Companion protocol for the ^{13}C-Methacetin Breath Test using the BreathID® MCS System for Conatus phase 2 study of Emricasan, an Oral Caspase Inhibitor, under Protocol IDN-6556-17 (IND111463)

Protocol No. CON-EX-0217

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Versions Control:

Version	**Date**	**Responsible Person**	**Description of Change**
1.0	March 01, 2017	Gil Guggenheim	Initial Release
2.0	May 24, 2017	Ora Msika	Addition of Breath tests at 24-week intervals

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1 ABBREVIATIONS

AE	-	Adverse Event
AUC	-	Area under the Curve
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
DOB	-	Delta over Baseline
eCRF	-	Electronic Case Report Form
GCP	-	Good Clinical Practice
HVPG	-	Hepatic Venous Pressure Gradient
IDE	-	Investigational Device Exemption
KOL	-	Key Opinion Leader
MBT	-	^{13}C-Methacetin Breath Test
MCS	-	Molecular Correlation Spectrometry
MEGX	-	Monoethylglycinexylidide
NAFLD	-	Nonalcoholic Fatty Liver Disease
NASH	-	Nonalcoholic Steatohepatitis
NPV	-	Negative Predictive Value
PDR	-	Percent Dose Recovered (expressed as % per hour)
PET	-	Thermoplastic Polyester
PH	-	Portal Hypertension
PO	-	Per Os (by mouth)
PPV	-	Positive Predictive Value
ROC	-	Receiver Operating Characteristic
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

2 PROTOCOL SYNOPSIS

Protocol Title:	Companion protocol for the ^{13}C-Methacetin Breath Test (MBT) using the BreathID® MCS System for Conatus phase 2 study of emricasan, an Oral Caspase Inhibitor, under protocol IDN-6556-17 (IND111463)
Short Title:	Companion protocol assessing MBT in subjects participating in the IDN-6556-17 study (IND111463)
Protocol Reference Number:	CON-EX-0217
Version and Date:	v 2.0, May24, 2017
Phase of Development:	Phase II/III
Sponsor:	**Exalenz Bioscience Ltd.** 4 Ha'Maayan Street Modi'in, Israel 7177872 Tel: +972-8-9737500 Fax: +972-8-9737501
Investigated Disease:	Subjects with decompensated Non-Alcoholic Steatohepatitis (NASH) Cirrhosis
Combination Product:	^{13}C-labeled Methacetin Breath Test Kit
Comparators:	Clinical Outcome
Primary Efficacy Objective:	To validate the ability of the MBT to predict deterioration by 48 weeks for all subjects, and at later time points for those followed longer, for subjects with decompensated NASH cirrhosis in the placebo treatment arm of Conatus' study IDN-6556-17.

Secondary Efficacy Objectives:

1. To validate the ability of the MBT to predict deterioration at 6 months for subjects with decompensated NASH cirrhosis in the placebo treatment arm of Conatus' study IDN-6556-17.
2. To validate the ability of the MBT to predict deterioration at 6 months and at least at 48 weeks and at final treatment visit for subjects with decompensated NASH cirrhosis in the emricasan treatment arms of Conatus' study IDN-6556-17.
3. To show the ability of the MBT to measure the effect of emricasan on the metabolic capacity of the liver at 24-week intervals and at the final treatment visit, as compared to changes in placebo treated subjects.

Safety Objective: Evaluation of safety related to BreathID MCS or MBT

Study Population: Includes a subset of subjects that are being evaluated for the treatment phase of study IDN-6556-17, which is planned for approximately 210 subjects in approximately 90 sites. Patients with decompensated NASH cirrhosis that meet the study criteria will be randomized for the study. A 45% screen failure (SF) rate is estimated.

Not all participating sites are required to perform the MBT. Approximately 80 sites (enrolling approximately 90% of the subjects) will be performing the MBT.

The total number of MBT's expected is approximately 310 at screening and 200 at respective study visits with 24-week intervals and at the final treatment visit

It is expected that the population performing the MBT at 24-week intervals and at the final treatment visit will approximately have an equal number of subjects from each of the 3 parallel treatment arms (5 mg, 25 mg or placebo).

This data may be pooled with other parallel recruiting studies where MBT is performed and clinical follow up information is collected, in order to validate an algorithm being developed based on data collected from IDE# G080227 (primary study endpoint).

Study Design: This study is a companion protocol that will use the data generated by Conatus' study of emricasan under protocol IDN-6556-17 (IND111463). The IDN-6556-17 study is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-response study to evaluate the safety and efficacy of emricasan in improving event-free survival based on a composite clinical endpoint (where all-cause mortality, new decompensation events, and MELD score progression are events) in subjects with decompensated NASH cirrhosis.

The study treatment duration will be at least 48 weeks with study visits every 4 weeks up to week 48 and every 8 weeks after week 48. All subjects will continue treatment until the last subject in the study reaches 48 weeks in the study. This subject will undergo the assessments of the final treatment visit at week 48. For all other subjects, the final treatment visit should take place on their last study visit prior to or on the day of the final treatment visit of the last subject who has been in the study for 48 weeks.

As part of the IDN-6556-17 study, the MBT will be performed during a screening visit, every 24 weeks and at the final treatment visit to assess whether emricasan compared to placebo improves liver metabolic function as determined by the Methacetin Breath Test.

The data obtained in this study will be sequestered from Exalenz in order to allow pooling of the data received from Conatus' study as well as other parallel recruiting studies where both the MBT and clinical outcome will be available. Once sufficient data will be accrued, it will be used to validate the algorithm being developed using data from IDE# G080227. Additional analyses may be performed by Exalenz on the data to be received from this Conatus study after validation of the aforementioned algorithm.

Inclusion Criteria: This protocol follows the inclusion criteria as defined in the main protocol, IDN-6556-17. This companion protocol assesses the data for all subjects that perform the breath test under the IDN-6556-17 protocol, including their clinical follow up information.

Exclusion Criteria: Exclusion criteria are defined in the main protocol, IDN-6556-17. Additionally, subjects designated to perform the MBT test that are known to be hypersensitive or allergic to acetaminophen (paracetamol) may 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 [emricasan 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

Clinical Outcome including all deterioration events at least at 48 weeks and at final treatment visit captured under protocol IND-6556-17 and the MBT derived algorithm developed using data from IDE# G080227 for the placebo treatment arm.

Secondary Efficacy Endpoints:

1. Clinical Outcome including all deterioration events at 6 months captured under protocol IND-6556-17 and the MBT derived algorithm developed using data from IDE# G080227 for the placebo treatment arm.
2. Clinical Outcome including all deterioration events at 6 months and at least at 48 weeks and at final treatment visit captured under protocol IND-6556-17 and the MBT derived algorithm developed using data from IDE# G080227 for the emricasan treatment arms.
3. MBT before, during and after treatment as well as changes in MBT results (CPDR30/PDR peak or other breath test parameters) in subjects with and without treatment (emricasan) for non-alcoholic steatohepatitis (NASH) at 24- week intervals and at the final treatment visit.

Statistical Analysis: The data obtained in this study will be sequestered from Exalenz in order to allow pooling of the data received from Conatus' study as well as other parallel recruiting studies where MBT and clinical outcome measures will be available. Once sufficient data will be accrued, it will be used to validate the algorithm being developed on data collected as part of IDE# G080227.

Additionally, all available breath test parameters (Delta Over Baseline [DOB] at the respective times) will be collected from the completed eCRFs. The DOBs will be transformed into percentage dose recovery (PDR) by normalizing the DOB using patient weight and height. The area under the DOB and PDR curves will be calculated for each 5 minute time interval resulting in CDOB and CPDR at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 minutes. Additional breath test parameters will be extracted based on the features being developed under the Exalenz algorithm training study CSPH-EX-0414, IDE# G140190 as well as IDE# G080227.
The primary endpoints of this study are clinical outcome measures and the MBT derived algorithm.

The primary efficacy analysis as well as the first two secondary endpoints will include the point estimates of Hazard Ratio or Relative Risk with respective exact two-sided 95% confidence intervals.

The Methacetin Breath Test will be assessed to measure the effect of

emricasan on the metabolic capacity of the liver at 24-week intervals, and at the final treatment visit as compared to placebo, by modelling the change from baseline MBT to each of the 24-week intervals visit using an analysis of covariance model. The change from baseline will also be derived.

Treatment comparisons will be conducted using a linear mixed-effects model using treatment (3 levels), visit, treatment-by-visit interaction, presence of prior variceal hemorrhage, and presence of prior SBP as fixed effects. The unstructured covariance model will be used. These models will use all available information from all subjects randomized and assume that all missing data is missing at random. Least-square adjusted means (LSMeans) at each visit and the estimated difference and associated 95% CIs between each of the emricasan treatment groups and the placebo group will be reported. The LSMeans difference will be tested for each emricasan treatment group versus the placebo group at specified time points.

3 BACKGROUND

The background of cirrhosis especially in NAFLD/NASH and its pathogenesis is described in the Conatus' IDN-6556-17 study main protocol.

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.

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

The rate and pattern of changes in the $^{13}CO_2/^{12}CO_2$ ratio curve 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 using ^{13}C-Methacetin.

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

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 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.

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 group.

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 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-Methatecin) 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 end of test.

Breath tests using the ^{13}C-Methacetin are being evaluated in this protocol in an attempt to find an effective 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 Cirrhosis (compensated and de-compensated) and Portal Hypertension

As described in the Conatus protocol IDN-6556-17 part 4.1.

3.3 Rationale to use the MBT for assessment of Liver Disease Severity

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 and HVPG measures.

In advanced liver disorders, the liver has reduced ^{13}C-Methacetin metabolic capacity, leading to low MBT values. Low values of Methacetin metabolism are suggestive of patients who are likely to have advanced liver disease and thus increased portal pressure. Several MBT output variables (percentage dose recovery rate and cumulative percentage dose recovered - PDR/CPDR values at different time points) could be used to assess disease progression.

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 could therefore produce immediate results to aid in decision making in patients with cirrhosis awaiting liver transplant. Such a test may in future help in decision-making regarding transplantation priority and provide point of care assessment of therapeutic interventions if relevant.

This study's aim is to show the ability of the ^{13}C-methacetin breath test to identify patients at risk for decompensation and to determine the effect of Conatus' study drug emricasan on the metabolic capacity of the liver at 24 week intervals of treatment and at final treatment visit at different treatment doses compared to placebo.

4 INTENDED USE / INDICATION FOR USE

The ^{13}C-Methacetin Breath Test is a non-invasive test intended as an aid in assessment of adult patients at risk for disease deterioration by measuring the ability of the liver to metabolize ^{13}C-Methacetin and may be used to assess disease progression before and after treatment in adult subjects with decompensated NASH cirrhosis.

5 STUDY DESIGN

Please refer to protocol IDN-6556-17.

This study is a companion protocol that will use the data generated by Conatus' study of emricasan under protocol IDN-6556-17. The IDN-6556-17 study is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-response study to evaluate the safety and efficacy of emricasan in improving event-free survival based on a composite clinical endpoint (where all-cause mortality, new decompensation events, and MELD score progression are events) in subjects with decompensated NASH cirrhosis.

The study treatment duration will be at least 48 weeks with study visits every 4 weeks up to week 48 and every 8 weeks after week 48. All subjects will continue treatment until the last subject in the study reaches 48 weeks in the study. This subject will undergo the assessments of the final treatment visit at week 48. For all other subjects, the final treatment visit should take place on their last study visit prior to or on the day of the final treatment visit of the last subject who has been in the study for 48 weeks.

As part of the IDN-6556-17 study, the MBT will be performed during a screening visit, every 24 weeks and at the final treatment visit, to assess whether emricasan compared to placebo improves liver metabolic function as determined by the Methacetin Breath Test.

The data obtained in this study will be sequestered from Exalenz in order to allow pooling of the data received from Conatus' study as well as other parallel recruiting studies where both the MBT and clinical outcome will be available. Once sufficient data will be accrued, it will be used to validate the algorithm being developed using data from IDE# G080227. Additional analyses may be performed by Exalenz on the data to be received from this Conatus study after validation of the aforementioned algorithm.

6 STUDY OBJECTIVES

The data generated in this study will be used to validate an algorithm being developed under parallel Exalenz studies. Additionally, the companion study aims to evaluate the capabilities of the MBT to assess the severity of NASH and monitor changes in subjects with and without NASH treatment compared to clinical outcome events.

6.1 Primary Efficacy Objective

To validate the ability of the MBT to predict deterioration at by 48 weeks for all subjects, and at later time points for those followed longer, for subjects with decompensated NASH cirrhosis in the placebo treatment arm of Conatus' study IDN-6556-17.

6.2 Secondary Efficacy Objectives

1. To validate the ability of the MBT to predict deterioration at 6 months for subjects with decompensated NASH cirrhosis in the placebo treatment arm of Conatus' study IDN-6556-17.
2. To validate the ability of the MBT to predict deterioration at 6 months and at least at 48 weeks and at final treatment visit for subjects with decompensated NASH cirrhosis in the emricasan treatment arms of Conatus' study IDN-6556-17.
3. To show the ability of the MBT to measure the effect of emricasan on the metabolic capacity of the liver at 24 week- intervals and at the final treatment visit, as compared to changes in placebo treated subjects.

6.3 MBT Safety Objective

All adverse events, serious adverse events (SAE), 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 adverse events are expected. For more information please refer to the Investigator's Brochure.

6.4 Primary Efficacy Endpoint

Clinical Outcome including all deterioration events at least at 48 weeks and at final treatment visit captured under protocol IND-6556-17 and the MBT derived algorithm developed using data from IDE# G080227 for the placebo treatment arm.

6.5 Secondary Efficacy Endpoints

1. Clinical Outcome including all deterioration events at 6 months captured under protocol IND-6556-17 and the MBT derived algorithm developed using data from IDE# G080227 for the placebo treatment arm.
2. Clinical Outcome including all deterioration events captured at 6 months and at least at 48 weeks and at final treatment visit under protocol IND-6556-17 and the MBT derived algorithm developed using data from IDE# G080227 for the emricasan treatment arms.

3. MBT before, during and after treatment as well as changes in MBT results (CPDR30/PDR peak or other breath test parameters) in subjects with and without treatment (emricasan) for nonalcoholic steatohepatitis (NASH) at 24 week intervals and at the final treatment visit..
4. Safety Endpoints

All 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 substrates or related to the procedure will be reported according to local regulations.

7 SUBJECT SELECTION

This companion protocol assesses the data for all subjects being evaluated under IDN-6556-17 at sites performing MBT. Subjects will be screened according to the inclusion/exclusion criteria of the IDN-6556-17 protocol, and will be randomly assigned to a study arm if they meet all the criteria.

7.1 Inclusion Criteria

Inclusion criteria are as those in the Conatus protocol number IDN-6556-17. This companion protocol assesses the data for all subjects that perform the breath test under the IDN-6556-17 protocol.

7.2 Exclusion Criteria

Exclusion criteria are as those in the Conatus protocol number IDN-6556-17. Additionally, subjects designated to perform the MBT test that are known to be hypersensitive or allergic to acetaminophen (paracetamol) may not perform the MBT.

7.3 Exclusion Criteria On the day of the MBT

1. Subject should be fasting, including all oral morning medications (except for beta-blockers and study drug [emricasan 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

7.4 Consenting

Subjects' and/or their representative will be consented and sign the appropriate form as part of Conatus' IDN-6556-17 study prior to study participation.
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.

8 SAFETY TERMINATION AND EARLY WITHDRAWAL OF SUBJECTS OR STUDY

For safety termination and early withdrawal of subjects please refer to Conatus' protocol IDN-6556-17.

8.1 Expected Study Duration

Conatus' protocol IDN-6556-17 plans to have subjects remain on study therapy for a total of at least 48 weeks unless intolerable side effects develop, or the subject is withdrawn from study participation. In addition, subjects will have up to a 4 week screening period and a 2 week post-treatment follow-up visit for a total duration of at least 54 weeks.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design and Aim

This study is designed under a companion protocol that will use the data generated by Conatus' study of emricasan under protocol IDN-6556-17 for which one of the secondary

goals is to assess whether emricasan compared to placebo improves liver metabolic function as assessed by the Methacetin Breath Test. The data obtained from this study will be sequestered from Exalenz in order to allow pooling of the data received from Conatus' study as well as other parallel recruiting studies where MBT and clinical outcome data will be available. The aim of the current study is to collect sufficient data to validate the algorithm being developed using data from IDE# G080227. Additional analyses may be performed by Exalenz on the data to be received from this Conatus study after validation of the aforementioned algorithm.

9.2 Endpoint Measures

9.2.1 Primary endpoint measure

The primary endpoint measures will be point estimates of Hazard Ratio or Relative Risk at least at 48 weeks for classifying patients into risk groups for clinical deterioration with respective exact two-sided 95% confidence intervals in the placebo treatment arm, as determined in the training study using the algorithm developed based on data from IDE# G080227.

9.2.2 Secondary endpoint measures

1. The secondary endpoint measures will be point estimates of Hazard Ratio or Relative Risk at 6 months for classifying patients into risk groups for clinical deterioration with respective exact two-sided 95% confidence intervals in the placebo treatment arm, as determined in the training study using the algorithm developed based on data from IDE# G080227.
2. The secondary endpoint measures will be point estimates of Hazard Ratio or Relative Risk at 6 months and at least at 48 weeks and at final treatment visit for classifying patients into risk groups for clinical deterioration with respective exact two-sided 95% confidence intervals in the emricasan treatment arms, as determined in the training study using the algorithm developed based on data from IDE# G080227.
3. Repeat MBT results (CPDR30/PDR peak or other breath test parameters) and their changes in subjects with and without treatment (emricasan) for nonalcoholic steatohepatitis (NASH) at 24 week intervals and at the final treatment visit. Change is measured as the difference between baseline and each of the week 24 interval visits as well as at the final treatment visit MBT measurements in each of the three 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 all 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 substrates or related to the procedure.

9.3 Acceptance Criteria (Study Hypotheses)

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

Final success criteria will be defined and discussed with FDA as part of separate Pre-submissions.

9.4 Sample Size

The plan is to enroll a subset of subjects that will be screened under Conatus' IDN-6556-17 study. This Conatus study plans to enroll 210 subjects (70 subjects per treatment arm) to be randomly assigned to 1 of 2 treatment groups of emricasan or placebo (25 mg, 5 mg, or matching placebo in a 1:1:1 ratio). A 45% screen failure (SF) rate is estimated. It is expected that approximately 90% of the patients enrolled will perform the MBT. The total number of MBT results expected is approximately 310 at screening and 200 at respective study visits with 24-week intervals and at the final treatment visit The data obtained in this study may not suffice to support the primary endpoint. It will therefore be sequestered from Exalenz in order to allow pooling of the data received from Conatus' study including data from screen failures as well as data from other parallel recruiting studies where MBT clinical outcome measures will be available. Once sufficient data will be accrued, it will be

used in order to validate an algorithm being developed based on data collected from IDE# G080227 (primary study endpoint).

9.5 Analysis sets

Safety Analysis Set:

All subjects screened under Conatus' IDN-6556-17 study who have performed the MBT test.

Efficacy Analysis Set:

All subjects enrolled under Conatus' IDN-6556-17 study who have performed the MBT test and have met the inclusion exclusion criteria for the current study and have valid MBT measurements.

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 SAS® v9.4 or higher (SAS Institute, Cary NC, USA).
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 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 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 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 Primary Efficacy Analysis

1. The ability of the algorithm, developed under the Exalenz training study IDE# G080227), to identify patients at risk for decompensation at least at 48 weeks and at final treatment visit will be validated using data from Conatus' IND-6556-17 study for the placebo treatment arm.

   Final success criteria will be defined and discussed with FDA as part of separate Pre-submissions.

9.6.6 Secondary Efficacy Analyses

1. The ability of the algorithm, developed under the Exalenz training study IDE# G080227), to identify patients at risk for decompensation at 6 months will be validated using data from Conatus' IND-6556-17 study for the placebo treatment arm.
2. Assessment of the ability of the MBT to predict Clinical Outcome (event free survival versus various deterioration events) at 6 months and at least at 48 weeks and at final treatment visit captured under protocol IND-6556-17 for the emricasan treatment arms.
3. The ability of the ^{13}C-methacetin breath test (MBT) to measure the effect of emricasan on the metabolic capacity of the liver at 24 week intervals of treatment and at the final treatment visit versus placebo treated subjects, will be assessed by comparing the differences between the MBT results at each of the 24 - week interval visitsand at the final treatment visit versus baseline in all subjects with and without treatment (emricasan) for nonalcoholic steatohepatitis (NASH). This will be done for each of the 3 treatment groups (5mg, 25mg and placebo) separately.

Treatment comparisons will be conducted using a linear mixed-effects model using treatment (3 levels), visit, treatment-by-visit interaction, presence of prior variceal hemorrhage, and presence of prior SBP as fixed effects. The unstructured covariance model will be used. These models will use all available information from all subjects randomized and assume that all missing data is missing at random. Least-square adjusted means (LSMeans) at each visit and the estimated difference and associated 95% CIs between each of the emricasan treatment groups and the placebo group. The LSMeans difference will be tested for each emricasan treatment group versus the placebo group at specified time points.

9.6.7 Interim Analysis

9.6.8 No interim analysis is planned for this study.Pooling

As there will be very few subjects enrolled at any given site, data from all sites will be pooled for analyses. Additionally, this data may be pooled with other parallel recruiting studies. The data obtained in these studies will be sequestered from Exalenz until sufficient data will be accrued to validate the algorithm being developed in a training study based on data from IDE# G080227.

9.6.9 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 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 IDN-6556-17 protocol. The first MBT will be performed during the screening period (Week -4 to Day 0). The subsequent MBTs will be performed at 24 -week interval visits and at the final treatment visit, respectively.

10.2 Breath Test Procedure

Preparation of the study subject

Once consented, the patients will perform the breath test. 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 [emricasan 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 device from switch in 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 the next day. The expected 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 90 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 on the screen.
7. At the completion of the procedure, the IDcircuit is 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 test 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 test 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. 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. In this case, 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 study will be conducted by Conatus as a Phase 2 study of emricasan in both the USA and in Europe. As such, regulatory requirements that are relevant for pharmaceutical investigations in all countries will be applicable during the study are to be conducted and overseen by Conatus.
Conatus will obtain for the main study IND-6556-17 the applicable regulatory approvals for the use of clinical data from both 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 Conatus study drug will be performed as described in Conatus protocol IDN-6556-17: *Safety Assessments.*

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 Conatus Phase 2 study of emricasan under protocol IDN-6556-17. Conatus 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. Conatus will be responsible for the funding of regulatory approvals in regards to the main protocol 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 Conatus from their Phase 2 study of emricasan under protocol IDN-6556-17. Conatus will be responsible for study termination procedures, when applicable.

18 REFERENCES

1. Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, Goodman Z. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011;53:1874-1882.
2. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98:960-967.
3. Stravitz RT, Reuben A, Mizrahi M, Lalazar G, Brown K, Gordon SC, Ilan Y, et al. Use of the methacetin breath test to classify the risk of cirrhotic complications and mortality in patients evaluated/listed for liver transplantation. J Hepatol 2015;63:1345-1351.