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 02
Site Number: All

Study Director/Central 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 new exclusion criterion. Subjects with a Screening DXA T-score less than or equal to -2.5 SD will be excluded from participating in this study. A T-score of -2.5 or less meets the W.H.O criteria for osteoporosis. Subjects diagnosed with osteoporosis at screening may choose to pursue drug treatment to reduce their fracture risk. This intervention could affect the bone safety endpoints in this trial, namely bone turnover markers and post-dosing measurement of bone density. An additional safety concern is that subjects with low bone density at baseline that experienced a further decline in bone density as a result of investigational drug administration would be at increased fracture risk than subjects with normal bone density at baseline. Although the original protocol excludes subjects with a history of osteoporosis, subjects who not been previously screened for low bone density may not be aware that they have the condition.

Secondary reasons for this amendment:

- To revise the Screening DXA scan window to ‘7 to 21 days prior to Day 1’, to allow enough time to return DXA scan results to the site in time to support the new DXA-related exclusion criterion 3.3.2 2g).
- To allow a repeat measurement of screening serum creatinine 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.
- To cross reference Section 4.3 to Section 4.1, previously missing.
- Associated with new DXA exclusion criterion 3.3.2 2g), Section 5.11 now reflects that central assessments of DXA scans will be sent to both the Sponsor and the Investigator.
- To delete a sentence in Section 5.12 Medical Research Sample, that is not applicable for this protocol.

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) 3.3.2 Exclusion criteria, 2. Physical and Laboratory Test Findings. A new exclusion criterion g) is added. g) Subjects with a centrally read (at Bioclinica) 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 for example).

2) 3.3.2 Exclusion criteria, 2. Physical and Laboratory Test Findings b) is revised, by addition of the following. 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.

3) Synopsis Table Study Design Table footnote a, and Table 3.1-1 footnote a: Dual emission X-ray Absorptiometry Note: - the Screening DXA scan window is revised to ‘7 to 21 days prior to Day 1’

4) Section 4.3 Selection and Timing of Dose for Each Subject. Text is added “Refer to Section 4.1 Study Treatments.”

5) Table 5.1-1 Screening Procedural Outline. In the row for Dual-emission X-ray Absorptiometry (DXA), the Notes are revised to read: ‘Within 7 to 21 days prior to the Day 1 dose. Please allow time prior to Randomization, for turnaround of data from both the initial screening DXA, and for a possible repeat scan (eg for scan quality). The central imaging vendor’s turnaround of Screening DXA scans is approximately 2-3 working days. Bone imaging (hip and lumbar spine at all imaging facilities.

6) Table 5.1-2 On Treatment Procedural Outline and Table 5.1-3 Post Treatment Procedural Outline. In the row for Dual-emission X-ray Absorptiometry (DXA), the Notes are revised to read: ‘Bone imaging (hip and lumbar spine at all imaging facilities.

8) 5.11 Results of DXA Central Assessments. First sentence now reflects that centralized assessment of DXA scan data will be sent to both the sponsor and site. Second sentence is deleted.

9) 5.12 Medical Research Sample, first paragraph, second sentence. The sentence ‘No additional sampling is required for residual collections’ is deleted.

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.)

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