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

Amendment Number 02
Site Number: All

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.
Amendment Rationale:

The primary purpose of this amendment is to provide changes to the protocol immunogenicity testing and endogenous FGF21 assessments as follows:

- Addition of immunogenicity testing and endogenous FGF21 assessments at the Day 292 follow up visit

This allows a more comprehensive analysis of whether potential anti-drug antibodies and/or anti-endogenous FGF21 antibodies affect endogenous FGF21 levels.

- 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 months) to determine whether anti-drug and/or anti-FGF21 antibodies are declining or stable.

The secondary purpose of this amendment is to provide minor adjustments to inclusion criteria and prohibited and/or restricted concomitant medications as follows:

- Adjustment of BMI inclusion criterion from > 30 to > 25 kg/m²
- Removal of Fatty Liver Index inclusion criterion
- Adjustment of restriction of Vitamin E from > 60 IU/day to > 120 IU/day

These changes allow the enrollment of a fuller spectrum of appropriate NASH patients. These changes do not alter the scientific merits of the protocol, nor do they change the protocol risks/benefits to subjects.

Additional minor revisions include:

- Clarification of imaging procedures
- Clarification of pregnancy testing assessments
- Correction of identified typographical errors
- Update of the Medical Monitor Assignment

These revisions impact both study conduct and data analysis related to immunogenicity and endogenous FGF21 assessments. These revisions apply to all subjects currently enrolled in the MB130-045 study in addition to any future enrolled subjects.

Documented IRB approval is required prior to implementation.
Changes to the Protocol:

1. Protocol Synopsis Study Design and Section 3.1, Table 3.1-1 - Study Design Schematic
   a) Footnote ‘a’ changed from “MRI, MRE and DXA baseline scans should be conducted between 14 to 35 days prior to the Day 1 dose.” to “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)” to support the clarification of imaging procedure assessments to be performed.
   b) Footnote ‘d’ changed from “DXA follow-up scanning is conducted 6 months (+/- 2 weeks after the last dose” to “DXA follow-up scan and immunogenicity sample collection are conducted 6 months (+/- 2 weeks) after the last dose.” to support the addition of immunogenicity sample collection at follow-up visit D292.

2. Protocol Synopsis Study Population and Section 3.3 Study Population, Inclusion Criteria subsection 3.3.1:
   a. changed BMI of ≥ 30 to ≥ 25 (Study Population Inclusion Criteria 2b)
   b. removed fatty liver index ≥ 60 (Study Population Inclusion Criteria 2c)
   c. removal of MRE scans (Study Population Inclusion Criteria 2e now mapped to 2d) - (as this is optional)
   d. Protocol Synopsis only: removal of “WOCBP must have negative pregnancy test within 24 hours prior to dosing with study medication”

   The above changes allow the enrollment of a fuller spectrum of appropriate NASH patients while maintaining scientific merits and ensuring risk/benefit assessment.

3. 

4. Section 1.5 Overall Risk/Benefit Assessment - adjusted “Data from this phase 2 study will be used to guide future clinical development of BMS-986036” to “Data from this phase 2a study will be used to guide future clinical development of BMS-986036” to support consistency.

5. Section 1.5.1 Risk Mitigation Strategy - Immunogenicity section
   a. The following paragraph was changed from: “All subjects will be monitored for occurrence of anti-drug and anti-FGF21 antibodies during dosing and for up to 4 weeks following the last dose. If present, antibodies will be assessed for neutralizing activity. Subjects with a positive result in the anti-FGF21 or anti-drug
antibody assay at the Day 142 follow-up visit will be followed for up to 6 months until antibody levels resolve or demonstrate a consistent decreasing trend.”
Changed to: “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.”

b. The following verbage was added: “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).”

These adjustments support the rationale for immunogenicity testing and endogenous FGF21 assessments follow-up visits to analyze whether potential anti-drug antibodies and/or anti-endogenous FGF21 antibodies affect endogenous FGF21 levels. This also provides background on the extension of follow-up immunogenicity testing and endogenous FGF21 assessments (for subjects with positive immunogenicity testing) for up to 12 months post-Day 142.

6. Section 3 - Investigational Plan - subsection 3.1 Study Design and Duration
Clarified the visit schedule assessment updates for endogenous FGF21 and immunogenicity sample collection at follow-up visits via the following verbage changes.
“For each subject, the total scheduled study duration from Screening to last Follow-up visit is approximately 12 months, comprised of screening (Day -42 to Day -8), placebo lead-in (approximately Day -7 to Day -1), on-treatment (Day 1 to Day 112) and a wash-out follow-up (Day 113 to Day 142) period, plus a scheduled follow-up visit that will be performed approximately 6 months after the last dose to perform DXA scanning.

a. Removed “after the last dose to perform DXA scanning”

b. After the removal of, “after the last dose to perform DXA scanning”, added the following: “(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).”
c. Adjusted the sentence, “The end of the study is defined as the date of the last follow-up DXA imaging visit, or immunogenicity follow-up visit, whichever is later, of the last subject in the study.” by removing DXA imaging and adding in the word “scheduled”.

7. Section 3.4 - Concomitant Treatments - 3.4.1 - Prohibited and/or Restricted Treatments
   Changed, “Use of Vitamin E (> 60 IU/Day) to “Use of Vitamin E (> 120 IU/day)” in order to expand vitamin supplement daily dosage allowance.

8. Section 3.4.3 - Imaging Contraindications (MRI, MRE and DXA)
   Removed “Subjects with a tattoo that could be exposed to MRI scan bore should be monitored closely. If skin irritation or burning occurs, the MRI should be terminated immediately.” This was removed since updated MRI scanners assessed as acceptable for this study would allow for tattoos without producing exposure to MRI scan bore.

9. Section 5 - Study Assessments and Procedures - Table 5.1-1 Screening Procedural Outline
   a. Eligibility requirements - Informed Consent : removed ‘enrolled’ and added ‘part of the study’ in order to differentiate definition of ‘enrollment’ (lead-in) and when subject is defined as part of the study.
   b. Imaging Facility Assessments
      i. DXA - Changed from: “Performed within approximately 14 to 35 days prior to the Day 1 dose. Please allow time prior to Lead-in, for turnaround of data from both the initial screening DXA, and for a possible repeat scan (for bone scan quality). The central imaging vendor’s turnaround of screening DXA scans is approximately 2-3 working days.”
         Changed to: “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).”
      ii. MRI - Changed from: “Performed within approximately 14 to 35 days prior to the Day 1 dose. Please allow time prior to Day 1 for turnaround of hepatic fat fraction (%) from central imaging vendor (approximately 14 days).”
         Changed to: “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).”
      iii. MRE - Changed from: “MRE will be conducted in addition to MRI at a subset of imaging facilities with the appropriate hardware/software. MRE is performed within approximately 14 to 35 days prior to the Day 1 dose.”
         Changed to, “Performed approximately 21 days prior to the Day 1 dose. MRE will be conducted in addition to MRI at a subset of imaging facilities with the appropriate hardware/software.”
   c. IVRS Call - “IVRS call to be conducted on the day of each subject visit where indicated.” was added for clarification purposes.
d. **Pregnancy Testing** - “Serum pregnancy testing performed at screening” was added for clarification of schedule assessments.

The adjustments above support internal consistency and clarify scheduling assessments for screening procedures.

10. **Section 5- Study Assessments and Procedures -Table 5.1-2 On Treatment Procedural Outline**
   a. **IVRS Call** - Added “IVRS call to be conducted on the day of each subject visit.” for clarification purposes.
   b. **Pregnancy Testing** - Added, “Urine pregnancy testing performed at all specified visits, with a reflex to serum pregnancy testing if urine pregnancy testing is positive.” for the purpose to support internal consistency and clarification of schedule assessments.
   c. **DXA** - removal of “vs nominal day” from the text, “Window +/- 1 week vs nominal day” to “Window +/- 1 week”
   d. **MRE** - added the following, “Please note that MRE is not required with Day 57 MRI.”

The adjustments above support internal consistency and clarify scheduling assessments for on-treatment procedures.

11. **Section 5- Study Assessments and Procedures -Table 5.1-3 Post Treatment Follow-up Procedural Outline**
   a. **Pregnancy Testing** - Added, “Urine pregnancy testing to be performed at post treatment specified visits with reflex to serum if urine pregnancy testing is positive.”
   b. **DXA**: Removed the following: “Body composition (whole body), an exploratory measure, will be additionally carried out at facilities with the appropriate equipment.”

The adjustments above are added for the purpose of supporting internal consistency and schedule assessment clarification.

c. **Footnote adjustments:**
   i. Moved footnote ‘a’ from “Early Termination Visit” column to “Follow-up for immunogenicity” column
   ii. Changed text for footnote ‘a’ from, “Early Termination is not a scheduled visit. For early termination PK and PD assessments, refer to Table 5.5.1-1” to align with footnote ‘b’ now moved to the ‘Early Termination Visit’ column
   iii. Changed text for footnote ‘a’ to: “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”.

d. Adjusted column heading, “Follow-up for immunogenicity (up to 6 months post Day 142) to “Follow-up for immunogenicity (up to 12 months post Day 142)”
e. Added “X” in Column D292 for PK Sampling and Immunogenicity sample to support addition of sample collection at these timepoints
f. Moved PK Sampling and Immunogenicity testing references for Table 5.5.1-1 from D142 column to the Notes column and added in “X” in Column D142 for PK sampling and Immunogenicity. These adjustments support the schedule updates for immunogenicity and PK sampling during follow-up visits.

12. Updated imaging language from ‘imaging core lab’ to ‘central imaging lab’ for consistency throughout the document

13. Section 5.3.1.1 - DXA
   a. Removal of the following: “DXA will be conducted at baseline, end of treatment and approximately 6 months after the end of the treatment to assess body composition and BMD.”
   b. Addition of the following: “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.”
   These adjustments to imaging support consistency and clarification of the DXA imaging component and provide schedule clarification.

14. Section 5.4 - Efficacy Assessments
   a. Added the sub-heading “5.4.1 - Efficacy Imaging Assessment for the Study”
   b. Added the following, “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.”

c. Addition of subsection, 5.4.1.1 - “MRI” with movement of text from Section 5.4 “Efficacy Assessments” to Section 5.4.1.1 “MRI” as follows:
“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.”

These adjustments support clarification for imaging while providing a more detailed explanation on the efficacy assessment for MRI from the central imaging lab and add clarification for the MRI imaging schedule.

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

a. Addition of the following Event, “Immunogenicity Follow-up” with Study Day specified as, “Approximately every 6-8 weeks between D142 or D292 and up to 12 months after D142” including the following changes within this row:

i. Addition of an “X” with a denoted footnote ‘h’ and ‘i’ in the column “BMS-986036 (a) PEG-C-Term-Intact; (b) PEG-Total; (c) Endogenous FGF21”

ii. Addition of an “X” with a denoted footnote ‘i’ in the column “Immunogenicity”

b. Addition of Event, “Follow-up” with Study Day specified as, “292” with the following changes within this row:

i. Addition of an “X” in the column with a denoted footnote ‘h’ in the column “BMS-986036 (a) PEG-C-Term-Intact; (b) PEG-Total; (c) Endogenous FGF21”

ii. Addition of an “X” in the column “Immunogenicity”
c. Adjustment of the following Event, “Early Term” with Study Day specified as “Early Term visit (post treatment prior to Day 142)”
   i. Addition of footnote ‘i’ in the column “BMS-986036 (a) PEG-C-Term-Intact; (b) PEG-Total; (c) Endogenous FGF21”
   ii. Addition of footnote ‘i’ in the column “Immunogenicity”

d. Addition of footnote ‘i’ text as follows: “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.”

These adjustments to the Pharmacokinetic and Pharmacodynamic Sampling Schedule provide consistency with the amendment rationale by updated the required schedule for immunogenicity testing and endogenous FGF21 assessments at Day 292 follow up visit and the extension of follow-up immunogenicity testing and endogenous FGF21 assessments (for subjects with positive immunogenicity testing) for up to 12 months post-Day 142).

19. Section 5.7 - Immunogenicity
   a. Addition of Day 292 visit for subjects asked to return for antibody testing (in addition to D142)
b. Addition of the following: “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.”

c. Adjustment of “Assessments may continue, approximately every 6-8 week, for up to 12 monts following Day 142” instead of 6 months following Day 142.

These adjustments are consistent with the rationale for the amendment in updated the assessment of scheduling for the addition of immunogenicity testing and endogenous FGF21 assessments at Day 292 follow-up visit and the extension of follow-up immunogenicity testing and endogenous FGF21 assessments (for subjects with positive immunogenicity testing) to up to 12 months post-Day 142).

Please maintain a copy of this amendment with your protocol. Please provide a copy to your Investigational Review Board / Ethics Committee, unless agreed otherwise with BMS.
AMENDMENT ACKNOWLEDGMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion by all necessary Health Authorities before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

________________________________________________________________________
Investigator's printed name and signature Date

________________________________________________________________________
Bristol Myers Squibb Medical Monitor Date
(If required by applicable regulations and guidelines.)

Protocol Number: MB130045
Site Number: Applies to all sites
Amendment Number: 02