Companion protocol for the ^{13}C-Methacetin Breath Test (MBT) for use in Bristol-Myers Squibb phase 2b studies for BMS-986036 (PEG-FGF21), under Protocols MB130-068 and MB130-069

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1.0	February 20, 2018	Ora Msika-Azuelos	Initial Release

1 ABBREVIATIONS

AE - Adverse Event
BMS - Bristol-Myers Squibb
CDOB - Cumulative Delta over Baseline
CI - Confidence Interval
CL - Confidence Limits
CO_2 - Carbon dioxide
CPDRxx - Cumulative Percentage Dose Recovery at xx minutes from ingestion
CRF - Case Report Form
CSPH - Clinically Significant Port Hypertension
CTP - Child-Turcotte-Pugh Score
DOB - Delta over Baseline
eCRF - Electronic Case Report Form
FDA - (United States) Food and Drug Administration
GCP - Good Clinical Practice
IDE - Investigational Device Exemption
IRT - Interactive Response Technology
MBT - ^{13}C-Methacetin Breath Test
MCS - Molecular Correlation Spectrometry
MEGX - Monoethylglycinexylidide
MELD - Model for End-Stage Liver Disease
MRI - Magnetic Resonance Imaging
MRE - Magnetic Resonance Elastography
NAFLD - Nonalcoholic Fatty Liver Disease
NAS - NAFLD Activity Score
NASH - Nonalcoholic Steatohepatitis
NPV - Negative Predictive Value
PDFF - Proton Density Fat Fraction
PDR - Percent Dose Recovered (expressed as % per hour)
PET - Thermoplastic Polyester
PO - Per Os (by mouth)
PTFU - Post treatment follow up
QW - Once weekly
SAE - Serious Adverse Event
SF - Screen Failures
SUSAR - Suspected unexpected serious adverse reaction
UADE - Unanticipated Adverse Device Effect

US - United States (of America)
USA - United States of America

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2 PROTOCOL SYNOPSIS

Protocol Title:	Companion protocol for the ^{13}C-Methacetin Breath Test for use in Bristol-Myers Squibb phase 2b studies for BMS-986036 (PEG-FGF21), under Protocols MB130-068 and MB130-069.
Short Title:	Companion protocol assessing the MBT in subjects participating in the MB130-068 and MB130-069-studies (PEG-FGF21)
Protocol Number:	BMS-EX-0118
Version and Date:	v 1.0, February 20, 2018
Phase of Development of BMS-986036:	Phase 2b (IND 125297)
Phase of Development of MBT:	The study is feasibility for drug response monitoring however the data may be used for Exalenz for future submissions
Sponsor:	**Exalenz Bioscience Ltd.** 4 Ha'Maayan Street Modi'in, Israel 7177872 Tel: +972-8-9737500 Fax: +972-8-9737501
Investigated Disease:	Subjects with Non-Alcoholic Steatohepatitis (NASH) and stage 3 liver fibrosis (MB130-068 study) or compensated liver cirrhosis (MB130-069 study)
Combination Product:	^{13}C-labeled Methacetin Breath Test
Comparators:	Liver Fibrosis stage as assessed by biopsy and additional liver health measures and their changes such as NAS, MELD, CTP, PDFF, Liver Stiffness, Serum Biomarker Pro-C3, and Liver-related Clinical Outcome.

Study Population:	Subjects that are enrolled into either of two separate BMS sponsored IND studies (MB130-068, MB130-069) at selected study sites will be offered the opportunity to perform the MBT. These will be considered as two separate study cohorts (cohort 1 and 2, respectively) within this companion protocol. Each cohort consists of four treatment arms (BMS-986036 10mg, 20mg, 40mg QW or matching placebo QW), as defined in the respective BMS sponsored protocols. Cohort 1 consists of Subjects with NASH and stage 3 fibrosis, as assessed by a central laboratory reader of the liver biopsies (n=160), and who meet all the MB130-068 study criteria. Cohort 2 consists of Subjects with NASH and compensated liver cirrhosis (stage 4 fibrosis), as assessed by a central laboratory reader of the liver biopsies (n=100), and who meet all the MB130-069 study criteria. This feasibility companion protocol will include the 2 cohorts of subjects, with a planned total of up to 260 subjects from approximately 75 sites worldwide (USA and Japan) for the two BMS IND studies, while the MBT will only be conducted in the USA. Not all participating sites will elect to perform the MBT. The total number of subjects expected to perform the MBT may reach up to 250 subjects (also accounting for drop outs). Each subject will perform up to 3 MBTs over 1 year; approximately one every 24 weeks.
Primary Efficacy Objectives:	To demonstrate the ability of the MBT to evaluate patient response to treatment with BMS-986036, comparing placebo to each treatment arm individually. Assessment will be performed at the 24 and 48 week visits and compared to day 1 (change from baseline) and the respective preceding visit (change between visits), when available. Assessments will be done for each study cohort independently, according to availability, and on the combined population of the two cohorts by dose of the BMS drug under study.

Secondary Efficacy Objectives:	The following assessments will be done by treatment arm and combined arms for each study cohort independently, according to availability, and on the combined population of the two study cohorts by dose of the BMS drug under study: 1. To demonstrate the short and long-term prognostic value (3 months, 6 months and 1 year, respectively) of MBT for liver disease deterioration (reported as liver-related clinical outcome events). Assessment will be performed using MBT from the day 1, and 24 and 48 week visits. 2. To assess the ability of changes in the MBT to reflect biopsy proven changes in fibrosis and/or NAS as assessed by a central reader at week 24 (or at least week 20 in cases of an early termination time point) (for cohort 1) or at week 48 (for cohort 2) compared to the baseline biopsy from the screening visit. 3. To assess the ability of changes in the MBT to reflect changes in liver stiffness as measured by Magnetic Resonance Elastography (MRE) where available at weeks 24 and 48 (or at early termination) compared to baseline MRE from the screening visit. 4. To assess the ability of changes in the MBT to reflect changes in Proton Density Fat Fraction (PDFF) as measured by Magnetic Resonance Imaging (MRI) where available - at weeks 24 and 48 (or early termination), compared to baseline MRI from the screening visit. To assess the ability of changes in the MBT to reflect changes in Serum Pro-C3 at 24 and 48 weeks of treatment (or early termination), compared to baseline Pro-C3 from the screening visit. The following additional objectives are applicable for cohort 2 only: 1. To assess the ability of changes in the MBT to reflect changes in liver stiffness as measured by "Fibroscan" elastography at the 48 week visit (or earlier if there was an early termination) compared to the screening visit. 2. To assess the ability of changes in the MBT to reflect changes in the Model for End-stage Liver Disease (MELD) score at 24 and 48 week visits compared to study day 1. 3. To assess the ability of changes in the MBT to reflect changes in the Child-Turcotte-Pugh Scoring (CTP) score at weeks 24 and 48 (or early termination) compared to study day 1.

Exploratory Efficacy Objectives:	To assess the ability of the MBT to monitor patient status in comparison to other available measures, such as Liver Fibrosis stage, NAS, MELD, CTP, PDFF, Liver Stiffness, Serum Biomarker or Pro-C3.
Safety Objective:	Evaluation of safety related to the MBT.

Study Design:	This study is a feasibility companion protocol that will rely on the data generated by BMS's studies of BMS-986036 (PEG-FGF21) under protocols MB130-068 and MB130-069 (IND 125297), which are assessed in this companion protocol as two separate study cohorts (1 and 2, respectively) with the exception of the MBT. The MB130-068 and MB130-069 studies are Phase 2b, multicenter, double-blind, randomized, placebo-controlled, parallel-group studies to demonstrate the safety and efficacy of BMS-986036 in the treatment of subjects with NASH and stage 3 liver fibrosis or compensated cirrhosis with up to 48 weeks of treatment. The study is feasibility for drug response monitoring however the data may be used for Exalenz for future submissions. As described in the BMS protocols, subjects will be enrolled and randomized via interactive response technology (IRT) to receive BMS-9860936 10mg QW, BMS-986036 20mg QW, BMS-9860936 40mg QW or matching placebo QW in a 1:1:1:1 ratio. The BMS studies' treatment durations will each consist of two periods: 1. A 48-week, Double-Blind Treatment Period, during which the subjects will receive blinded study medication (BMS-986036 10mg, 20 mg, 40mg QW or matching placebo QW). During the Double-Blind Treatment Period, subjects will be evaluated for safety and efficacy every 4 weeks (±5 days) through week 24 and every 8 weeks (±5 days) from week 24 through week 48. 2. A Follow up Period, during which subjects will be evaluated for safety and efficacy for 4 weeks through week 52. 3. A Follow-Up Period of at least 6 months and up to 14 months after the week 52/ PTFU Visit for the collection of additional DXA assessment (in all participants) and immunogenicity assessments (in participants for whom Long-Term Immunogenicity Follow-Up Visits are required.) Any liver related complication event will be recorded. The last dose of study medication will be at the week 48 visit. Subjects will have a safety and efficacy evaluation at week 48 and return for a post-treatment follow-up evaluation through week 52. As a sub-study of BMS protocols MB130-068 and MB130-069, MBT will be performed at the day 1 visit and every 24 weeks during the Double-Blind Treatment Period in order to allow the assessment whether BMS-986036 compared to placebo improves liver metabolic function as determined by the MBT.

Inclusion Criteria:	This protocol follows the inclusion criteria as defined in the respective main protocols; MB130-068 and MB130-069 are considered as two distinct study cohorts for this companion protocol. This feasibility companion protocol intends to assess the data for all subjects that perform the MBT under the MB130-068 and MB130-069 protocols, including their clinical follow up information.
Exclusion Criteria:	Exclusion criteria are defined in the respective main protocols; MB130-068 and MB130-069, and are considered as two distinct study cohorts for this feasibility companion protocol. Additionally, subjects designated to perform the MBT that are known to be hypersensitive or allergic to Methacetin or its metabolites, e.g. acetaminophen (paracetamol), will not perform the MBT.
Pre Breath Test Restrictions:	1. Subject should be fasting, including all oral morning medications (except for beta-blockers and study drug [BMS-986036 or placebo]), for at least 8 hours prior to the test 2. Subject should not smoke on the day of the breath test prior to the breath test 3. Subject should not take any of the following drugs within 48 hours prior to the test: acyclovir, allopurinol, carbamazepine, cimetidine, ciprofloxacin, daidzein (herbal), disulfiram, echinacea, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, montelukast, norfloxacin, phenylpropanolamine, phenytoin, propafenone, rifampin, terbinafine, ticlopidine, thiabendazole, verapamil, zileuton or any medication that might interfere with methacetin metabolism or might affect CYP1A2 (cytochrome P450 1A2) 4. Subject should not take amiodarone within 30 days prior to the test 5. Subject should not take paracetamol (acetaminophen) related medications within the 24 hours prior to the test 6. Subject should not perform the test if allergic or hypersensitive to Methacetin or its metabolites (paracetamol, acetaminophen) 7. Subject should not consume any alcohol or caffeine within 24 hours prior to the test 8. Subject should not have general anesthesia or sedation within 24 hours prior to the test 9. Subjects on beta-blockers or statins should be on a stable dose at least 30 days prior to the test

Primary Efficacy Endpoint	The MBT's ability to measure the effect of BMS-986036 treatment on the metabolic capacity of the liver at 24-week intervals during the Double-Blind Treatment Period, as compared to changes in placebo treated subjects.
Secondary Efficacy Endpoint measures:	In order to assess the correlation of MBT with other measures of liver disease, the following endpoint measures will be collected: For all study cohorts: MBT results for each MBT visit (day 1, week 24, week 48) as well as changes in MBT results (CPDR30/PDR peak or other breath test parameters). The other measures of liver disease that will also be collected in this study are as follows: Liver Fibrosis stage and NAS as determined by Liver Biopsy, PDFF as determined by MRI where available, Liver Stiffness as determined by MRE where available, Serum Biomarker Pro-C3. Additional measures for cohort 2 include: MELD and CTP scores, Liver Stiffness as determined by Fibroscan® Elastography, Liver-related Clinical Outcome defined as the first occurrence of any one of the following: all-cause mortality, MELD score ≥15, liver transplant, hepatocellular carcinoma (HCC), ascites requiring medical intervention, hospitalization (≥ 24 hours) for onset of variceal bleeding, hepatic encephalopathy and spontaneous bacterial peritonitis.
Statistical Analysis:	The ^{13}C-Methacetin Breath Test will primarily be assessed for its ability to measure the effect of BMS-986036 on the metabolic capacity of the liver at 24-week intervals during the Double-Blind Treatment Period as compared to placebo, by modelling the MBT results and the change in its value from previous visits, including the baseline MBT, to each of the subsequent visits using Mixed Effect Model for Repeat Measurements (MMRM). Secondary endpoints will be assessed through Cox and Linear regressions in order to test for prognostic value and correlations between MBT and other Liver related outcomes and measures.

3 BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the world today. Nonalcoholic steatohepatitis (NASH), which is the most progressive form of NAFLD, is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning), with or without fibrosis. NASH is associated with increased mortality rates due to cardiovascular-, liver-, and cancer-related deaths.

Currently, there are no approved drugs for the treatment of NASH. With the increasing prevalence of obesity and obesity-related diseases, NASH could soon become the leading indication for liver transplantation and the leading cause of hepatocellular carcinoma (HCC). There is an urgent need to develop preventative and therapeutic strategies against NASH, as clearly described in the BMS'-studies main protocols.

Standard biochemical and clinical tests are not capable of providing good correlations with disease staging and grading. Furthermore, it is known that in a substantial percentage of the diseased population, standard liver function tests do not show abnormal results.
Histological parameters have been shown to be correlated to liver disease severity,[(1)] but biopsies have limitations such as sampling error and the risks involved in the biopsy procedure itself. Furthermore, biopsies are not a measure that can be repeated often enough in standard practice in order to monitor disease progression and effect of therapeutic treatments.
The unmet clinical need for a non-invasive means to evaluate liver disease progression or response to therapy accurately is clearly a challenge that needs to be addressed as new NASH treatments are being developed.
The concept of a metabolic test that could be utilized to assess the severity of liver disease was first explored several decades ago. Such tests are performed by administering a compound, either orally or intravenously, with the compound being taken up by the liver or metabolized. The end-products of the metabolic process can be measured in either blood, bile, urine, saliva or exhaled breath, supplying a measurable value to the level of liver metabolic activity. Several compounds have been utilized to evaluate hepatic metabolic function in this manner, including indocyanine green, galactose, aminopyrine, caffeine, lidocaine, phenylalanine, Methacetin (N-(4-Methoxy-phenyl) acetamide) and Octanoate (sodium-octanoate). For example, previous studies have demonstrated that hepatic metabolism of lidocaine to monoethylglycinexylidide (MEGX) decreases with liver fibrosis and cirrhosis and improves with successful treatment of the underlying liver disease. Furthermore, these studies showed the lidocaine test could accurately predict

which subjects with stable cirrhosis awaiting liver transplantation were at risk of developing future hepatic decompensation. Most of these methods have been abandoned due to impracticality or undesired side effects.

Exalenz Bioscience Ltd. has developed breath test products consisting of a combination of a medical device and various ^{13}C-labeled substrates for gastrointestinal and liver applications.

The rate and pattern of changes in the $^{13}CO_2/^{12}CO_2$ ratio curve in exhaled breath reflect substrate metabolism, i.e. the liver's metabolic capacity.

The aim of the Company is to provide a non-invasive, point-of-care, breath test to assess disease severity and to monitor disease progression (improvement or deterioration) using ^{13}C-Methacetin.

3.1 Defining the need for a non-invasive test for the characterization of NASH progression

About 7.9% of the US population has persistently elevated liver enzymes with negative findings for viral hepatitis and other common causes of liver diseases[(2)]. Over 80% of such cases are estimated to be due to NAFLD (NAFL or NASH). In those who have concomitant features of the metabolic syndrome, the likelihood of developing NAFLD exceeds 90%. It is also known that in a substantial percentage of the diseased population, standard tests do not show abnormal results, especially in the NAFLD population.

Furthermore, the standard biochemical and clinical tests do not provide good correlation with disease staging and grading.

Currently, such subjects are offered a liver biopsy as standard of care to diagnose NASH and assess the risk of potential cirrhosis. Although histology results have been shown to be correlated to liver disease severity,[(1)], biopsies have limitations such as sampling error and risks involved in the actual biopsy procedure. Additionally, given the sheer numbers of subjects with NASH in the world, it is not logistically feasible to biopsy all subjects with NASH. Furthermore, biopsies are not a measure that can be repeated often enough in standard practice in order to monitor disease progression or response to treatment.

Based on all of the above, there is a great need for a simple non-invasive method to assess and monitor disease progression in the NAFLD/NASH population.

Breath testing with ^{13}C-labeled substrates provides a safe, non-invasive means for evaluating hepatic impairment as it pertains to liver metabolic function. ^{13}C is a stable, non-radioactive isotope, which can be incorporated into a specific location within a test substrate so it can be metabolized to $^{13}CO_2$ by the liver. ^{13}C-Methacetin has been identified as such an appropriate substrate.

The device being used is a molecular correlation based spectrometer, using a patented technology based on specific light source emissions and the different absorption of $^{13}CO_2$

and $^{12}CO_2$ gases. This technology is already implemented in a similar device approved for marketing in Europe and cleared in the USA for other disease testing, namely *H. pylori* infection.

The ^{13}C-labeled substrates (in this case ^{13}C-Methacetin) are metabolized by the target organ under investigation (in this case the liver), producing $^{13}CO_2$ which in turn leads to changes in the $^{13}CO_2/^{12}CO_2$ ratio in a subject's exhaled breath over time. These ratio changes are displayed in real time on the device's screen and printed at the end of the test.

Breath tests using the ^{13}C-Methacetin are being evaluated in this protocol in an attempt to find an effective non-invasive tool to monitor liver disease progression/regression with and without treatment in NAFLD/NASH, and to assist in assessing disease severity and risk for decompensation.

3.2 Rationale to use the MBT for assessment of Liver Disease Progression

Tests of true hepatic function that rely on the metabolism of administered exogenous compounds have not yet been widely adopted in clinical practice because they have been cumbersome to perform and the acquisition of results is slow. The recent development of the BreathID® MCS analyzer offers a unique opportunity to demonstrate a metabolism-based test showing agreement with disease progression/regression and liver biopsy measures.

In advanced liver disorders, the liver has reduced Methacetin metabolic capacity, leading to low MBT values. Low values of Methacetin metabolism are suggestive of Subjects who have advanced liver disease. Several MBT output variables (percentage dose recovery rate and cumulative percentage dose recovered - PDR/CPDR values at different time points and their combination) may be used to assess metabolic capacity and subsequently liver disease progression/regression.

It has been shown in preliminary studies that MBT correlates with both CTP and MELD values. It may be even more sensitive and a better predictor of liver function because generally function deteriorates prior to the development of complications of cirrhosis and a decline in liver function as assessed by CTP and MELD[3].

It is hypothesized that a decline in liver function as assessed by MBT measured serially over time will occur prior to the development of complications of cirrhosis (such as variceal bleeding, ascites and hepatic encephalopathy) and worsening in liver function as assessed by changes in CTP and MELD.

The MBT, by providing immediate results, could aid in decision making in Subjects with cirrhosis awaiting liver transplant. Such a test may in the future help in decision-making

regarding transplantation priority and provide point of care assessment of therapeutic interventions if relevant.

All liver-related clinical outcome events will be captured in this study (see section 7.7.2). One of this study's aims is to show the ability of the ^{13}C-methacetin breath test to identify Subjects at risk for decompensation and to determine the effect of BMS' study drug BMS-986036 on the metabolic capacity of the liver at 24-week intervals during the Double-Blind Treatment Period compared to placebo.

4 INTENDED USE / INDICATION FOR USE

The ^{13}C-Methacetin Breath Test is a non-invasive test intended as an aid to assess liver disease progression (improvement or deterioration) with or without treatment in adult subjects by measuring the ability of the liver to metabolize ^{13}C-Methacetin. The ^{13}C-Methacetin Breath Test may also have a prognostic value in assessment of adult Subjects at risk for liver disease deterioration.

5 STUDY DESIGN

Please refer to protocols MB130-068 and MB130-069.

This study is a feasibility companion protocol that will use the data generated by BMS's study of BMS-986036 under protocols MB130-068 and MB130-069 (IND 125297), which are considered in this companion protocol as two separate study cohorts (1 and 2, respectively). The MB130-068 and MB130-069 studies are Phase 2b, multicenter, double-blind, randomized, placebo-controlled, parallel-group studies to evaluate the safety and efficacy of BMS-986036 in improving fibrosis without worsening of NASH, and long term clinical outcomes in subjects with NASH and stage 3 liver fibrosis or compensated cirrhosis. The study is feasibility for drug response monitoring however the data may be used for Exalenz for future submissions.

The study will consist of 4 periods:

- A 4 to 8-week Screening Period
- A 48-week, Double-Blind Treatment Period, during which the subjects will receive blinded study medication (BMS-9860936 10mg QW, BMS-986036 20mg QW, BMS-9860936 40mg QW or matching placebo QW in a 1:1:1:1 ratio).
- Study visits every 4 weeks up to week 24 and every 8 weeks after week 24 up to week 48, while MBT will only be performed every 24 weeks.
- A Follow up Period, during which subjects will be evaluated for safety and efficacy for 4 weeks through week 52.

- A Follow-Up Period of at least 6 months and up to 14 months after the week 52/PTFU Visit for collection of any liver related complication event.

As part of the MB130-068 and MB130-069 studies, the MBT will be performed on Day1 and every 24 weeks during the Double-Blind Treatment Period, to assess whether BMS-986036 compared to placebo improves liver metabolic function as determined by the Methacetin Breath Test.

6 SUBJECT SELECTION

This feasibility companion protocol assesses the data for all subjects being enrolled under MB130-068 and MB130-069 protocols that consent to perform the MBT at sites performing MBT. Subjects will be screened according to the inclusion/exclusion criteria of the MB130-068 and MB130-069 protocols, and will be randomly assigned to a study treatment arm if they meet all the criteria. Those Subjects enrolled into those two separate BMS sponsored studies (MB130-068, MB130-069, respectively) and will be considered as two separate study cohorts (cohort 1 and 2, respectively) for this companion protocol.

6.1 Inclusion Criteria

This protocol follows the inclusion criteria as defined in the respective main protocols; MB130-068 and MB130-069 considered as two distinct study cohorts for this companion protocol. This feasibility companion protocol assesses the data for all subjects that perform the breath test under the MB130-068 and MB130-069 protocols, including their clinical follow up information.

Cohort 1 includes study Subjects with NASH and stage 3 fibrosis that meet all the MB130-068 study criteria that performed the MBT.

Cohort 2 includes study Subjects with NASH and compensated liver cirrhosis that meet all the MB130-069 study criteria that performed the MBT.

6.2 Exclusion Criteria

Exclusion criteria are as those in the respective BMS protocols; MB130-068 and MB130-069 considered as two distinct study cohorts for this companion protocol. Additionally, subjects designated to perform the MBT that are known to be hypersensitive or allergic to Methacetin or its metabolites, e.g. acetaminophen (paracetamol), may not perform the MBT.

6.3 Exclusion Criteria from MBT testing On the day of the test

1. Subject should be fasting, including all oral morning medications (except for beta-blockers and study drug [BMS-986036 or placebo]), for at least 8 hours prior to the test
2. Subject should not smoke on the day of the breath test prior to the breath test
3. Subject should not take any of the following drugs within 48 hours prior to the test: acyclovir, allopurinol, carbamazepine, cimetidine, ciprofloxacin, daidzein (herbal), disulfiram, echinacea, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, montelukast, norfloxacin, phenylpropanolamine, phenytoin, propafenone, rifampin, terbinafine, ticlopidine, thiabendazole, verapamil, zileuton or any medication that might interfere with methacetin metabolism or might affect CYP1A2 (cytochrome P450 1A2)
4. Subject should not take amiodarone within 30 days prior to the test
5. Subject should not take paracetamol (acetaminophen) related medications within the 24 hours prior to the test
6. Subject should not perform the test if allergic or hypersensitive to Methacetin or its metabolites (paracetamol, acetaminophen)
7. Subject should not consume any alcohol or caffeine within 24 hours prior to the test
8. Subject should not have general anesthesia or sedation within 24 hours prior to the test
9. Subjects on beta-blockers or statins should be on a stable dose at least 30 days prior to the test

6.4 Consenting

Prior to study participation Subjects' and/or their representative will be consented and sign two informed consent forms (ICFs): One appropriate consent form as part of BMS's MB130-068 or MB130-069 studies and another appropriate separate ICF as part of BMS' s MBT sub-study according to IRB preference.

The consent will include willingness to share data with Exalenz and allow acquisition and collation of blood, clinical and imaging data taken on entry to the study, and incorporate all other data from the time of admission until the subject's termination from the study.

7 STUDY OBJECTIVES

The feasibility companion study aims to evaluate the capabilities of the MBT to assess the progression of NASH and monitor changes in NASH subjects with significant fibrosis or compensated cirrhosis with and without treatment.

7.1 Primary Efficacy Objective

To demonstrate the ability of the MBT to evaluate patient response to treatment with BMS-986036 comparing placebo to each treatment arm individually. Assessment will be performed at 24 and 48 weeks and compared to day 1 (change from baseline) and the respective preceding visit (change between visits), when available. Assessments will be done for each study cohort independently, according to availability and on the combined population of the two cohorts by dose of the BMS drug under study.

7.2 Secondary Efficacy Objectives

The following assessments will be done by treatment arm and combined arms for each study cohort independently, according to availability, and on the combined population of the two study cohorts by dose of the BMS drug under study:

1. To demonstrate the short and long-term prognostic value (3 months, 6 months and 1 year, respectively) of MBT for liver disease deterioration (reported as liver-related clinical outcome events). Assessment will be performed using MBT from the day 1, and 24 and 48 week visits.
2. To assess the ability of changes in the MBT to reflect biopsy proven changes in fibrosis and/or NAS as assessed by a central reader at week 24 (or at least week 20 in cases of an early termination time point) (for cohort 1) or at week 48 (for cohort 2) compared to the baseline biopsy from the screening visit.
3. To assess the ability of changes in the MBT to reflect changes in liver stiffness as measured by Magnetic Resonance Elastography (MRE) where available at weeks 24 and 48 (or at early termination) compared to baseline MRE from the screening visit.
4. To assess the ability of changes in the MBT to reflect changes in Proton Density Fat Fraction (PDFF) as measured by Magnetic Resonance Imaging (MRI) where available - at weeks 24 and 48 (or early termination), compared to baseline MRI from the screening visit.
5. To assess the ability of changes in the MBT to reflect changes in Serum Pro-C3 at 24 and 48 weeks of treatment (or early termination), compared to baseline Pro-C3 from the screening visit.

The following additional objectives are applicable for cohort 2 only:

1. To assess the ability of changes in the MBT to reflect changes in liver stiffness as measured by "Fibroscan" elastography at the 48 week visit (or earlier if there was an early termination) compared to the screening visit.
2. To assess the ability of changes in the MBT to reflect changes in the Model for End-stage Liver Disease (MELD) score at 24 and 48 week visits compared to study day 1.
3. To assess the ability of changes in the MBT to reflect changes in the Child-Turcotte-Pugh Scoring (CTP) score at weeks 24 and 48 (or earlier if there was an early termination) compared to study day 1.

7.3 Exploratory Efficacy Objectives

To assess the ability of the MBT to monitor patient status in comparison to other available measures, such as Liver Fibrosis stage as assessed by NAS, MELD, CTP, PDFF, Liver Stiffness, Serum Biomarker or Pro-C3.

7.4 MBT Safety Objective

All adverse events, serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSAR) and unanticipated adverse device effects (UADE) will be reported according to local regulations. The actual reporting is discussed in section 11. No breath-test related serious adverse events are expected. For more information please refer to the Investigator's Brochure.

7.5 Primary Efficacy Endpoint

MBT measurements throughout this feasibility companion study and all clinical measures and outcomes as assessed under protocols MB130-068 and MB130-069 will be collected in order to assess the MBT's ability to measure the effect of BMS-986036 treatment on the metabolic capacity of the liver at 24 week intervals during the Double-Blind Treatment Period, up to 48-weeks, as compared to changes in placebo treated subjects.

Assessments will be done for each study cohort independently and according to availability, on the combined population of the two study cohorts by dose of the BMS drug under study.

7.6 Secondary Efficacy Endpoint measures

In order to assess the correlation of MBT with other measures of liver disease the following endpoint measures will be collected:

For all study cohorts: MBT results for each MBT visit (day 1, week 24, week 48,) as well as changes in MBT results (CPDR30/PDR peak or other breath test parameters).

The other measures of liver disease that will be collected in this study are as follows:

Liver Fibrosis stage and NAS as determined by Liver Biopsy, PDFF as determined by MRI where available, Liver Stiffness as determined by MRE where available, Serum Biomarker Pro-C3

Additional measures for cohort 2: MELD and CTP scores, Liver Stiffness as determined by Fibroscan® Elastography, Liver-related Clinical Outcome defined as the first occurrence of any one of the following: all-cause mortality, MELD score ≥15, liver transplant, hepatocellular carcinoma (HCC), ascites requiring medical intervention, hospitalization (≥ 24 hours) for onset of variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis.

7.7 Efficacy Variables

Study procedures and timing are summarized in the Schedule of Events of protocols MB130-068 and MB130-069.

The following procedures or tools will be used to assess subjects' disease activity during the study:

- MBT at selected sites in subjects who opt in at Day 1, week 24 and week 48.
- Liver biopsy at Screening (if no biopsy is available from within 6 months of the Screening Visit), week 24 (for subjects in protocol MB130-068/cohort 1) or week 48 (for subjects in protocol MB130-069/cohort 2)
    - Histological assessments of fibrosis stage and NASH activity (NAS)
- Liver stiffness as determined by MRE at selected sites at screening, week 24 and week 48
- Hepatic fat fraction as determined by MRI at selected sites at screening, week 24 and week 48.
- Serum Biomarker Pro-C3 at Screening, Day 1, week 24, week 48 and week 52.

Additional variables for cohort 2:

- Fibroscan® elastography at Screening and week 48 or early termination
- MELD Scores at Screening, Day 1, every 4 weeks up to week 24, every 8 weeks up to week 48 and week 52.

- Child-Pugh scores at Screening, Day 1, every 4 weeks up to week 24 and every 8 weeks up to week 48 and week 52.
- Liver-related Clinical outcome events at each visit from Day 1 through week 52 and during the Long-Term Bone Mineral Density and Immunogenicity Follow-Up Period (up to 14 Months after week 52).

7.7.1 Liver Biopsy

Liver biopsy will be conducted at Screening if no liver biopsy is available within 6 months prior to Screening. Liver biopsy will also be performed at week 24 (for cohort 1) or week 48 (for cohort 2).

All histological assessments will be performed by a blinded central reader. The central reader will be a medical doctor, board certified in pathology, with experience in liver pathology in a clinical study setting. Details on the acquisition, quality requirements, histological preparation, and shipping of histological samples are in the respective Study Reference Manual.

7.7.1.1 Histological Assessments

The NASH Clinical Research Network (CRN) system will be used to score the histologic samples. The NASH CRN system is based on the concept that necro-inflammatory lesions and stage of fibrosis should be evaluated separately; it assesses liver biopsies for degree of steatosis (0-3), lobular inflammation (0-3), hepatocellular ballooning (0-2), and fibrosis (0-4). The first 3 components are added together in an unweighted fashion to determine the NASH activity score (NAS) that ranges from 0 to 8. Fibrosis is staged separately on a 0-4 scale: 0 (none); 1 (perisinusoidal or periportal); 2 (perisinusoidal and portal/periportal); 3 (bridging fibrosis); 4 (cirrhosis). It should be noted, the NAS should not be considered a replacement for a pathologist's diagnosis of NASH.

Table 1 NAS Scoring System

Histology Variable	Grade	Score
Steatosis Grade	< 5%	0
	5-33%	1
	> 33-66%	2
	>66%	3
Lobular Inflammation[a]	none	0

Histology Variable	Grade	Score
	< 2	1
	2-4	2
	> 4	3
Ballooning	none	0
	few	1
	many	2

[a] foci per x200 field

Liver biopsy samples will be used by the site to assess NASH and fibrosis stage as per the site's standard practice.

7.7.2 Clinical Outcome Events

Cohort 2 will be evaluated for the following liver-related clinical outcome events at every visit during the treatment periods:

- All-cause mortality
- MELD score ≥15 (with at least a 2-point increase from Baseline)
- Liver transplant
- Ascites requiring medical intervention
- Hospitalization (≥24 hours) for onset of variceal bleed
- Hospitalization (≥ 24 hours) for hepatic encephalopathy
- Hospitalization (≥ 24 hours) for spontaneous bacterial peritonitis
- HCC

7.7.3 Magnetic Resonance Elastography (MRE)

Magnetic Resonance Elastography (MRE) is a non-invasive medical imaging technique that measures the stiffness of soft tissues by introducing shear waves and imaging their propagation using MRI. In NASH Subjects, MRE is reproducible, and it has a higher inter-observer agreement for staging fibrosis compared to histopathology. Additionally, an improvement in MRE has been associated with an improvement in liver fibrosis, as observed on liver biopsy.

While the ability to perform MRE is expanding, appropriate hardware and software is not available at every institution and therefore, MRE use is still limited. In this study, MRE will only be conducted at selected sites with MRE capability. Images will be collected by

the site and submitted to a central imaging vendor for evaluation. Sites will be trained before collecting images.

Adequacy of MRE should be confirmed by the central imaging vendor prior to randomization and throughout the study and repeat imaging may be required due to QC failure.

Detailed instructions on the conduct of the MRE, and the acquisition and submission of MRE data to the central reader will be provided in the study specific Imaging Manual.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the study should be evaluated and handled by the investigator per the site's standard of care and clinical judgment.

MRE will be performed at selected sites at Screening, week 24 and week 48 or early termination.

For subjects discontinuing study treatment, MRE will only be conducted if the date of discontinuation is more than 8 weeks from the date of the previous MRE.

7.7.4 Fibroscan® Elastography

Fibroscan® is a non-invasive device that assesses the 'hardness' (or stiffness) of the liver via the technique of transient elastography. This procedure will only be performed for study cohort 2. Liver hardness is evaluated by measuring the velocity of a vibration wave (also called a 'shear wave') generated on the skin. Shear wave velocity is determined by measuring the time the vibration wave takes to travel to a particular depth inside the liver. Because fibrous tissue is harder than normal liver, the degree of hepatic fibrosis can be inferred from the liver hardness.

With the subject lying supine, an ultrasound-like probe is placed on the skin over the liver area, typically in the right mid-axillary line. The subject will feel a gentle 'flick' each time a vibration wave is generated by the probe.

A minimum of 10 valid readings, with at least a 60% success rate and an interquartile range of ≤ 30% of the median value, are taken with the results expressed in kilopascals (kPa).

7.7.5 Magnetic Resonance Imaging (MRI)

At selected sites, proton density hepatic fat fraction Hepatic Magnetic Resonance Imaging (MRI) will be employed to determine hepatic fat fraction. This is a non-invasive and accurate MRI-based biomarker utilized for liver fat quantification by measuring the proportion of mobile proton density of the liver. In NASH Subjects, MRI-Proton Density Fat Fraction accurately classifies grades and changes in hepatic steatosis, and a ≥ 29%

reduction in MRI-Proton Density Fat Fraction has been associated with histological NAS improvement.

Images will be collected by the site and submitted to a central imaging vendor for evaluation. Sites will be trained before collecting images.

Adequacy of MRI will be confirmed by the central imaging vendor prior to randomization and throughout the study and repeat may be required due to QC failure.

Detailed instructions on the conduct of the MRI, and the acquisition and submission of MRI data to the central reader will be provided in the study specific Imaging Manual.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the study are intended to be evaluated and handled by the investigator per the site's standard of care and clinical judgment.

Hepatic fat fraction is determined by MRI-based proton density fat fraction (PDFF) at Screening, week 24, and week 48/ET

For subjects discontinuing study treatment, MRI should only be conducted if the date of discontinuation is more than 8 weeks from the date of the previous MRI

7.7.6 Serum Biomarker Pro-C3

Blood samples will be collected at each visit for the assessment of exploratory biomarkers. Exploratory biomarkers in serum, plasma, and whole blood, will be used to assess markers of fibrosis and associated diseases and pathways (including cardiovascular disease, inflammation, diabetes, kidney disease as well as liver disease, and possibly bone). These studies include amongst others, Serum Pro-C3, AN N-terminal propeptide of type 3 procollagen (P3NP) and specific fragment of MMP-9-mediated degradation of type III collagen (C3M)

Pro-C3 levels in Subjects will be measured at week 4, week 8, week 12, week 24, week 48, and week 52 (post treatment follow up)

7.7.7 MELD Scoring

MELD scoring, to be performed for cohort 2 (see Appendix 10 of study protocol MB130-069) is a score for assessing the severity of chronic liver disease that does not include subjective variables such as ascites and encephalopathy. It employs the subject's bilirubin, serum creatinine, and prothrombin time (INR).

Blood samples will be taken for bilirubin, serum creatinine, and prothrombin time as part of the hematology and serum chemistry assessments conducted at each visit. The same central laboratory will be used for each evaluation. The central laboratory will calculate the

MELD score based on the laboratory values and communicate the score to the site. MELD scores will be determined at each study visit.

7.7.8 Child-Turcotte-Pugh (CTP) Scoring

The Child-Turcotte-Pugh (CTP) score assesses the severity of cirrhosis and will be done for cohort 2 Subjects. It has been shown to be an accurate measure across a broad spectrum of liver disease. It employs numerical scores of 5 measures of liver disease: total bilirubin, serum albumin, international normalized ratio for INR, ascites, and encephalopathy and is scored according to the scheme in Appendix 8 of study protocols MB130-068 and MB130-069. The sum of scores from each component is the final score.

Blood samples will be collected for the total bilirubin, serum albumin, and prothrombin time assessments used to calculate the CTP score as part of the hematology and serum chemistry assessments conducted at each visit. The same central laboratory will be used for each evaluation. Evaluations of ascites and encephalopathy are to be conducted by the same site personnel at each visit wherever possible.

CTP scores will be determined at each study visit.

7.7.9 ^{13}C-Methacetin Breath Test (MBT)

The ^{13}C-Methacetin Breath Test (MBT) is a non-invasive tool that provides an estimate of liver function by assessing microsomal capacity to metabolize the non-radioactive ^{13}C-labeled Methacetin. MBT measures carbon dioxide exhaled into a nasal cannula before and after drinking a non-radioactive solution (called ^{13}C-methacetin), using a device called the BreathID® MCS device. The amount of ^{13}carbon dioxide ($^{13}CO_2$) exhaled over 60-85 minutes will then be measured. The MBT, which consists of both a device and an unapproved drug component, is considered an investigational device that has not been reviewed, approved or cleared by the FDA for marketing purposes.

In Subjects evaluated/listed for liver transplantation, a reduction in exhaled $^{13}CO_2$ has been associated with an increased risk of cirrhotic complications [(3)]. MBT will be conducted at selected sites in subjects who provide consent. The test will be performed after an 8-hour fast according to study guidelines and as per the manufacturer's instructions.

MBT will be conducted at Day 1 visit prior to first dose of treatment, week 24 and week 48. For participants discontinuing study treatment at sites selected for the MBT sub-study, MBT should be conducted only if the date of discontinuation is more than 12 weeks from the date of the previous MBT.

8 SAFETY TERMINATION AND EARLY WITHDRAWAL OF SUBJECTS OR STUDY

For safety termination and early withdrawal of subjects please refer to BMS's protocols MB130-068 and MB130-069.

8.1 Expected Study Duration

BMS's protocols MB130-068 and MB130-069 plan to have subjects remain on study for a total of at least 52 weeks including the Double-Blind Treatment Period and the post-treatment follow-up visit (PTFU), unless intolerable side effects develop or the subject is withdrawn from study participation. Subjects will have up to an 8-week screening period, a 4 week post-treatment follow-up visit and a Follow-Up Period of at least 6 months and up to 14 months after the week 52/PTFU.

For participants discontinuing study treatment at sites selected for the MBT sub-study, MBT should be conducted only if the date of discontinuation is more than 12 weeks from the date of the previous MBT.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design and Aim

This study is designed as a feasibility companion protocol that will use the data generated by BMS' studies of BMS-986036 under protocols MB130-068 and MB130-069 for which one of the exploratory objectives is to assess whether BMS-986036 compared to placebo improves liver metabolic function as assessed by the ^{13}C-Methacetin Breath Test.

Additional analyses may be performed by Exalenz on the data to be received from these BMS studies. The study is feasibility for drug response monitoring however the data may be used for Exalenz for future submissions.

9.2 Endpoint Measures

9.2.1 Primary endpoint measure

In order to show the ability of the MBT to measure the effect of BMS-986036 treatment on the metabolic capacity of the liver after 24 weeks, 48-weeks, as compared to changes in placebo treated subjects the primary endpoint will be analyzed using a Mixed Effect Repeated Measures (MMRM) Model. An unstructured correlation matrix will be used to model within-patient errors and restricted maximum likelihood estimation will be used. The Kenwood-Roger method will be used for the denominator

degrees of freedom. Should the model fail to converge with an unstructured covariance matrix, Toeplitz and Compound-Symmetric structures will be applied.

The MMRM model will include change from baseline as outcome, and Study Arm, Visit, Study Arm*Visit Interaction, Baseline value and site as covariates.

Assessments will be done for each study cohort independently and according to availability and on the combined population of the two study cohorts by dose of the BMS drug under study.

A sensitivity analysis of the primary endpoint will be performed excluding subjects with significant protocol violations. Additional sensitivity analyses will be performed if deemed necessary. Such analyses as well as additional details will be described in the SAP.

9.2.2 Secondary endpoint measures

The following assessments will be done by treatment arm and combined arms for each study cohort independently, according to availability and on the combined population of the two study cohorts by dose of the BMS drug under study:

1. In order to assess the prognostic value of MBT in prediction of liver disease deterioration (reported as liver-related clinical outcome events), the endpoint measures will be point estimates of Cox Regression's Hazard Ratio or Logistic Regression's Relative Risk (as appropriate) at least at 48 weeks for classifying Subjects into risk groups for clinical deterioration with respective exact two-sided 95% confidence intervals in the placebo and treatment arms as determined by MBT.
2. Repeat MBT results (CPDR30/PDR peak or other breath test parameters) and their changes in subjects with and without treatment (BMS-986036) for nonalcoholic steatohepatitis (NASH) at Day 1, week 24 and 48 (or early termination) will be compared and tested for correlation to baseline as well as repeat results for the following measurements:
    a. Biopsy based Fibrosis and/or NAS score
    b. Liver stiffness as measured by MRE
    c. PDFF as measured by MRI
    d. Serum Pro-C3 results
    e. Liver elastography by Fibroscan (in cohort 2 only)
    f. MELD scores (in cohort 2 only)

CTP scores (in cohort 2 only) Linear Regression will be applied in order to test for significance of the correlations between MBT and the liver measurements listed above.

Changes in MBT are measured as the difference between baseline and each of the MBT visits as well as the change in measurements between two subsequent visits in each of the two treatment groups.

The metabolic capacity of the liver as determined by the MBT cumulative percentage dose recovery at 30 minutes (CPDR30) will be the main MBT parameter of interest.

Nevertheless, available breath test parameters (Delta Over Baseline - DOB at the respective times) will be collected from the completed eCRFs. The DOBs will be transformed to percentage dose recovery – PDR, by normalizing the DOB using patient weight and height. The Area under the DOB and under the PDR curve will be calculated at 5-minute time intervals resulting in cDOB and cPDR at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes respectively. Analyses may be done using any of the MBT derived parameters.

9.2.3 Safety endpoints measure

The cumulative incidence of adverse events, serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSAR) and unanticipated adverse device effects (UADE) possibly or probably related to the use of the BreathID MCS device and its substrate or related to the procedure, will be collected and reported.

9.3 Acceptance Criteria (Study Hypotheses)

At least one cut-off in changes of MBT values will be determined to show that MBT is a potential measure that can assess the response to treatment for BMS-986036.

At least one cut-off, to be determined by the algorithm being developed by Exalenz using data from IDE# G080227, will be validated in this study to classify Subjects into risk groups for deterioration of liver function related events.

9.4 Sample Size

Subjects that are enrolled into two separate BMS sponsored IND studies (MB130-068, MB130-069, respectively) at selected study sites will be offered the opportunity to perform the MBT and will be considered as two separate study cohorts (cohort 1 and 2, respectively) for this companion protocol. Each cohort consists of four treatment arms (BMS-986036 10mg, 20mg, 40mg QW or matching placebo QW) as defined in the respective BMS sponsored protocols.

Cohort 1 consists of Subjects with NASH and stage 3 fibrosis, as assessed by a central laboratory reader of the liver biopsies (n=160), and who meet all the MB130-068 study criteria.

Cohort 2 consists of Subjects with NASH and compensated liver cirrhosis (stage 4 fibrosis) as assessed by a central laboratory reader of the liver biopsies (n=100), and who meet all the MB130-069 study criteria.

This feasibility companion protocol will include those 2 cohorts of subjects, which are planned for up to 260 subjects) from approximately 75 sites worldwide (USA and Japan) for the two BMS IND studies, while the MBT will only be conducted in the USA.
Not all participating sites will elect to perform the MBT. The total number of subjects expected to perform the MBT may reach up to 250 subjects (also accounting for drop outs). Each subject will perform up to 3 MBTs over 1 year.

9.5 Analysis sets

Safety Analysis Set:

All subjects enrolled under BMS' MB130-068 and MB130-069 studies who have performed the MBT test at least one time.

Efficacy Analysis Set:

All subjects enrolled under BMS' MB130-068 and MB130-069 studies who have successfully performed the MBT test and did not have any major protocol deviations for the current study.

Safety analyses will be performed on the safety analysis set and efficacy analyses on the efficacy analysis set.

9.6 Statistical Analysis

9.6.1 General Considerations

Statistical analyses will be performed using R software version 3.4.3 or higher (R Development Core Team. Vienna, Austria).
If any statistical tests are performed, they will be two-sided. The required significance level of findings will be equal to or lower than 5%. Where confidence limits (CL) are appropriate, the confidence level will be 95%.

Baseline values are defined as the last valid value prior to investigational treatment start.
Study data will be summarized by descriptive statistics. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count frequency and percentage. Confidence intervals will be provided where relevant.

9.6.2 Demographic and other Baseline Characteristics

Demographic, medical and clinical history variables will be tabulated. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count frequency and percentage.

9.6.3 Disposition of Subjects

The numbers of subjects who were enrolled will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, poor compliance). A list of discontinued subjects, protocol deviations, and subjects excluded from the efficacy analysis will be provided as well.

9.6.4 Safety Analysis

The adverse events possibly or probably related to Methacetin and/or the BreathID® MCS device will be presented along with a two sided 95% exact binomial confidence interval. The analysis of all adverse events will include incidence tables and will include analyses by severity, relationship to device or drug and baseline variables.

9.6.5 Interim Analysis

As part of BMS's MB130-068 protocol, an unblinded interim analysis of efficacy data will be conducted by a team separate from the blinded study team conducting and monitoring the study for the purpose of re-assessment of the response rate assumptions for the primary endpoint for BMS-986036 and placebo and re-estimate the sample size to provide adequate power if necessary. This interim analysis will be performed at a time to maximize the information available for the primary endpoint but without necessitating a pause in the recruitment for the study. Based on enrollment projections and given the 48-week follow-up prior to liver biopsy, this interim analysis is expected to occur when post-treatment liver biopsy measurements are available for at least the first 100 randomized subjects from cohort 1. The sample size re-estimation will be based only on the primary histological endpoint from the liver biopsy, proportion of subjects with ≥ 1-stage improvement in fibrosis without worsening of NASH. The primary histology endpoint will be compared between BMS-986036 and placebo using a Wald statistic at a one-sided level of

significance of 0.005. It is also expected that the final sample size will be no more than 50% higher than the original planned sample size.

9.6.6 Pooling

As there will be very few subjects enrolled at any given site, data from all sites will be pooled for analyses for each study cohort separately and combined cohorts.

9.6.7 Handling of Missing Data

The study variables cannot be evaluated for subjects for whom BreathID® MCS device MBT results are not available and therefore these subjects will be left out of the efficacy analysis. Subjects missing clinical outcome and biopsy results will be excluded from the analyses.

10 STUDY PROCEDURES

10.1 General

The schedule of the breath tests is based on the schedule of the MB130-068 and MB130-069 protocols. The first MBT will be performed on Day 1. The subsequent MBTs will be performed at 24 -week interval visits in the Double-Blind Treatment Period.

10.2 Breath Test Procedure

Preparation of the study subject

Once consented, the Subjects will perform the breath test on day 1 prior to first dose treatment, at 24 and 48 weeks of treatment prior to dose uptake and biopsy procedure if relevant. In preparation for each breath test the patient will be asked to comply with the following precautions:

1. Subject should be fasting, including all oral morning medications (except for beta-blockers and study drug [BMS-986036 or placebo]), for at least 8 hours prior to the test
2. Subject should not smoke on the day of the breath test prior to the breath test
3. Subject should not take any of the following drugs within 48 hours prior to the test: acyclovir, allopurinol, carbamazepine, cimetidine, ciprofloxacin, daidzein (herbal), disulfiram, echinacea, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, montelukast, norfloxacin, phenylpropanolamine, phenytoin, propafenone, rifampin, terbinafine, ticlopidine, thiabendazole, verapamil, zileuton or any medication that might interfere with methacetin metabolism or might affect CYP1A2 (cytochrome P450 1A2)
4. Subject should not take amiodarone within 30 days prior to the test

5. Subject should not take paracetamol (acetaminophen) related medications within the 24 hours prior to the test
6. Subject should not perform the test if allergic or hypersensitive to Methacetin or its metabolites (paracetamol, acetaminophen)
7. Subject should not consume any alcohol or caffeine within 24 hours prior to the test
8. Subject should not have general anesthesia or sedation within 24 hours prior to the test
9. Subjects on beta-blockers or statins should be on a stable dose at least 30 days prior to the test

Preparation of ^{13}C-Methacetin

Exalenz Bioscience Ltd. will provide 75 mg ^{13}C-Methacetin doses in a 0.05% solution of ^{13}C-Methacetin in purified water, supplied, in amber thermoplastic polyester (PET) bottles with a child resistant plastic cap. No preparation is needed other than pouring the contents of the solution into a cup for ingestion.

Performance of the breath test

Only trained personnel will perform the breath test procedure. The actual breath collection is automatically performed by the device and is not operator dependent. If the IDcircuit (a nasal cannula manufactured specifically for Exalenz) is not connected properly to the subject (e.g. the breath does not reach the device), the BreathID® MCS device will prompt the operator to adjust the IDcircuit.

1. Turn on the device from the switch in the rear and allow up to 1 hour for warm-up to complete. To perform the test, ensure that the BreathID® MCS screen shows that the device is in 'Ready' state.
2. The IDcircuit will be attached to the BreathID® MCS device and to the patient. Pressing the "Start" button on the device will begin the collection of the patient's baseline exhaled breath. This will take approximately 5-10 minutes.
3. The ^{13}C-Methacetin solution is poured into a disposable cup and administrated to the patient when prompted by the device. The solution should be administered by a medical practitioner registered on the delegation log or a research nurse if specific training for administration has been given. Immediately after ingestion, the operator will press the "Continue" button, which activates the actual measurement. CO_2 production with ^{13}C may be visible within a few minutes in cases with relatively functional livers.

Note: In rare cases, the administration of fluids may cause vomiting. If this happens, the test should be aborted and repeated on one of the subsequent days. The experienced adverse event should be reported in the appropriate CRF section.

4. The patient should remain in a seated position breathing in a normal manner for up to 85 minutes, while data is collected.
5. The BreathID® MCS device continuously measures and analyzes the patient's exhaled breath in real time. As the ^{13}C-Methacetin is metabolized, the value of the $^{13}CO_2/^{12}CO_2$ ratio in the exhaled breath will change and will be calculated in real time by the device.
6. If at any time the device does not detect patient's breath, or if there is any other deviation from the desired test requirements, the device will produce an appropriate warning message on the screen.
7. At the completion of the MBT, the device screen will indicate that the test is completed and a printout will be generated. The IDcircuit is then removed and the patient is disconnected from the BreathID® MCS device.

The patient will be under the supervision of the physician or any other qualified medical staff during the entire test.

The operators will be trained how to terminate the breath test early. In the following situations, the MBT will be terminated and a termination form will be completed:

1. The patient vomits after ingestion of the substrate.
2. The BreathID® MCS device malfunctions (in this case, the operator will complete a technical complaint form in addition to the termination form and contact Exalenz immediately for further instructions) after ingestion of the substrate.

In all these cases, MBT cannot be repeated the same day for that specific subject that has already ingested ^{13}C-Methacetin. Efforts should be made to repeat the MBT on one of the subsequent days. An entry will be made in the drug/kit accountability log and the ^{13}C-Methacetin bottles will be kept for inspection by the study monitor.

10.3 Investigational Product Handling

The Investigator and Research Pharmacist (if relevant) will be provided with Investigational Product Handling Guidelines that will provide details regarding the packaging and labeling requirements, receipt of investigational product, dispensing and accountability procedures, preparation instructions, storage and stability of the Investigational product and disposition of the Investigational Product.

10.4 Investigational Product Accountability

The Investigator and Study Pharmacist (if relevant) are responsible for ensuring that all study supplies received at the site are inventoried and accounted for throughout the study. The dispensing of study substrate to the subject must be documented in the respective accountability form. The study Investigational Product must be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study materials must be available for verification by the sponsor's site monitor during on-site monitoring. The destruction of unused study materials (both, expired or unexpired) will be documented on the return/disposition form. The Sponsor will authorize destruction of excess supplies on site according to local policy or arrange collection of unused supplies. In the case of local destruction, before proceeding, the site must seek authorization from the Sponsor using the return/destruction form and this must also be documented on the Study Supply Return Form.
Study substrate should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by hospital clinical pharmacist.

11 ETHICS & REGULATORY CONSIDERATIONS

The protocol will be conducted in the US and Japan by BMS as Phase 2b studies of BMS-986036, MB130-068 and MB130-069. As such, regulatory requirements that are relevant for pharmaceutical investigations in US and Japan that will be applicable during the studies are to be conducted and overseen by BMS.
BMS will obtain for the main study an IND (IND-125297) and the applicable regulatory approvals for the MBT sub-study and the use of clinical data from all regulatory authorities (if relevant) and ethics committees/IRBs.

12 SAFETY CONSIDERATIONS

All adverse events (AE), serious adverse events (SAE), suspected unexpected serious adverse reactions (SUSAR) and unanticipated adverse device effects (UADE) possibly or probably related to the use of the MBT product or related to the MBT procedure will be collected and reported according to local regulations.

Safety assessments of the BMS study drug (BMS-986036) will be performed as described in BMS protocols MB130-068 and MB130-069.

13 SUBJECT CONFIDENTIALITY

The subject's name and personal data will remain confidential and will not be published in any way. All data will be coded and stored in locked offices or on password protected computers.

14 MONITORING AND QUALITY ASSURANCE

This study is a companion protocol that will use the data generated by the BMS Phase 2b studies of BMS-986036, under protocols MB130-068 and MB130-069. BMS will ensure compliance with GCP, local regulations and scientific integrity and will manage and oversee the study conduct.

15 PUBLICATION POLICY AND FINANCE

It is intended that the results of the companion study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. The policy regarding publications appears in the non-disclosure agreement signed by each study participant prior to signing of the contract.

16 FINANCIAL ASPECTS

The BreathID® MCS device and test kit including a nasal cannula and a solution containing ^{13}C-Methacetin will be provided by Exalenz Bioscience. BMS will be responsible for the funding of regulatory approvals in regards to their main protocols and administration as well as for the funding for study support of staff at local sites.

17 STUDY TERMINATION

This study is a companion protocol that will use the data generated by BMS from its Phase 2b studies of BMS-986036 under protocols MB130-068 and MB130-069. BMS will be responsible for study termination procedures, when applicable.

18 REFERENCES

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