Protocol MB130002: A randomized, double-blind, placebo-controlled, parallel-group, multiple dose study to evaluate the safety, pharmacokinetics and pharmacodynamic effects of BMS-986036 in obese adults with type-2 diabetes

Amendment Number 03
Site Number: All

Study Director

Medical Monitor

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 add a Day 57 urine collection and to add assays for both BMS-986036 and Endogenous FGF21 in urine. (See Protocol Changes 2a, 2b, 4, 5a, 5b, 5c, 8, 9, 19a, 19b, 19c, 20, 21)

Secondary reasons for this amendment:

- To update the Study Director and Medical Monitor assignments. (see Protocol Change 1)
- The upper limit for BMI is adjusted from 40.0 to 50.0. This supports enrollment without compromising subject safety. (See Protocol Change 3a, 11b)
- The lower limit for HbA1c is adjusted from >7.0 to ≥6.5%. This supports enrollment without compromising subject safety. As a consequence of this, the diagnosis T2DM is no longer qualified with the term ‘inadequately controlled’. (see Protocol Changes 3b, 3c, 11a)
- Primary Biomarker Analyses wording is corrected and clarified (see Protocol Changes 6, 22)
- Secondary Biomarker Analyses wording is corrected and clarified (see Protocol Changes 7a, 7b)
- Day 1 predose values are no longer required in addition to Screening values to determine eligibility. Screening values are sufficient to determine eligibility. This supports enrollment without compromising subject safety. (see Protocol Changes 10, 15c)
- The lower limit for Creatinine Clearance is adjusted from <60 to <49 mL/min. This supports enrollment without compromising subject safety. (see Protocol Change 12a)
- ECG related exclusion criteria are simplified to just the QTcF value. This better supports enrollment without compromising subject safety. (see Protocol Change 12b)
- The glucocorticoid restriction is adjusted to better support enrollment without compromising subject safety. (see Protocol Change 13)
- To make explicit the visits requiring an IVRS call. (see Protocol Changes 14a, 15a, 15b, 16a, 16b)
- To remove ambiguity in describing the visit window for visit Day 57, relative to visit Day 57 (see Protocol Change 15d).
- To correct typographical errors in Tables 5.1-2 and Table 5.1-3, removing table footnote links that were present in error. (see Protocol Changes 15e, 16c)
- To add urine creatinine assays to Urinalysis to support the measurement of BMS-986036 in urine (See Protocol Change 17)
- To correct and clarify the Pharmacokinetics assessments (see Protocol Changes 18a, 18b)
This amendment should be Ethics Committee-reviewed and approved prior to implementation. This revision applies only to future enrolled subjects.

**Changes to the Protocol:**

1. **Title page.** The Study Director and Medical Monitor assignments have been updated.

2. **Synopsis Study Population.**
   a) the upper limit for BMI is revised from 40.0 to 50.0
   b) For the diagnosis of Type 2 Diabetes Mellitus the term ‘inadequately controlled’ is removed.
   c) The lower limit for HbA1c is revised (in 2 places in the same paragraph) from >7.0 to ≥6.5%.

3. **Synopsis Pharmacokinetic Measures.** A sentence is added at the end “Urine concentrations of BMS-986036 and Endogenous FGF21 will also be measured.”

4. **Synopsis Primary Analysis.** A sentence is added at the end “Summary statistics will be tabulated by treatment, study day for HbA1c with corresponding change and percent change from baseline. Plot of mean profile over time will also be provided for HbA1c by treatment.”

5. **Synopsis Secondary Biomarker Analysis, Paragraph 3, and also in Section 8.4.6 Secondary Biomarker Analysis, Paragraph 3.**
   a) First sentence: The biomarker measurements are qualified as secondary biomarker measurements.
   b) After the first sentence the following sentence is added: “Plot of mean profiles over time will be provided for all secondary biomarker endpoints by treatment. Exploratory biomarkers may be summarized with descriptive statistics and plotted over time by treatment.”

6. **Synopsis Pharmacokinetic Analysis and Section 8.4.4 Pharmacokinetic Analysis.** A sentence is added at the end “Urine concentrations of BMS-986036 and Endogenous FGF21 will not be included in the clinical study report and will be reported separately.”
9. Section 1.4.4.1 Clinical Pharmacokinetics of BMS-986036. The 6th and 7th sentences "Therefore, urine concentration of BMS-986036 was not monitored in the clinical study." is deleted, and replaced with 2 new sentences at the end of the paragraph. "Due to the large size of the molecule, BMS-986036 is not expected to be excreted through urine intact. However urine will be collected for possible future confirmation when analytical method is available."

10. Section 3.3 Study Population. Inclusion / Exclusion criteria are now based on Screening measures. Day 1 measures are not additionally part of the inclusion/exclusion decision.

11. Section 3.3.1 Inclusion Criteria
   a) The lower limit for HbA1c is revised from >7.0 to ≥6.5%.
   b) The upper limit for BMI is revised from 40.0 to 50.0

12. Section 3.3.2 Exclusion Criteria, 2. Physical and Laboratory Test Findings
   a) Exclusion 2b) the GFR limit is revised from <60 to <49 mL/min
   b) Exclusion 2c) PR, QRS and QT exclusion criteria are removed.

13. Section 3.4.1 Prohibited and/or Restricted Treatments Item 7). The glucocorticoid restriction is revised from ‘within 12 weeks of screening up to Study Discharge’ to ‘within 6 weeks of screening’.

14. Table 5.1-1 Screening Procedural Outline
   a) IVRS visits are specified.
   b) Screening DXA repeat is clarified as applicable for bone scan quality.

15. Table 5.1-2 On Treatment Procedural Outline
   a) IVRS visits are specified.
   b) IVRS is added to Footnote b
   c) The Inclusion Exclusion row, relating to a Day 1 exclusion event, is removed.
   d) The “+3” day window for Day 58 is deleted
   e) Footnote link ‘c’ in Column ‘Rescue or Early Termination Visit’ for the row 'Prescribe rescue medication', is deleted.

16. Table 5.1-3 Post Treatment Follow Up Procedural Outline.
   a) IVRS visits are specified.
   b) IVRS is added to Footnote a
   c) Footnote links ‘d’ and ‘e’ in Column ‘Rescue or Early Termination Visit’ for the rows 'PK Sampling’ and ‘Prescribe rescue medication’ respectively, are deleted.

17. Section 5.3.2 Laboratory Test Assessments, Urinalysis. Urine Creatinine is added to the Urinalysis assays.

18. Section 5.5 Pharmacokinetic Assessments, Final paragraph.
   a) Cmax is clarified as ‘within the dosing interval’
   b) The half-life assessment is deleted.

19. Table 5.5.1-1 Pharmacokinetic and Pharmacodynamic Sampling Schedule for BMS-986036.
   a) A urine collection is added on Day 57.
   b) Footnote 5 is relocated from the header to specify just the applicable samples.
c) Footnote 8 is added to specify applicable samples for which urine will be collected to explore endogenous FGF21 and BMS-986036 concentration.

20. Section 5.5.2 Pharmacokinetic Sample Analysis. A second paragraph is added “The urine samples will be collected and may be analyzed when a bioanalytical method is available to explore BMS-986036 (C-terminal intact or Total or both) levels in urine, to assess the renal excretion.”

22. Section 8.4.5 Primary Biomarker Analysis. A sentence is added at the end “Summary statistics will be tabulated by treatment, study day for HbA1c with corresponding change and percent change from baseline. Plot of mean profile over time will also be provided for HbA1c by treatment.

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  
(If required by applicable regulations and guidelines.)

Protocol Number: MB130002  
Site Number: All  
Amendment Number: 03