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 01
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 address FDA input:

- Addition of a Data Monitoring Committee by independent reviewers to support safety data review for all treated subjects
- Revision for discontinuation criteria identified in subjects with a repeated recurrence of a reported adverse event(s) classified as a Grade 3 or any Grade 4 adverse event(s) (or higher) per CTCAE classification to support subject safety
- Additional reference for Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (or most recent version available) - for adverse event(s) grading to support consistent safety reporting across subjects and data review/trend analysis

Secondary revisions include:

- Additional Immunogenicity sample collection added at Day 15
- PK endpoints have been revised to remove unnecessary parameters for characterization. Associated PK assessments and PK analyses are revised accordingly.
- The interim analysis is corrected to reflect ‘summaries’, instead of ‘summaries and graphs’.
- To permit additional members of the study team to review the aggregate results of the interim analysis.

Additional reasons for this amendment include

- The secondary objective is reworded to clarify that it applies to patients with NASH.
- Additional clarifications are made throughout, to better support internal consistency.
- Correction of typographical errors

These revisions impact both study conduct and data analysis. These revisions apply to all subjects. IRB review is required prior to implementation.

Changes to the Protocol:

1. Synopsis and Section 1.3.2 Secondary Objectives. The secondary objective is reworded to clarify that it applies to patients with NASH.
2. Synopsis and Section 8.3.2 - Secondary Endpoint(s)
   - The secondary endpoint objective was adjusted to clarify the pharmacokinetic assessments: “The first secondary objective (to assess the effect of daily or weekly doses of BMS-986036 on the pharmacokinetics of C-terminal and total BMS-986036 in NASH subjects) will be
assessed by the following secondary endpoints: Model-based pharmacokinetic parameters: Cavg, Cmin, Cmax and AUC(TAU) at time points specified in Table 5.5.1-1.

The new text states “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

3. Synopsis Pharmacokinetic Analyses and Section 8.4.4 Pharmacokinetic Analyses: Second sentence is deleted ‘PK parameters will be tabulated. Geometric means for Cmin will be plotted against study day/week by BMS-986036 dose.’

4. Synopsis Interim Analyses, and Section 8.5 - Interim Analysis
a) Removed that analysis will consist of “graphs” as it will consist of summaries only
b) Removed verbiage, ‘external to the study team’ regarding interim analysis data review to expand the relevant members who will be able to review the results of the interim analysis.

5. Section 3.1 - Study Design and Duration, Section 3.5 - Discontinuation of subjects following any treatment with study drug: Updated grammar, capitalization of letters and added in acronyms

7. Section 1.5.1 - Risk Mitigation Strategy - Under Immunogenicity: Changed the amount of weeks from 6 weeks to 4 weeks in the sentence, “All subjects will be monitored for occurrence of anti-drug and anti-FGF21 antibodies during dosing and for up to 6 weeks following the last dose” to provide the correct duration (4 weeks) after the last dose in which subjects that tested positive for anti-drug antibodies will be followed.

8. Section 3.4 - Concomitant Treatments; 3.4.1: Prohibited and/or Restricted Treatments: Added the word ‘systemic’ to prohibited treatment #13 in this section to clarify the scope of prohibited concomitant medications for subjects previously exposed to the compound: “Prior or current exposure to prescription or investigational PEGylated drug(s)”

9. Section 3.5 - Discontinuation of Subjects following any Treatment with Study Drug: To support the discontinuation of a subject treated with study drug for safety monitoring purposes and safety reporting consistency, this section was adjusted as follows:
   a) Provided clarification by adding “Per the subject’s request to stop study treatment and/or retract willingness to provide consent to continue participation in the study” in the sentence, “Subject’s request to stop study treatment and/or participation in the study” to emphasize the willingness for consent must be provided by any subject who requests discontinuation.
   b) An additional reference of the Common Termination Criteria for Adverse Events (CTCAE) to be used for Grade 3 and Grade 4 or above AE reporting for consistency across sites and additional rules on handling a clinical adverse event was added to support safety monitoring
c) Emphasized the wording the investigator ‘must’ discontinue any subject instead of using the wording, ‘discontinuation will commence’, to support safety monitoring for subjects experiencing a grade 3 or grade 4 AEs considered study drug related

d) Added clarification to support safety monitoring follow-up for any subject(s) who discontinues as a result of an AE: “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 and will the investigator provide documented justification of the decision”

e) Under sub-section, Laboratory or Clinical Criteria: Changed the sentence: “Any Grade 4 AE or clinically significant laboratory abnormality considered study drug related” to: ‘Any Grade 3, Grade 4 or above AE reported according to the current version of the CTCAE grade criteria or clinically significant laboratory abnormality considered study drug related (as described above) - to support safety monitoring clarification

10. Section 4.0 - Study Drug: Under Diagnostic agents, removed reference to glucose challenge as this is not applicable.

11. Section 4.6 - Blinding/Unblinding
   a) Removed ‘external to the study team’ from “The access to unblinded interim individual data will be limited to pre-specific personnel external to the study team”
   b) Removed the following: “(e.g. statistician, programmer, and BMS physicians from Exploratory Clinical and Translational Research and Global Research not otherwise involved in the study, as well as a PK scientist, a pharmacometrician, Biomarker scientist and a data integration programmer from Clinical Pharmacology and Pharmacometrics)” as specific team members unblinded to any interim analysis data will be documented separately and outside of the protocol scope

12. Section 4.7 - Treatment Compliance
   a) Removed the verbiage ‘and background antihyperglycemic medication as this is not applicable in this study.
   b) Clarified the sentence about the education to be performed by the site to subjects to support subcutaneous self-injections as follows: “The subject should be educated/properly instructed by designated site personnel on taking the study medication in accordance with the protocol”

13. Synopsis and Section 5.5 - Pharmacokinetic Assessments
   a) Changed the verbiage of, “The following pharmacokinetic parameters of BMS-986036 (Total and C-Terminal intact) will be generated directly from population PK model; these parameters are called primary PK parameters” to state “The following pharmacokinetic parameters of BMS-986036 (Total and C-Terminal intact) will be generated and summarized” to clarify the pharmacokinetic assessments to be performed for the study

14. Section 5.5 - Pharmacokinetic Assessments
   Removed the following sections as this is no longer applicable for pharmacokinetic assessment:
   
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F</td>
<td>Apparent clearance after extra-venous administration</td>
</tr>
<tr>
<td>V/F</td>
<td>Apparent volume of distribution after extra-venous administration</td>
</tr>
</tbody>
</table>
The following pharmacokinetic parameters of BMS-986036 (Total and C-Terminal intact) will be derived from the primary PK parameters; these parameters are called secondary PK parameters:

- **Cmax**  Maximum calculated serum concentration
- **T1/2**  Elimination half-life
- **AUC(TAU)**  Area under the concentration-time curve in one dosing interval
- **Cmin**  Minimal concentration within dosing interval
- **Cavg**  Average concentration within dosing interval

15. Section 5 Study Assessments and Procedures, Table 5.1-2 - On Treatment Procedural Outline: Added a sentence next to footnote a stating, “For early termination, PK and PD assessments, refer to Table 5.5.1-1” to clarify treatment schedule

16. Section 5.2 - Study Materials
   a) Added the sponsor will supply training materials and subject supplies to support subcutaneous injections
   b) Added the sponsor will supply forms to the site. Clarified ‘case report forms’ are electronic by adding this in front of CRF

17. Section 5.5 Pharmacokinetic Assessments, Table 5.5.1-1 Pharmacokinetic and Pharmacodynamic Sampling Schedule
   a) Added in Day 15 Immunogenicity sample to be collected
   b) Clarified early termination visit PK and PK assessment schedule of sample collection while on-treatment and post-treatment by adding an additional and separate row for post treatment PK/PD assessments labeled ‘post treatment prior to Day 142’ and adding ‘on treatment’ to the current ‘early termination visit’ assessment row
   c) Removed the footnote, ‘i’ - stating, ‘only when early termination happens after at least 4 weeks of treatment’ based on the change above to clarify the early termination visit schedule differentiation

18. Section 5.7 - Immunogenicity: Added the following, “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” to provide clearer differentiation between the two

19. Section 7.0 - Data Monitoring Committee and Other External Committees
   This section was added as a Data Monitoring Committee (DMC) will be implemented to support safety monitoring for subjects this study. The scope of the DMC will include:
   a) 3 independent consultants - appointed based on their expertise in hepatology, biostatistics and internal medicine as selected by the Sponsor
   b) Ability to review masked treatment group data but can request unblinded data by treatment group or by individual subject as warranted
   c) Data reviewed at meetings will include (but is not limited to) adverse events and laboratory value(s)
d) Data review if more than 3 subjects develop an AE of Grade 3 or higher in the same CTCAE category OR if more than 2 subjects develop an AE or CTCAE Grade 4

e) Will review data of all expedited Serious Adverse Events reported

f) Assessment of benefit vs risk based on available efficacy data

g) Collaborate with the medical safety team after each meeting - provide recommendations

h) and the medical safety team will inform the DMC of any action that will be taken

i) Provides meeting minutes to the medical safety team blinded to treatment assignment after each review

j) DMC charter to provide additional information about roles and responsibilities, operational procedures, methods of communication with the sponsor and meeting frequency

20. Section 11 - List of Abbreviations: Updated acronym terms utilized in the protocol and removed obsolete terms from the Abbreviations List

21. Section 12 References - CTC-AE reference is added.

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

___________________________________ _______________
Medical Monitor/Study Director Date

Protocol Number: MB130045
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Amendment Number: 01