performed locally (i.e., relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. The site will have a centrifuge (refrigerated, if possible), a monitored and alarmed refrigerator, and freezer (-20°C or below, -70°C preferred), as well as containers and dry ice for shipment and storage of blood samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study.

Supplied by the Central Lab

The Central Lab will supply the Laboratory manual, tubes and labels for collection of samples.

Supplied by the Central Imaging Lab

The central imaging lab will supply the Imaging manual(s) for MRI for hepatic fat fraction, MRE for liver stiffness, DXA scanning and, if applicable, phantoms.

Supplied by the Sponsor

BMS will provide a BMS-approved protocol and any amendment(s) or administrative letter(s) (if required), an Investigator Brochure, electronic case report forms, patient education training materials and subject supplies to support subcutaneous injections, site support tools and forms study drug logs, emergency contact cards and patient diaries.

## 5.3 Safety Assessments

### *5.3.1 Safety Imaging Assessment for the Study*

Image acquisition guidelines and submission processes will be outlined in the MB130045 Imaging Manual, to be provided by the central imaging lab.

A central imaging lab will perform all imaging analyses.

The clinical site will be trained in imaging procedures prior to scanning the first study subject. Images will be submitted to the central imaging lab for central review. The site will be informed of quality issues or needs for repeat scanning via queries from the central imaging lab.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

#### *5.3.1.1 DXA*

DXA is recognized as the reference method to measure BMD as well as soft-tissue composition (body composition: lean mass, fat mass) with acceptable accuracy errors and good precision and reproducibility. Subjects with a centrally read screening DXA T-score (total spine, total hip or femoral neck) greater than a -2.5 S.D. will be enrolled and randomized for treatment. Adequacy of DXA scans should also be confirmed by the central imaging lab prior to randomization.

Screening results to confirm eligibility (DXA T-score) will be returned to the site by the central imaging lab. No other results will be provided to the site.

Bone imaging (hip and lumbar spine) will be performed at all imaging facilities and body composition (whole body), an exploratory measure, will be additionally carried out at imaging facilities with the appropriate hardware/software.

DXA will be conducted at baseline, end of treatment (Day 112, (+/- 1 week) and approximately 6 months after the end of the treatment (Day 292, +/- 2 weeks).

Screening DXA 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).

A repeat DXA may be performed if clinically indicated.

Imaging assessments will be performed at time points indicated in Table 5.1-1, Table 5.1-2 and Table 5.1-3.

### *5.3.2 Laboratory Test Assessments*

A central/local laboratory will perform the analyses and will provide reference ranges for these tests. Results of clinical laboratory tests performed prior to Day 1 must be available prior to dosing.

The following clinical laboratory tests will be performed:

**Hematology**

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

**Serum Chemistry**

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Direct bilirubin
Total Protein
Albumin
Sodium
Potassium

Alkaline phosphatase
Lactate dehydrogenase (LDH)
Gamma-glutamyl transferase (GGT)
Creatinine
Blood Urea Nitrogen (BUN)
Uric acid
Fasting glucose
Chloride
Calcium
Phosphorus
Magnesium
Creatine kinase
Creatine Clearance (ClCr) - at Screening only calculated using Modification of Diet in Renal Disease (MDRD) equation.

**Urinalysis**

Protein
Glucose
Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

**Serology**
Serum for hepatitis C antibody, hepatitis B surface antigen (screening only)

**Other Analyses**

INR (per Table 5.1-1. Table 5.1-2 and Table 5.1-3)

HbA1c (Screening, and per Table 5.5.1-1)

AFP (Screening - for inclusion/exclusion)
FSH (Screening only; females)
Lipid panel (triglycerides, total cholesterol, LDL and HDL at Screening and per Table 5.5.1-1)

Pregnancy test (WOCBP only: per Table 5.1-1, Table 5.1-2 and Table 5.1-3)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (e.g., provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.3 Laboratory Test Result Abnormalities).

### *5.3.3 Monitoring of Injection site reactions*

Injection site reactions will be monitored from Day -7 though 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.

**Table 5.3.3-1: Monitoring of injection site reactions**

| Erythema | | Edema | |
|---|---|---|---|
| **Description** | **AE Grade** | **Description** | **AE Grade** |
| No erythema | - | No edema | - |
| Very slight erythema (barely perceptible) | Mild | Very slight edema (barely perceptible) | Mild |
| Well defined erythema | Mild | Well defined edema | Mild |
| Moderate erythema | Moderate | Moderate edema (raised approx. 1 mm) | Moderate |
| Severe erythema (beet redness to slight eschar formation) | Severe | Severe edema (raised more than 1 mm and beyond exposure area) | Severe |

## 5.4 Efficacy Assessments

### *5.4.1 Efficacy Imaging Assessment for the Study*

Image acquisition guidelines and submission processes will be outlined in the MB130045 Imaging Manual, to be provided by the central imaging lab. A central imaging lab will perform all imaging analyses. The clinical site will be trained in imaging procedures prior to scanning the first study subject. Images will be submitted to the central imaging lab for central review. The site will be informed of quality issues or needs for repeat scanning via queries from the central imaging lab.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

#### *5.4.1.1 MRI*

Proton density hepatic fat-fraction MRI will be employed at screening phase to determine hepatic fat fraction (%). Subjects with a centrally read hepatic fat fraction ≥10% at screening will be enrolled and randomized for treatment. Adequacy of MRI should also be confirmed by the central imaging lab prior to randomization.

Screening results to confirm eligibility (hepatic fat fraction) will be returned to the site by the central imaging lab. No other results will be provided to the site.

MRI will be conducted during the screening period, Day 57 (+/- 1 week), and at the end of treatment visit (Day 112, +/- 1 week), or if applicable, at the early termination visit (conducted only if subject received ≥ 6 weeks of study drug and was ≥1 month from previous MRI).

Screening MRI 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). A repeat MRI may be performed if clinically indicated.

Imaging assessments will be performed at time points indicated in Table 5.1-1, Table 5.1-2 and Table 5.1-3.

## 5.5 Pharmacokinetic Assessments

The following pharmacokinetic parameters of BMS-986036 (Total and C-Terminal intact) will be generated and summarized

| | |
|---|---|
| Ctrough | Observed serum concentration before the next dose is administered; the pre-dose concentration |

### *5.5.1 Pharmacokinetics and Pharmacodynamics: Collection and Processing*

Table 5.5.1-1 lists the sampling schedule to be followed for the assessment of pharmacokinetics and pharmacodynamics. Further details of blood and urine collection and processing will be provided to the site in the procedure manual.

**Table 5.5.1-1: Pharmacokinetic and Pharmacodynamic Sampling Schedule for BMS-986036**

| Study Day | Event | Time (Relative To BMS-986036 Dose) Hour: Min | BMS-986036 (a) PEG-C-Term-Intact (b) PEG-Total (c) Endogenous FGF21 | Immunogenicity | [redacted] | [a]Fasting lipids | [redacted] | [c]NASH FibroSure | [redacted] | Additional Research |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Predose | 0:00 | X | X | | X | | X | | X |
| 15 | Predose | 0:00 | X | X | | | | | | |
| 29 | Predose | 0:00 | X | X | | X | | | | |
| 43 | Predose | 0:00 | X | | | | | | | |
| 57 | Predose | 0:00 | X | X | | X | | | | |
| 57 | | 6:00 | X | | | | | | | |
| 86 | Predose | 0:00 | X | X | | X | | | | |
| 112 | Predose | 0:00 | X | X | | X | | X | | |
| 142 | Follow-up | | X[h] | X | | X | | | | |
| Approximately every 6-8 weeks between D142 or | Immunogenicity Follow-Up | | X[h,i] | X[i] | | | | | | |

**Table 5.5.1-1: Pharmacokinetic and Pharmacodynamic Sampling Schedule for BMS-986036**

| Study Day | Event | Time (Relative To BMS-986036 Dose) Hour: Min | BMS-986036 (a) PEG-C-Term-Intact (b) PEG-Total (c) Endogenous FGF21 | Immunogenicity | [redacted] | [a]Fasting lipids | [redacted] | [c]NASH FibroSure | [redacted] | Additional Research |
|---|---|---|---|---|---|---|---|---|---|---|
| D292 and up to 12 months after D142 | | | | | | | | | | |
| 292 | Follow-up | | X[h] | X | | | | | | |
| Early Term Visit on treatment | Early Term | | X | X | | X | | X | | |
| Early Term visit (post treatment prior to Day 142 | Early Term | | X[h,i] | X[i] | | X | | | | |

[a] Lipids include triglycerides, total cholesterol, LDL and HDL

[b] Residual samples will analysis of be banked for further biomarkers defined in the section.

[c] NASH FibroSure includes measurement for α2-macroglobulin, ApoA1, haptoglobin, gamma-glutamyl transpeptidase (GGT), bilirubin; fasting glucose, triglycerides, cholesterol, ALT, AST, age and BMI.

[d] Bone biomarkers: BSAP, P1NP, CTX.

[redacted]

h Only Endogenous FGF21 to be collected.

i Only applies to subjects with positive immunogenicity at D142 and/or D292. Immunogenicity follow-up visits will commence after D142 or D292, if immunogenicity results are positive at D142 or D292, respectively, without evidence of decreasing or stable antibodies. 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 the Medical Monitor to be decreasing or stable.

### 5.5.2 Pharmacokinetic Sample Analyses

The serum samples for BMS-986036 (C-terminal intact and Total) will be analyzed by a validated assay. Pharmacokinetic samples collected for BMS-986036 (C-terminal intact and Total) from a subject who received placebo will not be analyzed.

### 5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

[redacted]

## 5.7 Immunogenicity

Subjects will be monitored for antibodies to study medication using a validated ADA homogenous bridge assay with BMS-986036 and electrochemical luminescence detection. Samples will first be screened for potential positive ADA responses. Then the samples with positive ADA responses will be confirmed for specificity using an immunodepletion format with drug BMS-986036 and un-PEGylated drug. The reactivity of confirmed positive responses will be characterized as "BMS-986036" (specific to the FGF21 region) or "PEG" (specific to the PEGylated region) based on the immunodepletion specificity. Additionally, samples with confirmed positive responses will be tittered to determine the relative positive response. The sensitivity was determined to be 20 ng/mL and the drug tolerance at antibody concentrations of 50, 100, 500, and 10,000 ng/mL was determined to be 1, 4, 16, and 48µg/mL of BMS-986036 respectively.

Subjects will also be monitored for antibodies to FGF21 using a validated homogenous bridge assay with Met-FGF21 (recombinant produced) and electrochemical luminescence detection. Samples will first be screened for potential positive anti-FGF21 responses. Then the samples with positive anti-FGF21 responses will be confirmed for specificity using an immunodepletion format with wild type sequence FGF21 (WSFGF-21). Samples with confirmed positive anti-FGF21 responses will be titrated to determine the relative positive response. The sensitivity was determined to be ≤ 5 ng/mL and the drug tolerance at antibody concentrations of 50, 100, 500, and 10,000 ng/mL was determined to be > 48 µg/mL of BMS-986036.

Samples positive for ADA or positive for anti-FGF21 antibodies will be tested for neutralizing activity in a validated cell based neutralizing antibody assay. The assay measures the ability of an ADA or anti-FGF21 antibody to inhibit or block Elk1 activation that is induced when FGF21 or drug binds to the βKlotho and FGF receptors. The sensitivity was determined to be 4000 ng/mL and the drug tolerance at antibody concentrations of 400, 16,000 and 32,000 ng/mL was determined to be 0.4, >1.0, and >1.0 µg/mL of BMS-986036 respectively.

Samples will be banked for additional immunogenicity characterization if needed.

Subjects with positive ADA and /or anti-FGF21 antibody results at the Day 142 visit and/or the Day 292 visit may be asked to return for antibody testing. Immunogenicity follow-up visits will commence after D142 or D292, if immunogenicity results are positive at D142 or D292, respectively, without evidence of decreasing or stable antibodies. 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 the Medical Monitor to be decreasing or stable.

## 5.8 Outcomes Research Assessments

Not applicable.

## 5.9 Other Assessments

### *5.9.1 Height and Body Mass Index (BMI)*

- Measurement of height should be performed with the subject's shoes removed. The subject's knees should be straightened, head held erect and eyes forward
- Weight must be recorded using a calibrated scale, preferably the same scale at each clinic visit. Subject should remove shoes and heavy clothing before standing on scale.
- BMI is used as an index of obesity and is a method of defining normal body weight and excess body fat. It correlates in a population with percent body fat. BMI is determined by weight, (kg) divided by height (m) squared

Method of BMI Calculation:

- Use actual height and weight
- To calculate BMI:
  - Convert pounds (lbs) to kilograms (kg = lb / 2.2)
  - Convert inches (in) to centimeters (cm = in X 2.54)
  - BMI = (weight in kg) / (height in cm/100)$^2$
  - Round to one decimal place (if 0.05 or greater, round up)

The BMI calculation is used for assessment for inclusion. All analysis calculations for BMI will be derived internally by BMS using the weight and height at the specified time point or the most recent high measurement (if not applicable).

[redacted]

### 5.9.3 Other Supplemental (Unscheduled Visits)

At any time during the study, the Investigator may at his/her discretion, arrange for a subject to have an unscheduled (supplemental) assessment(s) including immunogenicity especially in the case of AEs that require follow-up. If the subject is seen for an unscheduled assessment, the appropriate Supplemental Pages of the eCRF must be completed.

## 5.10 Results of Central Assessments

Centrally analyzed DXA and MRI data supporting eligibility will be returned to the site. Any subsequent imaging results from centralized analyses will not be returned to the site. Safety samples will be assayed at a Central Laboratory and results returned to the Site.

## 5.11 Sampling for Additional Research

Where individual subjects have provided separate consent for Additional research collection, prospective samples of blood will be collected at selected time points (see Table 5.5.1-1) and banked. Additionally, residual serum from adiponectin, insulin and 7α-hydroxy-cholesten-3-one (C4) collections will also be retained by the BMS Biobank for additional research purposes. No additional sampling is required for residual collections. Additional research collections and retention should be presented to all subjects, except where prohibited by local laws or regulations. However, enrollment into the main study is not contingent upon consent to participate in future additional research sample banking. Further details of sample collection and processing will be provided to the site in the procedure manual.

# 6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

## 6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

**NOTE**:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases

- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

### *6.1.1 Serious Adverse Event Collection and Reporting*

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB)[7] represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

**SAE Email Address:** Refer to Contact Information list.

**SAE Facsimile Number:** Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

**SAE Telephone Contact** (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

## 6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

### *6.2.1 Nonserious Adverse Event Collection and Reporting*

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

## 6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

## 6.4 Pregnancy

If following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

## 6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

## 6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

1. ALT ≥ 5 times baseline or nadir value, whichever is lower, AND ≥ 10 x ULN (upper limit of normal),

AND

2. Total bilirubin ≥ 2 times ULN,

AND

3. No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

## 6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

# 7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

An independent Data Monitoring Committee (DMC) will meet at prespecified times as outlined in the DMC charter, and at times when the following criteria are met:

- More than 3 subjects develop an adverse event of Grade 3 or higher in the same CTCAE category, OR
- If more than 2 subjects develop an AE of CTCAE Grade 4 or higher.

When meeting at the regularly scheduled times, the DMC will review data by masked treatment group, but can request unblinded data by treatment group or by individual subject as they deem necessary. When meeting based on preset criteria, the DMC will review unblinded data to determine clinical significance.

Data to be reviewed at DMC meetings will include, but is not limited to adverse events and laboratory value(s). In addition, all expedited serious adverse event report(s) will be provided to the DMC members concurrent with the submission to the regulatory authorities. Available efficacy data will also be provided to the DMC to facilitate an assessment of benefit vs. risk. After each review, the DMC will provide the Medical Safety Team (MST) with meeting minutes blinded to treatment assignment and any further recommendations as discussed and to be considered for implementation. After consideration, the MST will inform the DMC of any action that will be taken in response to the recommendations from the DMC.

The role and responsibilities of the DMC, its operational procedures and method(s) of communication with the Sponsor will be described in further detail in a separate DMC Charter. The DMC will consist of a minimum of 3 members with previous DMC knowledge and expertise who are independent of the Sponsor. The members will be appointed by the Sponsor based on their expertise in biostatistics, hepatology, and internal medicine. All DMC members will have experience in the conduct of clinical trials. DMC members will not include any investigator or sub investigator involved in the study, nor will selected members hold any conflict of interest with the Sponsor. DMC membership will not include BMS Sponsor representatives.

# 8 STATISTICAL CONSIDERATIONS

## 8.1 Sample Size Determination

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[37,38]. 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.

## 8.2 Populations for Analyses

- All Enrolled Subjects, defined as all subjects who signed an informed consent;
- All Randomized Subjects, defined as all subjects who are randomized to a treatment;
- All Treated Subjects, defined as all subjects who have received at least one dose of study treatment;
- Pharmacodynamic (PD) Population, defined as all subjects who have received any study medication and have PD biomarker data available. Only subjects who have both a baseline and at least one post-baseline PD biomarker data available are included in the statistical analysis.
- Pharmacokinetic (PK) Population, defined as all subjects who receive any study medication and have any available concentration-time data.

## 8.3 Endpoints

### *8.3.1 Primary Endpoint(s)*

The primary objective to assess the effect of daily or weekly doses of BMS-986036 on safety, tolerability and hepatic fat fraction (%) by MRI in patients with biopsy proven NASH will be assessed by the primary endpoint of:

- Change in percent hepatic fat fraction (%) by MRI from baseline to Week 16.
- 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.

### *8.3.2 Secondary Endpoint(s)*

The first secondary objective is to assess the pharmacokinetics of C-terminal and total BMS-986036 in NASH subjects to be assessed by the following secondary endpoint:

- Ctrough

The second secondary objective (to assess the effect of daily or weekly doses of BMS-986036 on immunogenicity) will be measured by the following secondary endpoints:

- anti-BMS-986036 antibodies and anti-FGF21 antibodies, from the time points specified in Table 5.5.1-1.

[redacted]

## 8.4 Analyses

### *8.4.1 Demographics and Baseline Characteristics*

Frequency distributions of gender and race will be tabulated by treatment group. Summary statistics for age, body weight, height, and Body Mass Index (BMI) and diabetic status will be tabulated by treatment group.

### *8.4.2 Efficacy Analyses*

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 (%) at Week 16 from baseline 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 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 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.

### *8.4.3 Safety Analyses*

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment group. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings and clinical laboratory results will be listed. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed. Bone mineral density (BMD) results will be tabulated.

### *8.4.4 Pharmacokinetic Analyses*

Summary statistics will be tabulated for observed BMS-986036 serum concentrations (Total and C-Terminal intact).

[redacted]

### *8.4.6 Immunogenicity Analyses*

Responses of anti-BMS-986036 antibodies and anti-FGF21 antibodies will be listed and tabulated by treatment and study day. The relationship between immunogenicity and PK and/or PD may be explored.

### *8.4.7 Outcomes Research Analyses*

Not applicable.

### *8.4.8 Other Analyses*

Not applicable.

## 8.5 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 4.6.1 for details regarding blinding/unblinding. The results of the interim analysis will be reviewed by a pre-specified panel of personnel.

# 9 STUDY MANAGEMENT

## 9.1 Compliance

### *9.1.1 Compliance with the Protocol and Protocol Revisions*

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

### *9.1.2 Monitoring*

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

#### *9.1.2.1 Source Documentation*

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

### *9.1.3 Investigational Site Training*

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

## 9.2 Records

### *9.2.1 Records Retention*

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to BMS.

### *9.2.2 Study Drug Records*

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (e.g., lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

### *9.2.3 Case Report Forms*

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

## 9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator(s) will be selected as appropriate based on the following criteria:

- Involvement in trial design
- Subject recruitment (e.g., among the top quartile of enrollers)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in

the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

# 10 GLOSSARY OF TERMS

| Term | Definition |
|---|---|
| Complete Abstinence | If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.<br>**Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. |
| Medical Research | Those scientific activities which cannot be reasonably anticipated at the time of trial design, for which we would like to collect and/or retain samples from study participants. Examples of additional research include, but are not limited to, new assay development and validation, companion diagnostic development, new hypotheses in the interaction of drug and the human body, and exploration of emerging science in the understanding of disease. |

# 11 LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| AE | adverse event |
| ADA | anti drug antibody |
| AFP | Alpha fetoprotein |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANOVA | analysis of variance |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AT | aminotransaminases |
| AUC | area under the concentration-time curve |
| AUC(INF) | area under the concentration-time curve from time zero extrapolated to infinite time |
| AUC(0-T) | area under the concentration-time curve from time zero to the time of the last quantifiable concentration |
| AUC(TAU) | area under the concentration-time curve in one dosing interval |
| A-V | atrioventricular |
| β-HCG | beta-human chorionic gonadotrophin |
| BA/BE | bioavailability/bioequivalence |
| BID, bid | bis in die, twice daily |
| BLQ | below limit of quantification |
| BMD | Bone mineral density |
| BMI | body mass index |
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| | |
| | |
| BUN | blood urea nitrogen |
| C | Celsius |
| $Ca^{++}$ | calcium |
| Cavg | average concentration |

| Term | Definition |
|---|---|
| CBC | complete blood count |
| Cexpected-tau | expected concentration in a dosing interval |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| $C1^-$ | chloride |
| CLcr | creatinine clearance |
| CLT | total body clearance |
| CLT/F (or CLT) | apparent total body clearance |
| CLT/F/fu or CLT/fu | Apparent clearance of free drug or clearance of free if (if IV) |
| cm | centimeter |
| Cmax, CMAX | maximum observed concentration |
| Cmin, CMIN | trough observed concentration |
| | |
| | |
| CRF | Case Report Formelectronic |
| Ct | Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.) |
| CTA | Clinical trial agreement |
| Ctau | Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.) |
| CTCAE | Common Terminology Criteria for Adverse Events (CTCAE) |
| Ctrough | Trough observed plasma concentration |
| CV | coefficient of variation |
| CYP | cytochrome p-450 |
| D | Day |
| DBP | Diastolic Blood Pressure |
| D/C | discontinue |
| DILI | Drug Induced Liver Injury |
| DMC | Data Monitoring Committee |
| dL | deciliter |

| Term | Definition |
|---|---|
| DSM IV | Diagnostic and Statistical Manual of Mental Disorders (4th Edition) |
| DXA | Dual Energy X-Ray Absorptiometry |
| E | % response relative to baseline prior to dosing |
| Eo | Placebo effect |
| EA | extent of absorption |
| ECG | electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| | |
| eg | exempli gratia (for example) |
| EHR | electronic health records |
| EMR | electronic medical records |
| ESR | Expedited Safety Report |
| F | bioavailability |
| Fb | fraction of bound drug |
| FDA | Food and Drug Administration |
| FGF | Fibroblast Growth Factor |
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| GCP | Good Clinical Practice |
| G criteria | adjusted $R^2$ value of terminal elimination phase |
| GGT | gamma-glutamyl transpeptidase OR glutamyl transferase |
| GLT | gluacogon-like peptide 1 receptor |
| GFR | glomerular filtration rate |
| h | hour |
| HDL | High-Density Lipoprotein |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |

| Term | Definition |
|---|---|
| $HCO_3^-$ | bicarbonate |
| HDL | high density lipoprotein |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HOMA | Homeostasis Model Assessment |
| HOMA-IR | Homeostasis Model Assessment - Insulin resistance |
| HPF | hepatic Fat Fraction |
| HR | heart rate |
| HRT | hormone replacement therapy |
| ICD | International Classification of Diseases |
| ICF | informed consent |
| ICH | International Conference on Harmonisation |
| IDF | International Diabetes Federation |
| ie | id est (that is) |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal products |
| IP | Investigational product |
| IND | Investigational New Drug Exemption |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IU | International Unit |
| IUD | intrauterine device |
| IV | intravenous |
| IVRS | interactive voice response system |
| K | slope of the terminal phase of the log concentration-time curve |
| | |
| $K^+$ | potassium |
| kg | kilogram |
| $\lambda\sigma z$ | terminal disposition rate constant |
| L | liter |

| Term | Definition |
|---|---|
| | |
| LDH | lactate dehydrogenase |
| LDL | Low-Density Lipoprotein |
| LLN | Lower Limit normal |
| MAD | Multiple ascending dose |
| MDRD | Modification of Diet in Renal Disease |
| mg | milligram |
| $Mg^{++}$ | magnesium |
| MIC | minimum inhibitory concentration |
| min | minute |
| mL | milliliter |
| mmHg | millimeters of mercury |
| MR | medical research |
| MRE | Magnetic Resonance Elastography |
| MRI | Magnetic resonance imaging |
| MS | mass spectrometry |
| MTD | maximum tolerated dose |
| μg | microgram |
| N | number of subjects or observations |
| $Na^{+}$ | sodium |
| N/A | not applicable |
| NAFLD | Non-alcoholic fatty liver disease |
| NASH | Non-alcoholic Steatohepatitis |
| ng | nanogram |
| NIMP | non-investigational medicinal products |
| NOAEL | no observed adverse effect level |
| NSAID | nonsteroidal anti-inflammatory drug |
| OCA | Obeticholic acid |
| | |
| PD | pharmacodynamics |

| Term | Definition |
|---|---|
| PE | physical exam |
| PEG | polyethylene glycol |
| PID | patient identification number |
| PK | pharmacokinetics |
| PO | per os (by mouth route of administration) |
| PSF | pregnancy surveillance form |
| PT | prothrombin time |
| PTH | parathyroid hormone |
| | |
| Pu | percent of unbound drug |
| QC | quality control |
| QD, qd | quaque die, once daily |
| QW | quaque die, once weekly |
| $R^2$ | coefficient of determination |
| RBC | red blood cell |
| SAD | single ascending dose |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SOP | Standard Operating Procedures |
| Subj | subject |
| t | temperature |
| T | time |
| TAO | Trial Access Online, the BMS implementation of an EDC capability |
| TBILI | total bilirubin |
| T2DM | Type 2 Diabetes Mellitus |
| TG | triglyceride levels |
| T-HALF | Half life |
| TID, tid | ter in die, three times a day |
| Tmax, TMAX | time of maximum observed concentration |
| TZD | thiazolidinedione |

| Term | Definition |
|---|---|
| ULN | upper limit normal |
| | |
| W | washout |
| WBC | white blood cell |
| WHO | World Health Organization |
| WOCBP | women of childbearing potential |
| x g | times gravity |

## APPENDIX 1 DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

The following is taken from DSM-IV:

Diagnostic Criteria for Psychoactive Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect,
   b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
   a) The characteristic withdrawal syndrome for the substance,
   b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking) or recover from its effects.
6. Important social, occupational or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induce depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.)

Criteria for Severity of Psychoactive Substance Dependence:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate: Symptoms or functional impairment between “mild” and “severe”.

Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

In Partial Remission: During the past six months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past six months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

A. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring at any time in the same 12-month period:

   1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household).
   2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use).
   3. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct).
   4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights).

B. The symptoms have never met the criteria for substance dependence for this class of substance.