The Prediction Value of the BreathID ^{13}C-Methacetin Breath Test for Hepatic Decompensation; a Retrospective Analysis (#HIS-FU-EX-1213)

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The Prediction Value of the BreathID ^{13}C-Methacetin Breath Test for Hepatic Decompensation; a Retrospective Analysis (#HIS-FU-EX-1213)

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Versions Control:

Version	Date	Responsible Person	Description of Change
1.0	6-JAN-2014	Avraham Hershkowitz	Initial Document
1a	02-FEB-2014	Avraham Hershkowitz	Minor change of anonymity
1b	1-APR-2015	Avraham Hershkowitz	Addition of PLT study subjects to protocol.

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CLINICAL STUDY PROTOCOL

Protocol Number: HIS-FU-EX-1213

Version: **1.0**

Study Title: The prediction value of the BreathID, ^{13}C-Methacetin breath test, of for Hepatic Decompensation; a retrospective analysis.

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Date of Protocol: **April 01, 2015**

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SYNOPSIS

Investigational Product: 0.05% ^{13}C-Methacetin solution and the BreathID® Device

Phase of Development: Retrospective clinical investigation

Background: This study is a follow up study to be conducted in selected sites, that participated in Exalenz' Pivotal HIS-EX-408 and/or PLT-BID-1108 study using the MBT in chronic liver patients. The aim of the study was to compare the breath test to the liver biopsy to assess the capability to detect cirrhosis.

Study Rationale: Previous studies have shown that the MBT can be used to predict liver decompensation. In the present study Exalenz wishes to evaluate the prognostic value of MBT and Biopsy in a long term retrospective surveillance of the described study population.

Objectives: To evaluate the ability of the MBT to predict hepatic decompensation events, in patients with chronic liver disease.

Primary outcome measures: MBT results and Hepatic decompensation measured with the time to each event, defined as the occurrence of at least one of the following events in the time frame between the last *[13]C-Methacetin Breath Test* (MBT) to the time of data collection:

1. Death (liver related)
2. Transplantation (cadaveric and living donors)
3. Ascites
4. HE (Hepatic Encephalopathy)
5. Newly diagnosed varices or variceal bleeding
6. SBP (spontaneous bacterial peritonitis)/Sepsis
7. HRS (Hepatorenal syndrome)
8. HCC (hepatocellular carcinoma)
9. Increase in CTP (Child Turcotte Pugh) Score by 3 points
10. Increase in MELD score by 5 points

Primary Endpoints: Time to the first occurrence of a hepatic decompensation event (as defined in the primary outcome measures).

Secondary endpoints:

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- Histological liver biopsy results (obtained in the initial study) versus clinical outcome at time of current data collection
- Time to each of the individual events as follows:
    1. Death (liver related)
    2. Transplantation (cadaveric and living donors)
    3. Ascites
    4. HE (Hepatic Encephalopathy)
    5. Newly diagnosed varices or variceal bleeding
    6. SBP (spontaneous bacterial peritonitis)/Sepsis
    7. HRS (Hepatorenal syndrome)
    8. HCC (hepatocellular carcinoma)
    9. Increase in CTP (Child Turcotte Pugh) Score by 3 points.
    10. Increase in MELD score by 5 points

Study Design: Retrospective, multicenter clinical evaluation of patients' outcome initially enrolled (n=414+165=579) into the Exalenz pivotal studies (protocols HIS-EX-408 and/or PLT-BID-1108 respectively). The information collected in this study will be anonymous.

Study Population: A maximum of 579 adult male or female patients enrolled into the Exalenz studies (protocols HIS-EX-408 and/or PLT-BID-1108) who performed a ^{13}C-Methacetin Breath Test.

Main Inclusion Criteria: Patient has been tested with the MBT in the past Exalenz pivotal studies protocols HIS-EX-408 and/or PLT-BID-1108 (from August 2008 to September 2012).

Main Exclusion Criteria: Patient had been enrolled into the pivotal study but not included in the final analysis due to conditions / factors interfering with the MBT (i.e. exclusion criteria within the HIS-EX-408 and/or PLT-BID-1108 study).

Statistical Analysis:

Introduction:

It is anticipated that 3-5% of patients with stable cirrhosis will develop hepatic decompensation and achieve an end-point within a year. An additional 1-2% would be expected to die from these complications per year. This study is conducted 6 years post initial enrollment, accordingly the expected amount of complications are expected to be 6 times higher. Furthermore some of the patients that were not considered as cirrhotic at the time of enrollment may progress to cirrhosis and deteriorate.

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All patients with valid breath test results from the HIS-EX-408 and/or PLT-BID-1108 trials will be candidates for this follow up trial.

Analyses:

All statistical analyses and data presentations, including tabulations and listings, will be performed using the SAS version 9.3 (or higher) software. Statistical tests will be two-sided and the level of significance is 0.05. Nominal p-values will be presented.

The ability of MBT to predict morbidity and mortality and other complications will be evaluated using survival analysis methods, mainly Kaplan-Meier curves and Cox regression analyses.

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1.   BACKGROUND INFORMATION

1.1.   Clinical outcome in patients with chronic liver disease

Chronic liver disease is the 9th most common cause of death in the United States. Unfortunately, mortality secondary to chronic liver disease, cirrhosis and its complications is expected to increase in the future. This is primarily due to the maturation of the Hepatitis C Virus (HCV) epidemic, a rising rate of hepatocellular carcinoma (HCC) and an increasing prevalence of non-alcoholic steatohepatitis (NASH).

Mortality in patients with chronic liver disease is typically confined to patients with cirrhosis; and the mortality risk in these patients has long been assessed by the Child-Pugh-Turcotte (CTP) score. More recently, the Model of End-Stage Liver Disease (MELD) has been shown to more accurately predict 30 day survival in patients with cirrhosis. The MELD score is now utilized by the United Network for Organ Sharing (UNOS) to prioritize patients awaiting liver transplantation. Those factors which contribute to the CTP scoring systems are: Bilirubin, INR, albumin, ascites, encephalopathy and creatinine. The MELD score uses only blood tests and is thus less prone to subjective assessments such as ascites or encephalopathy.

In general, declining liver function and an increase in the CTP and/or MELD scores appear prior to complications of cirrhosis; gastrointestinal bleeding from portal hypertension (varceal and non-variceal), ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepato-renal syndrome (types 1 and 2) and HCC. Patients are considered to have stable cirrhosis when they have normal or near-normal hepatic function and no prior complications of cirrhosis. Such patients have a CTP score of less than 7; reflective of Childs class A cirrhosis. Approximately 3-5% of patients with stable Child class A cirrhosis will develop worsening in hepatic function and/or complications of cirrhosis and decompensate on a yearly basis. In many patients the development of these complications, the deterioration in global liver function and the rise in MELD is a slow gradual process which allows sufficient time for successful transplantation. In contrast, approximately one-third of patients with cirrhosis develop rapid hepatic decompensation a precipitous rise in MELD and die from complications of cirrhosis before they can either be considered for or receive a liver transplant. This observation explains why pre-transplant mortality for patients on the UNOS waiting list is actually greatest in patients with low MELD, not high MELD scores. It is currently believed that such patients have marginal hepatic metabolic capacity or hepatic reserve which both places them at risk for developing complications of cirrhosis and for rapid deterioration when complications occur.

1.2.   Identifying patients with marginal hepatic reserve at risk for complications and decompensation:

Tests to assess hepatic metabolic function are conducted by administering either intravenously or orally a compound with high hepatic extraction ratio and/or rapid hepatic metabolism.   The rate at which the parent compound is removed from the serum or a metabolic product of the parent compound appears in either the blood, urine, breath or saliva reflects hepatic metabolic function.   Some of the compounds which have been successfully

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utilized for this purpose include choline, caffeine, galactose, aminopyrine, erythromycin, lidocaine and methionine and Methacetin [N-(4-Methoxy-phenyl) acetamide]. Previous studies utilizing a battery of liver function tests have demonstrated that these tests correlate with worsening fibrosis and cirrhosis. The hepatic metabolism of lidocaine to monoethylglycinexylodide (MEGX) has been shown to decline with increasing liver fibrosis and with worsening stages of cirrhosis, improve with successful treatment of the underlying liver disease, and to accurately predict which patients with stable cirrhosis awaiting liver transplantation were at risk to develop future hepatic decompensation. Unfortunately, administering lidocaine to perform this test is associated with parasthesias and could precipitate cardiac arrythmias. Thus, while promising as a potential liver function test the use of lidocaine for this purpose has been largely abandoned.

1.3. Identifying patients with progression of liver disease and fibrosis at earlier stages (pre-cirrhosis) of liver disease:

Chronic liver patients that have varied levels of fibrosis based on biopsy need to be monitored for progression of disease as well. A significant percentage of these patients in earlier stages of liver disease have recurrent normal blood tests in the standard liver panel blood tests. Additionally, even patients where the blood tests do show irregular values, the values do not always correlate with disease progression and a non-invasive test that is both safe and accurate would be very beneficial to monitor their liver health. This is especially important in decision making regarding the decision to begin treatment when signs of disease progression are apparent to prevent deterioration to cirrhosis. Furthermore, a non-invasive test is necessary to monitor these patients once they begin treatment in order to assess the effectiveness of the treatment.

1.4. Breath Tests

Breath tests that are based on monitoring the $^{13}CO_2$, which is a by-product of ^{13}C labeled substrates metabolism by the liver, have been proposed as a tool for non-invasive evaluation of liver health and have been used for over 30 years.

Methacetin may be utilized for the evaluation of liver functional capacity and/or the extent of liver impairment. The biochemical basis for the evaluation of functional capacity is that the compound is metabolized by the cytochrome P450 enzyme CYP1A2. Diseases of the liver that cause a loss in functional mass and/or impact the metabolic function of CYP1A2 in hepatic microsomes hepatocytes are associated with and may be correlated to a decrease in the liver capacity to metabolize Methacetin.

One of the most common methods for determining the rate of metabolism of Methacetin is to analyze the rate of metabolism of the methoxy group (CH_3O) of Methacetin to carbon dioxide, which is excreted in exhaled breath. To distinguish the carbon dioxide derived from Methacetin from all other sources of carbon dioxide, the methoxy group is labeled with ^{13}C, a stable isotope of carbon. Thus all the CO_2 derived from Methacetin will contain ^{13}C ($^{13}CO_2$) in contrast to all other sources of CO_2, which will contain approximately 99% ^{12}C, and 1% ^{13}C, the naturally abundant isotope. Thus, the rate of excretion of CO_2 (normalized

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to CO_2) above background following the administration of Methacetin-methoxy-^{13}C indicates its rate of metabolism, which relates to the hepatic cell "health" and to the functional mass of the liver.

1.5. BreathID[®] System:

Exalenz has developed the BreathID device to perform automatic breath tests based on a unique molecular correlation spectrometer (MCS). Based on specific optical-radiation emission and absorption by [13]CO2 and [12]CO2 gases, the portable BreathID MCS device continuously senses exhaled breath and analyzes CO2 in real-time through a nasal cannula worn by the patient The primary output of the BreathID is thePDR (percentage dose recovery) and CPDR (Cumulative PDR) which quantify the amount of ^{13}C labeled substrate metabolized by the liver..

1.6. ^{13}C-labeled substrate - ^{13}C-Methacetin:

The substrate used in the pivotal study breath test was [13]C- Methacetin whose resultant [13]CO_2 can be measured in the exhaled breath. The amount of metabolized Methacetin indicates the capability of the liver to accomplish one of its main physiological tasks and has been shown to correlate with liver fibrosis and cirrhosis. ^{13}C-Methacetin meets all of the qualifications for an in-vivo diagnostic test. It is a non-toxic small molecule. No reports of any complications using this substance have been reported. The compound is considered to remain stable over an extended period of time.

1.7. Utility as follow-up tool

Biopsies, the gold standard of liver health are not repeated as routine patient care and blood test results are not always indicative or sensitive enough to foresee deterioration in liver function in a timely manner.

A safe, non-invasive accurate test that assesses liver function and, when relevant, shows trends compared to previous breath tests, could highly improve patient management.

Preliminary data utilizing the MBT has demonstrated that the results from this system correlated with hepatic fibrosis in patients with chronic HCV and with the clinical course in patients pre and post transplantation and with fulminate hepatitis.

1.7.1. *Hepatic Impairment Score Using the BreathID MBT*

Exalenz has developed an algorithm for the scoring of hepatic impairment in patients suffering from a wide range of chronic liver diseases. The algorithm developed was named the "Hepatic Impairment Score" (HIS). The HIS is a probability score based on breath test and other demographic parameters. It was developed using logistic regression methodology. The linear predictor of the model selected is transformed into a probability score of disease severity. The HIS is intended to be used as the device output.

The use of the MBT test and its resultant continuous HIS for a particular patient enables the practitioner to assess the liver disease severity. This claim/label of the MBT is supported by several medical key opinion leaders (KOL).

Assessing the severity of chronic liver disease is important for following reasons:
- To make a timely decision to perform liver biopsy

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- To aid in assessment of the risk of developing cirrhosis and its complications, including bleeding varices, infections, ascites, and hepatic encephalopathy.
- To decide when to initiate certain diagnostic investigations and therapeutic interventions including: Anti –viral treatment, upper endoscopy, use of beta blockers for varices and determination of frequency of monitoring of disease progression.
- To decide when to begin surveillance for liver cancer, such as blood tests (serum levels of alpha feto protein) and imaging (ultrasound).
- To decide when to prepare or list a patient for liver transplantation.

1.7.2. *Biopsy Scoring*

Repeat biopsy scoring, where available, will be collected according to the standard scoring procedure at each site. The study itself does not call for additional biopsies to be carried out.

1.8. Safety and Efficacy of the Investigational Product

Information on the Safety of the Investigational New Drug and safety and efficacy of the MBT and the BreathID device are provided in the Investigator Brochure, though no safety issues are expected since this is a retrospective non-interventional study.

1.9. Rationale for the Current Study

Timely assessment of disease progression associated morbidity and mortality is important for educated/proper management of cirrhotic patients. For example:

- Instrumental in determining the long-term prognosis of the patient

- Establishing the risk for hepatic complications in chronic liver patients regarding conditions that are common in these patients, such as portal hypertension and subsequent esophageal varices and cancer.

- Cirrhosis often is an indolent disease/condition; many of the patients remain asymptomatic until the occurrence of decompensation, characterized by ascites, spontaneous bacterial peritonitis, hepatic encephalopathy or variceal bleeding from portal hypertension. Thus, early diagnosis of patients at higher risk for such complications may lead to treatment that can prevent development of these complications and others such as hepatocellular carcinoma, overt encephalopathy and liver decompensation after surgery.

1.10. Summary of Overall Risk and Benefits

Since this proposed study is retrospective no adverse events and/or risk associated with the MBT are expected.

The MBT BreathID system consists of the device and ^{13}C-Methacetin. The same device but with a different substrate (^{13}C-Urea) for the diagnosis of H. Pylori was cleared as a 510(K). The software of the cleared device was upgraded in order to allow the BreathID system to be used in the assessment of liver disease severity. Therefore, the BreathID device does not pose any increased risk to patients participating in this study.

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The ^{13}C-methacetin substrate has been used for various breath tests in numerous patients including special populations such as neonatals and pregnant women. To the best of our knowledge no adverse events had ever been reported using ^{13}C-Methacetin.

Furthermore, Methacetin is a well known drug that has been available and described in literature for over 30 years and is currently used in medications (such as acetaminophen) for human therapeutic use. No risks have been reported in literature using much higher doses of Methacetin than currently used in the MBT.

During the test procedure, patient contact with the device is through a nasal cannula for collection and analysis of the breath samples. Nasal breathing cannulae are a well-known and proven medical tool having minimum side effects. No discomfort has been reported during prior feasibility studies conducted by Exalenz involving over 400 patients performed with the nasal cannula.

The data analyzed in this study will be used to validate the hypothesis claiming a single ^{13}C-Methacetin breath test in chronic liver patients may correlate with liver related morbidity and mortality. This claim had been already been demonstrated in previous studies done by the company, showing a hazard ratio of up to 12 between a single MBT and complications and mortality in chronic patients within one year of the breath test. If such a claim is to be validated, it is expected to influence the clinical practice for such patients preventing the onset of complications and death.

Furthermore, if the second endpoint shows that the predictive value of MBT is greater than that of liver biopsy, many patients would be able to avoid the invasive nature and economically burdensome liver biopsy.

In consideration of the rationale and rating the benefits and risks, the conduct of this clinical trial is ethically justified.

1.11. Guidance for Investigator

The investigator is responsible for ensuring the study will be conducted according to GCP, ethical conduct as well as all applicable laws and regulations.

We expect that the study would be granted a waiver from obtaining an informed consent since it is retrospective in nature.

2. OBJECTIVES

The objectives of this study are:

- To evaluate the ability of the Methacetin Breath Test to detect hepatic decompensation events

- To evaluate the relationship between liver Biopsy and clinical outcome and show that the MBT has a better predictive ability of clinical outcome than liver biopsy.

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- To evaluate the ability of the MBT to predict each of the individual liver related complications.

3. ENDPOINTS

3.1. Primary Efficacy Endpoints

The MBT results and the time to hepatic decompensation events:
Hepatic decompensation is defined as the occurrence of at least one of the following events in the time frame between the last ^{13}C-Methacetin Breath Test (MBT) to the time of data collection:
1. Death (liver related)
2. Transplantation (cadaveric and living donors)
3. Ascites
4. HE (Hepatic Encephalopathy)
5. Newly diagnosed varices or variceal bleeding
6. SBP (spontaneous bacterial peritonitis)/Sepsis
7. HRS (Hepatorenal syndrome)
8. HCC (hepatocellular carcinoma)
9. Increase in CTP (Child Turcotte Pugh) Score by 3 points
10. Increase in MELD score by 5 points

3.2. Secondary Efficacy Endpoints

- Histological liver biopsy results (obtained in the initial study) versus clinical outcome at time of current data collection

- Time to each of the individual events as follows:
    1. Death (liver related)
    2. Transplantation (cadaveric and living donors)
    3. Ascites
    4. HE (Hepatic Encephalopathy)
    5. Newly diagnosed varices or variceal bleeding
    6. SBP (spontaneous bacterial peritonitis)
    7. HRS (Hepatorenal syndrome)
    8. HCC (hepatocellular carcinoma)
    9. Increase in CTP (Child Turcotte Pugh) Score by 3 points.
    10. Increase in MELD score by 5 points .

3.3. Safety Endpoint

No safety endpoint will be evaluated since this is a retrospective study.

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4.   STUDY DESIGN

This is a retrospective, multi-center, non-randomized, open label study of the ^{13}C-Methacetin BreathID Test (MBT) that will include all patients previously enrolled into the BreathID pivotal study (HIS-EX-408) and/or the PLT-BID-1108 study, that have performed a valid MBT. The information collected in this study will be anonymous.

5.   STUDY POPULATION

All subjects previously enrolled into the BreathID pivotal study (HIS-EX-408) and/or the PLT-BID-1108 study and had a valid ^{13}C-Methacetin breath test result with or without a valid liver biopsy result at the time of MBT will be included in this retrospective investigation.

5.1.   Entry Criteria

5.1.1.   *Inclusion Criteria (screening visit)*

To be eligible for inclusion into this study, the subjects must fulfill all of the following criteria:

- Previously enrolled into a BreathID Methacetin study according to study protocol.

- Has a valid Methacetin breath test result.

- Patient file is available for review.

5.1.2.   *Exclusion Criteria (screening visit)*
Subjects that meet any of the following criteria will not be included in this study:

a.   Patient was not enrolled into the pivotal or PLT studies according to study protocol.

b.   Patient file is not available for review.

6.   STUDY PROCEDURES AND ASSESSMENTS

6.1.   General Instructions

This study is based on review of patients source file (patient's file) as well as the CRFs gathered from the BreathID Methacetin Breath Test studies (HIS-EX-408 and PLT-BID-1108).

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6.2. Outline of Study Procedures and Assessments

6.2.1. *Screening and baseline*

Subjects' existing CRFs will be reviewed to identify eligible subjects. The following data will be recorded:

- Demographic data

- Medical history

- History of all prescription or non-prescription drugs, vitamins, and dietary supplements History of drug and alcohol use.

- Disease history, including date of initial diagnosis, stage of disease , previous treatments and responses

- Status of disease activity

- Concomitant medication and procedures

- MBT results

- Most recent biopsy results if available.

6.3. Safety Observations and Measurements

Hepatic complication events occurring as described in the patient's file from the time of enrollment in the previous pivotal study and the time of this proposed investigation will be recorded.

6.4. Concomitant Medications and Therapies

All concomitant medications administered as described in the patient's file from the time of enrollment in the previous pivotal study and the time of this proposed investigation will be recorded. all medication prescribed from the time of enrollment to the time of this proposed investigation as described within the patient's file will all be recorded.

6.5. Subject Completion and Withdrawal

Not applicable.

7. INVESTIGATIONAL NEW DRUG USED IN THE STUDY

Not applicable.

7.1. Treatment of Overdose

Not applicable

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8.   STATISTICAL CONSIDERATIONS

8.1.   Study Design and Objectives

This is a retrospective, multi-center, non-randomized, open label study of the ^{13}C-Methacetin BreathID Test (MBT) that will include all patients previously enrolled into the BreathID pivotal study who have performed a valid MBT.

The main objective of the study is to evaluate the ability of the MBT to predict time to hepatic decompensation events.

The secondary objective of the study is show that MBT predictive ability is better than that of liver biopsy/MELD in predicting time to these events.

8.2.   Primary Endpoint

The MBT results and the time to hepatic decompensation events:

Hepatic decompensation event is defined as the occurrence of at least one of the following events in the time frame between the last 13C Methacetin Breath Test (MBT) to the time of data collection:

1.   Death (liver related)
2.   Transplantation (cadaveric and living donors)
3.   Ascites
4.   HE (Hepatic Encephalopathy)
5.   Newly diagnosed varices or variceal bleeding
6.   SBP (spontaneous bacterial peritonitis)/Sepsis
7.   HRS (Hepatorenal syndrome)
8.   HCC (Hepatocellular carcinoma)
9.   Increase in CTP (Child Turcotte Pugh) Score by 3 points
10.   Increase in MELD score by 5 points
.

8.3.   Secondary Endpoint

Histological liver biopsy results (obtained in the initial study) versus clinical outcome at time of current data collection. .

8.4.   Safety Endpoints

There are no safety endpoints in this trial since it is retrospective and observational only.

8.5.   Sample size

This protocol is looking back on retrospective data from Exalenz clinical studies HIS-EX-408 and/or PLT-BID-1108 . In the initial studies there were 414 and 165 subjects enrolled respectively, thus this retrospective study may include up to 579 subjects.

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8.6. Statistical Analyses

All statistical analyses and data presentations, including tabulations and listings, will be performed using the SAS version 9.3 (or higher) software. Statistical tests will be two-sided and the level of significance is 0.05. Nominal p-values will be presented.

Baseline demographics and medical characteristics will be presented in tabular format. The statistical evaluation of baseline characteristics will include all available data.

For continuous variables, the following descriptive statistics will be given: N, Mean, Standard Deviation, Minimum, Median and Maximum values; for discrete variables, the Frequency and Percentage of patients or events will be provided.

For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-squared test or Fisher's exact test will be used as appropriate.

Kaplan-Meier curves of the time event data will be presented. For comparison of time to event data, the log rank test will be used. Cox regression will be used to estimate hazard ratios, their level of significance and 95% confidence limits.

Risk stratification may be performed by categorizing the MBT into risk groups, for these groups Kaplan-Meier Curves of the time to clinical outcome will be presented for the MBT categories as well as the liver biopsy results to compare predictive value.

9. ADVERSE EVENTS

Not applicable in this retrospective observational study.

10. STUDY ADMINISTRATION

10.1. Regulatory and Ethical Considerations

This study is to be performed in accordance with the protocol, the Declaration of Helsinki, the ICH Harmonized Tripartite Guideline for GCP, and all applicable regulatory requirements.

10.1.1. *Informed Consent*
  * It is expected that no additional consenting will be required.

10.1.2. *Institutional Review Board*

Before initiation of the study at a given center, written approval of the protocol, and waiver for the Informed Consent Form must be approved from the appropriate IRB. If any amendments to any of these documents occur during the study, written approval must be obtained prior to their implementation.

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10.1.3. *End of the study*

For administrative reporting purposes the end of the study will be defined as the date of the final clinical database lock. This provides for a single and conservative definition across all study sites.

10.2. Investigator Responsibilities

Investigators are responsible for ensuring that the investigation is conducted according to the signed Investigator Agreement, the investigational plan (Protocol Approval Signature page– Appendix A), applicable FDA regulations, local regulations, and any conditions of approval imposed by an IRB or FDA, in order to protect the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation.

Investigators are responsible for ensuring that informed consent is available from each subject, or re-obtained if applicable.

10.3. Data Management

The Investigator or designee will be responsible for recording study data in the paper CRF. It is the Investigator's responsibility to ensure the accuracy of the data entered in the CRFs. A copy of the paper CRF will be kept at site and the original sent for data processing.

The data will then be entered into a validated database. Database lock will occur once quality assurance procedures have been completed.

10.4. Study Monitoring

The Investigator must ensure that CRFs are completed in a timely manner and must allow a Sponsor representative (CRO) periodical access to CRFs, subject records and all study-related materials. The frequency of monitoring visits will be determined by factors such as the design of the study. In order to verify that the study is conducted in accordance with ICH GCP, regulatory requirements, and the study protocol and that the data are authentic, accurate and complete, the CRA will review CRFs and other study documents and will conduct source data verification.

Upon study completion, the CRA will visit the site to conduct a study termination visit. This will involve collection of any outstanding documentation.

10.5. Subject Confidentiality

The Investigator must ensure that the patients' anonymity is maintained. On the CRFs or other documents, patients should not be identified by their names, but by their assigned identification number and initials. If subject names are included on copies of documents, the names (except for initials) must be obliterated and the assigned subject numbers added to the documents.

The Investigator should keep a separate log of patients' identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Non anonymized

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documents, such as signed Informed Consent Forms, should be maintained in strict confidence by the Investigator.

10.6. Quality Assurance

In compliance with GCP and regulatory requirements, agencies or IRB may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

10.7. Retention of Essential Study Documents

Essential documents as defined by ICH GCP include the signed protocol and any amendment(s), copies of the completed CRFs, signed Informed Consent Forms from all patients who consented, hospital records, diary cards and other source documents, IRB approvals and all related correspondence including approved documents, drug accountability records, study correspondence and a list of the patients' names and addresses.

The Investigator must retain copies of the essential documents for the period for at least 5 years as specified by ICH GCP and longer if required by applicable regulatory requirements.

10.8. Agreements

A clinical trial letter of agreement (CTLA) between the Sponsor and Investigator will be used as a separate study related document.

11. PUBLICATION

Any manuscript, abstract or other publication or presentation of results or information arising from the study (including ancillary studies involving trial patients) must be prepared in conjunction with Exalenz. Such materials must be submitted to Exalenz for review and comment at least 30 days prior to submission for publication or presentation.

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Appendix A

<u>APPROVAL SIGNATURE</u>

Protocol No: HIS-FU-EX-1213

Protocol Title: *The predictive value of the BreathID, ^{13}C-Methacetin breath test for Hepatic Decompensation; a retrospective analysis*

Version: 1b

Date of Protocol: 01-APR-2014

Site Name:

Principal Investigator (Print name):

I have read this protocol and agree to conduct the study as outlined herein and as per GCP and local regulations.

Principal Investigator_____ Date_____