Validation Study for the BID-CSPH Test: Companion protocol for the ^{13}C-Methacetin Breath Test using the BreathID® MCS System in Conatus phase 2 study of Emricasan, an Oral Caspase Inhibitor, under Protocol IDN-6556-14

Protocol No. CON-EX-0616

Document Nº: CSD00091	**Total pages:** 50
Version Level: 5.0	**Last update on:** Oct. 17, 2018

	Name	Position
Author / Owner	Gil Guggenheim	Clinical Research Development Manager
Reviewed by	Ofer Schlesinger	VP R&D
Reviewed by	Lisa Deutsch, PhD	Biostatistician (BioStats Ltd.)
Approved by	Michal Hershkovitz	VP Regulatory Affairs & Quality Assurance
Approved by	Yaron Ilan, MD	Medical Director
Electronic signatures and approvals, effective information and Lifecycle Status can be obtained by accessing the system generated approval page associated with this document. The system generated approval page can be retrieved from the PDM system.		

Versions Control:

Version	Date	Responsible Person	Description of Change
1.0	Jul. 18, 2016	Gil Guggenheim	Initial Release
2.0	May 08, 2017	Ora Msika	Addition of Breath test at week 48
3.0	Oct. 10, 2017	Gil Guggenheim	Increase sample size
4.0	Jul. 25, 2018	Gil Guggenheim	Implementing FDA comments from Pre-Sub Q180599
5.0	Oct. 17, 2018	Gil Guggenheim	Implementing FDA comments from Pre-Sub Q180599/S001, mainly: 1. Intended use was updated to reflect clinically diagnosed NASH 2. Modification of primary endpoint performance goals to be more clinically meaningful 3. Addition of analyses for data pooling 4. Addition of Sub-Group Analysis 5. Revised Appendix A for more clarity

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1 ABBREVIATIONS AND DEFINITIONS

1.1 Abbreviations

AE - Adverse Event
AUC - Area under the Curve
BID-CSPH Test - BreathID® CSPH ^{13}C-Methacetin Breath Test
BID-CSPH Algorithm - BID-CSPH MBT based algorithm used in the BID-CSPH Test
$cDOB_{x\_min}$ - Cumulative Delta over Baseline at x minutes from ingestion
CI - Confidence Interval
CL - Confidence Limits
CO_2 - Carbon dioxide
$cPDR_{x\_min}$ - Cumulative Percentage Dose Recovery at x minutes from ingestion
CRF - Case Report Form
CSPH - Clinically Significant Portal Hypertension
DOB_{x_min} - Delta over Baseline at x minutes from ingestion
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
NSBB - Non-Selective Beta Blocker
OUS - Out of US
PDR_{x_min} - Percent Dose Recovered (expressed as % per hour) at x minutes from ingestion
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)

1.2 Definitions

This companion protocol includes all randomized AND all screen failed subjects from the Conatus IDN-6556-14 study that performed an MBT. Only subjects that meet this companion study inclusion/exclusion criteria (sections 7.1, 7.2 and 7.3) will be considered for the performance analyses:

- The study population for the primary and secondary as well as the first two exploratory endpoints will be screened subjects with valid MBT and HVPG results prior to any investigational treatment. This population is defined as the ***Validation Population***.
- Those subjects from the Validation Population that were randomized into the Conatus IDN-6556-14 study and have at least one MBT on treatment are defined as the ***Treated Sub-Population***.

2 PROTOCOL SYNOPSIS

Protocol Title:	Validation Study for the BID-CSPH Test: Companion protocol for the ^{13}C-Methacetin Breath Test (MBT) using the BreathID® MCS System in Conatus phase 2 study of Emricasan, an Oral Caspase Inhibitor, under protocol IDN-6556-14
Short Title:	BID-CSPH Test validation: Companion protocol assessing MBT in subjects participating in the IDN-6556-14 study
Protocol Reference Number:	CON-EX-0616
Version and Date:	v 5.0, Oct. 17, 2018
Phase of Development:	Pivotal
Sponsor:	**Exalenz Bioscience Ltd.** 4 Ha'Maayan Street Modi'in, Israel 7177872 Tel: +972-8-9737500 Fax: +972-8-9737501
Investigated Disease:	Subjects with advanced chronic liver disease (ACLD) due to Non-Alcoholic Steatohepatitis (NASH)
Combination Product:	The Exalenz ^{13}C-labeled Methacetin and the BreathID® MCS System.
Investigated breath Test Measure:	The BID-CSPH Test with its MBT based BID-CSPH Algorithm and its predefined cut-off to identify clinically significant portal hypertension (defined by HVPG ≥ 10 mmHg), developed under the Exalenz study CSPH-EX-0414, IDE# G140190 and Companion Protocol to Galectin's study GT26 (GT-EX-0215), conducted in collaboration with Galectin Therapeutics Inc. under their IND 115459 and Exalenz' IDE G150125.
Comparator:	Hepatic Vein Portal Pressure Gradient (HVPG)
Primary Performance Objective:	To validate the ability of the BID-CSPH Test to identify clinically significant portal hypertension (CSPH) defined as HVPG ≥ 10mmHg in the Validation Population using the BID-CSPH Algorithm with a predefined cutoff in terms of PPV and NPV.

Secondary Performance Objective:

1. To present additional performance measures for the ability of the BID-CSPH Test to identify clinically significant portal hypertension (CSPH) defined as HVPG ≥ 10mmHg in the Validation Population using the BID-CSPH Algorithm with a predefined cut-off in terms of sensitivity and specificity.
2. To assess the ability of the BID-CSPH Test to identify severe portal hypertension defined as HVPG ≥ 12 mmHg in the Validation Population using the BID-CSPH Algorithm with a second predefined cut-off.

Exploratory Objectives:

1. To assess the correlation between MBT result parameters (see Appendix A, item 7) and HVPG results in the Validation Population.
2. To assess the effect of frequently used medications or other confounding factors on the correlation of MBT result parameters (see Appendix A, item 7) with HVPG readings in the Validation Population.
3. To show the ability of the MBT to measure the effect of Emricasan on the metabolic capacity of the liver at treatment week 24 (versus pre-treatment), as compared to placebo treated subjects in the Treated Sub-Population.
4. To show correlation of changes in the MBT results with changes in HVPG at treatment week 24 (versus pre-treatment), in subjects with and without treatment with Emricasan for nonalcoholic steatohepatitis (NASH) in the Treated Sub-Population.
5. To show the ability of the MBT to measure the effect of Emricasan on the metabolic capacity of the liver at treatment week 48 (versus pre-treatment), as compared to placebo treated subjects in the Treated Sub-Population.

Safety Objective: To evaluate safety events related to the BreathID MCS System or the MBT/BID-CSPH Test.

Study Population: This companion protocol includes all randomized AND all screen failed subjects from the Conatus IDN-6556-14 study that performed an MBT. Only subjects that meet the companion study inclusion/exclusion criteria (sections 7.1, 7.2 and 7.3) will be considered for the performance analyses.

The study population for the primary and secondary as well as first two exploratory endpoints will be screened subjects with valid MBT and HVPG results prior to any investigational treatment. This population is referred to as the ***Validation Population***.

Those subjects from the ***Validation Population*** that were randomized into the Conatus IDN-6556-14 study and have at least one MBT on treatment are defined as the ***Treated Sub-Population***.

Study Design:

This companion protocol is a validation study for the BID-CSPH Test with its BID-CSPH Algorithm for identification of CSPH (defined as HVPG ≥ 10 mmHg) that will analyze the data generated by Conatus' study of Emricasan under protocol IDN-6556-14.

The IDN-6556-14 study is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-response study to evaluate the safety and efficacy of Emricasan in improving portal hypertension in subjects with NASH cirrhosis and severe portal hypertension. The Conatus study IDN-6556-14 randomizes subjects into 4 parallel treatment arms (5 mg, 25 mg, 50 mg Emricasan or placebo) (see Section 5).

As part of the IDN-6556-14 study, the MBT will be performed during a screening visit.

In addition, the MBT will be performed at treatment week 24 and at the end of treatment (at week 48), in randomized subjects who had MBT at screening.

Inclusion Criteria:

Subjects must meet all of the following criteria for this validation study:

1. Male or female subjects 18 years or older, able to provide written informed consent and able to understand and willing to comply with the requirements of the study.
2. Cirrhosis due to NASH with exclusion of other causes of cirrhosis (e.g. chronic viral hepatitis, alcoholic liver disease, etc.)
   - Diagnosis of cirrhosis is based on:
     - Biopsy OR
     - Clinical evidence: platelet count <150,000, AST > ALT, and either nodular liver surface on imaging or splenomegaly
   - NASH is based on at least 1 of the following:
     - Prior or current biopsy showing steatohepatitis (fat, ballooning degeneration, inflammation) consistent with NASH
     - At least 2 metabolic risk factors for at least 5 years preceding the diagnosis of cirrhosis: diabetes mellitus, impaired fasting glucose, obesity (Body Mass Index (BMI) ≥30 kg/m2 or central obesity), hypertension, dyslipidemia (See Appendix IV of Conatus IDN-6556-14 protocol)
     - Prior or current biopsy showing some but not all diagnostic features of NASH (e.g. only fat or ballooning degeneration or inflammation) but with no evidence for viral hepatitis or other liver disease AND either fatty liver disease on prior imaging or at least 1 metabolic risk factor (as above) for at least 5 years preceding the diagnosis of cirrhosis

   Note: Previous viral hepatitis that was curatively treated (with sustained viral response) is not an exclusion as long as: 1) viral eradication was achieved at least 3 years prior to the diagnosis of cirrhosis

and 2) all other criteria are met for NASH as the etiology of cirrhosis

3. Compensated cirrhosis (no history of or presence of clinically evident ascites, variceal hemorrhage, or encephalopathy, and on no medications to treat these complications)
   OR
   Decompensated cirrhosis with no more than 1 prior significant decompensating event:
   a) If a prior decompensating event was variceal hemorrhage, event must have occurred at least 3 months prior to MBT or HVPG
   b) If a prior decompensating event was ascites requiring chronic diuretics, ascites should be well controlled (not clinically evident, i.e. no ascites or ascites only detectable by ultrasound examination) on a stable dose of diuretics for at least 3 months prior to MBT and HVPG
   c) If a prior decompensating event was hepatic encephalopathy ≥ grade II or requiring hospitalization, encephalopathy should be well-controlled (Stage 0 or 1) on stable medication for at least 3 months prior to MBT and HVPG

   Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count as a prior significant decompensating event

4. Subjects who are on NSBB or statins must be on a stable dose for at least 1 month prior to MBT and HVPG.
5. Subjects must have an initial MBT test performed during screening.

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from this validation study:

1. Evidence of severe decompensation, defined as:
   - Presence or history of more than one type of significant decompensating event (clinically evident ascites requiring chronic diuretics, variceal hemorrhage, and/or overt encephalopathy)

   Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count towards this exclusion.

   - One type of decompensating event with the following characteristics:
     - More than 1 episode of variceal hemorrhage or bleeding from a portal hypertensive source (e.g. portal hypertensive gastropathy)

- Ascites that has required more than 1 large-volume paracentesis (>5 L) for treatment or that has been complicated by spontaneous bacterial peritonitis, hyponatremia (serum Na <130), and/or hepatorenal syndrome
- More than 1 episode of overt hepatic encephalopathy requiring hospitalization

2. Estimated creatinine clearance <30 mL/min
3. Prior transjugular intrahepatic portosystemic shunt or other porto-systemic bypass procedure
4. Known portal vein thrombosis
5. Symptoms of biliary colic, e.g. due to symptomatic gallstones, within the last 6 months, unless resolved following cholecystectomy, other definitive treatment (e.g., sphincterotomy), or medical management (e.g., ursodeoxycholic acid)
6. Current use of medications that are considered inhibitors of OATP1B1 and OATP1B3 transporters: atazanavir, cyclosporine, eltrombopag, gemfibrozil, indinavir, lopinavir, ritonavir, rifampin, saquinavir, simeprevir, telaprevir, tipranovir, or some combination of these medications
7. Alpha-fetoprotein >50 ng/mL
8. History or presence of clinically concerning cardiac arrhythmias, or prolongation of screening (pre-treatment) QT Interval Corrected by the Fridericia Correction Formula (QTcF) interval of >500 msec
9. History of or active malignancies, other than those successfully treated with curative intent and believed to be cured
10. Significant systemic or major illness other than liver disease that in the opinion of the investigator would preclude the subject from participating in and completing the study, including but not limited to acute coronary syndrome or stroke within 6 months of screening or major surgery within 3 months of screening
11. Prior liver transplant
12. Previous restrictive bariatric surgery or bariatric device or prior malabsorptive bariatric surgery
13. Known human immunodeficiency virus infection
14. Use of controlled substances (including inhaled or injected drugs) or non-prescribed use of prescription drugs within 1 year of screening to the point of interfering with the subject's ability to comply with study procedures and study drug administration in the investigator's judgement
15. History of significant alcohol consumption (>20 g/day for females and >30 g/day for males on average) within the past 5 years
16. If female: planned or known pregnancy, positive urine or serum pregnancy test, or lactating/breastfeeding
17. Previous treatment with Emricasan or active investigational medication

(except Methacetin) in a clinical trial within 3 months prior to MBT and HVPG

18. Known allergy to acetaminophen (paracetamol)
19. Known hypotension (systolic pressure < 100mmHg),
20. Known pulmonary hypertension (right ventricular systolic pressure > 45mmHg)
21. Uncontrolled malabsorption or diarrhea

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 randomized subjects), 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 consume any alcohol or caffeine within 24 hours prior to the test
7. Subject should not have general anesthesia or sedation within 24 hours prior to the test
8. Subjects on beta-blockers or statins should be on stable dose at least 30 days prior to the test

Primary Endpoints

The primary endpoints are the positive and negative predictive value (PPV and NPV, respectively) of the BID-CSPH Test binary response for clinically significant portal hypertension (CSPH) as determined by HVPG, defined as HVPG ≥ 10 mmHg in the Validation Population.

Secondary Endpoints:

The secondary endpoints are:

1. Sensitivity and specificity of the BID-CSPH Test binary response for clinically significant portal hypertension (CSPH) as determined by HVPG, defined as HVPG ≥ 10 mmHg in the Validation Population.
2. Positive and negative predictive value (PPV and NPV, respectively) of the BID-CSPH Test binary response for severe portal hypertension as determined by HVPG, defined as HVPG ≥ 12 mmHg in the Validation Population. The cut-off value of the BID-CSPH Algorithm for identifying severe portal hypertension is different from the cut-off value used to identify CSPH.

Exploratory Endpoints:

1. Correlation between MBT result parameters (see Appendix A, item 7) and HVPG readings in the Validation Population.
2. Comparison of correlation between MBT result parameters (see Appendix A, item 7) and HVPG readings between frequently used medications or other confounding factors in the Validation Population.
3. Change in MBT result parameters (see Appendix A, item 7) at treatment week 24. Change is measured as the difference between pre-treatment and treatment week 24 MBT measurements in each of the four treatment arms.
4. Correlation between changes in the MBT result parameters (see Appendix A, item 7) and changes in HVPG to treatment week 24, both measured as the difference between pre-treatment and treatment week 24 values.
5. Change in MBT result parameters (see Appendix A, item 7) at treatment week 48. Change is measured as the difference between pre-treatment and treatment week 48 MBT measurements in each of the four treatment arms.

Sample Size

The plan is to enroll a subset of subjects that will be screened under the Conatus IDN-6556-14 study. It is expected that up to 510 subjects will perform the MBT during the screening visit of the Conatus study.

It should be noted that HVPG results (a primary endpoint in this companion protocol) may not be available for all subjects tested with MBT prior to the HVPG procedure (for screen failure subjects as part of the Conatus study). Thus, for the primary endpoint there will be fewer subjects with pairs of MBT and HVPG measurements. It is expected that approximately 250 subjects will have valid MBT and HVPG results during screening.

Statistical Analysis:

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, US).

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%.

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.

Primary performance analyses:
A 2x2 table of the results comparing the positive /negative results obtained from the BID-CSPH Algorithm compared to HVPG ≥ 10mmHg / < 10mmHg at baseline (screening) will be presented.

The primary performance analysis will present the estimation of the PPV and NPV of the diagnosis together with their respective Wilson' score two-sided 95% confidence intervals (CI).

The study will be deemed successful if:

- The lower limit of the Wilson' score two-sided 95% CI for the PPV is 5% higher than the observed prevalence; ***and***
- the lower limit of the Wilson' score two-sided 95% CI for the NPV is higher than 1 - the observed prevalence.

PPV and NPV will be presented for the prevalence of 65%, 70%, 75% and 80% in addition to the prevalence observed in the study.

Secondary performance analyses:
1. Secondary performance analysis will present the estimation of the sensitivity and specificity of the BID-CSPH Algorithm to identify CSPH, HVPG ≥ 10mmHg, together with their respective Wilson' score two-sided 95% confidence intervals (CI).

2. A 2x2 table of the results comparing the positive /negative results obtained from the BID-CSPH Algorithm (with a second cut-off for the detection of severe portal hypertension) compared to HVPG ≥ 12mmHg / < 12mmHg at baseline (screening) will be presented.

This secondary performance analysis of the detection of severe portal hypertension will present the estimation of the PPV and NPV as well as of the sensitivity and specificity of the diagnosis together with their respective Wilson' score two-sided 95% CI.

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 (screening) variables.

3 BACKGROUND

The background of non-alcoholic fatty liver disease (NAFLD) and its advanced stage of non-alcoholic Steatohepatitis (NASH) and its pathogenesis is described in the Conatus' IDN-6556-14 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 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 tests 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 with 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 potential 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 one such 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 the end of each test.

Breath tests using ^{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.

3.2 Cirrhosis and Portal Hypertension

As described in the Conatus protocol IDN-6556-14 part 4.1 (included in Appendix B).

3.3 Hepatic Venous Pressure Gradient (HVPG) assessing Portal Hypertension

As described in the Conatus protocol IDN-6556-14 section 8.2.1(included in Appendix B).

3.4 Limitations of HVPG

HVPG is highly clinically valuable[3], and the method used to measure it is reasonably safe, accurate and reproducible when adhering to guidelines[4]. However, there are limitations to the generalized use of HVPG such as the fact that it is an invasive procedure that uses contrast media injection and catheterization, has a need for expertise in execution to ensure reliable and reproducible measurements[5, 6]. Hence HVPG is generally limited in use to large medical facilities due to requiring resources beyond those of the hepatology clinic and point of care physician, and presents added risk to the patients. Berzigotti et al. in their recent review[7] determined that HVPG is the best method to assess CSPH, but they also cite the limitations of the procedure, especially in the context of therapy monitoring:

> *"HVPG measurements are not available in all centers, the technique is invasive and some patients are unwilling to be submitted to it. This is even more relevant when the repetition of the procedure is needed to monitor treatment response. These issues have raised interest to non-invasively determine when CSPH is present, so allowing defining a patient at risk of developing portal hypertension-related complications."* [7]

Hence, HVPG is a useful, but an impractical test for everyday clinical use. In fact, key opinion leaders (KOLs) have commented that many more HVPG measurements would be done since it is felt to be a good predictor of complications of cirrhosis[8], if it was not for the practical drawbacks and limitations. It is clearly desirable and necessary to have an equally reliable surrogate test that is non-invasive.

Moreover, although HVPG is clinically highly valuable[3], even in experienced hands, complications can occur with large hematomas of the neck or groin being the most common (as reported by a leading Spanish center that regularly measures HVPG with a complication rate of 2.3%)[8].

3.5 Rationale to use the MBT for assessment of Portal Hypertension and BID-CSPH Test for Clinically Significant Portal Hypertension (CSPH)

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 or presence of CSPH, as they were shown to be proportionally reduced in the presence of CSPH in two independent studies and in a meta-analysis described further below in this section.

Exalenz completed a study in eight large US centers and three non-US centers entitled "Pivotal study to evaluate the efficacy and safety of the BreathID® MCS system for detection of cirrhosis using the ^{13}C-Methacetin Breath Test MBT" (G080107) during which a subset of 21 patients with MBT data had undergone HVPG at the time of their liver biopsy. When comparing MBT variables and HVPG results, significant correlations were noted. For example, a statistically significant inverse relationship (r=-0.75) was found between the PDR values at 45 minutes (PDR_{45_min}) and HVPG values as depicted in ***Figure 1*** below. It can be concluded from the data of these 21 patients that the correlation does not seem to be affected by the use of non-selective beta-blockers or the presence of varices.

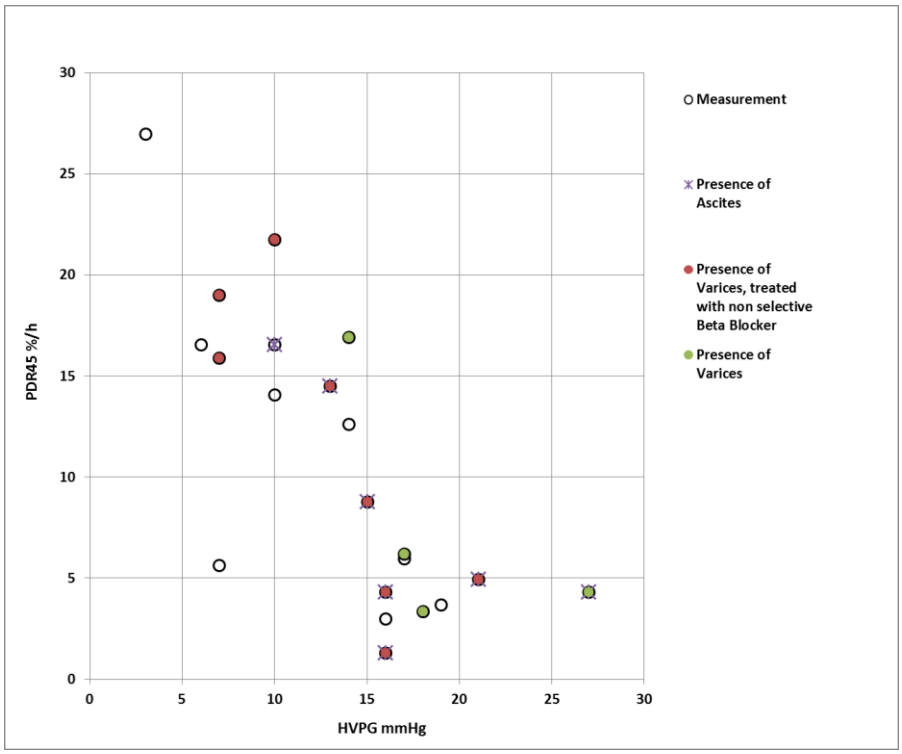

Figure 1: Correlation between HVPG and MBT measure (PDR_{45_min})

In addition, use of the Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) to assess the ability of an MBT variable to identify CSPH, demonstrated that the Cumulative Percent Dose Recovered at 15 minutes ($cPDR_{15\_min}$) distinguished

HVPG ≥10mmHg (CSPH) from lower HVPG values (non-CSPH). The AUC of the MBT parameter ($cPDR_{15}$_min) was 0.89 (95% CI [0.72-1.00], $p < 0.0001$)[9] (see ***Figure 2***). The patient population tested included 5 non-CSPH subjects and 16 subjects with CSPH.

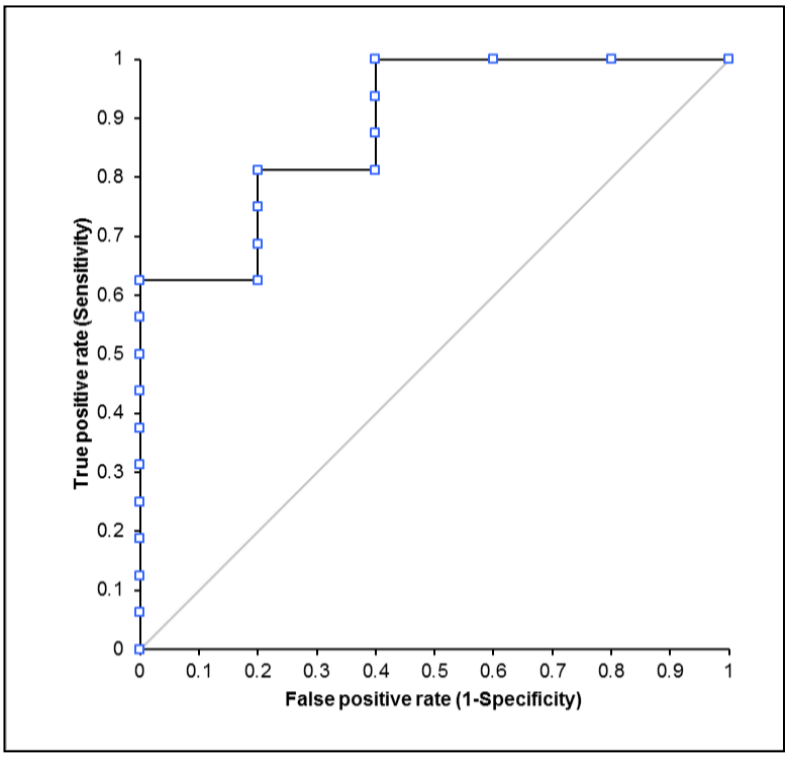

Figure 2: ROC curve for the detection of CSPH as measured by $cPDR_{15\_min}$

Based on these findings, an additional study was conducted in India to compare MBT to HVPG in 31 subjects clinically identified as cirrhotic. All subjects underwent both tests within 2 days of each other. The results showed a statistically significant correlation of approximately r= -0.6 for most MBT parameters compared to HVPG. The ROC AUC for the detection of CSPH remained at 0.90 for $cPDR_{15}$_min (Cumulative PDR at 15 minutes) (see ***Figure 3***). There were, however only two subjects with HVPG measures lower than 10mmHg *[Data on File]*.

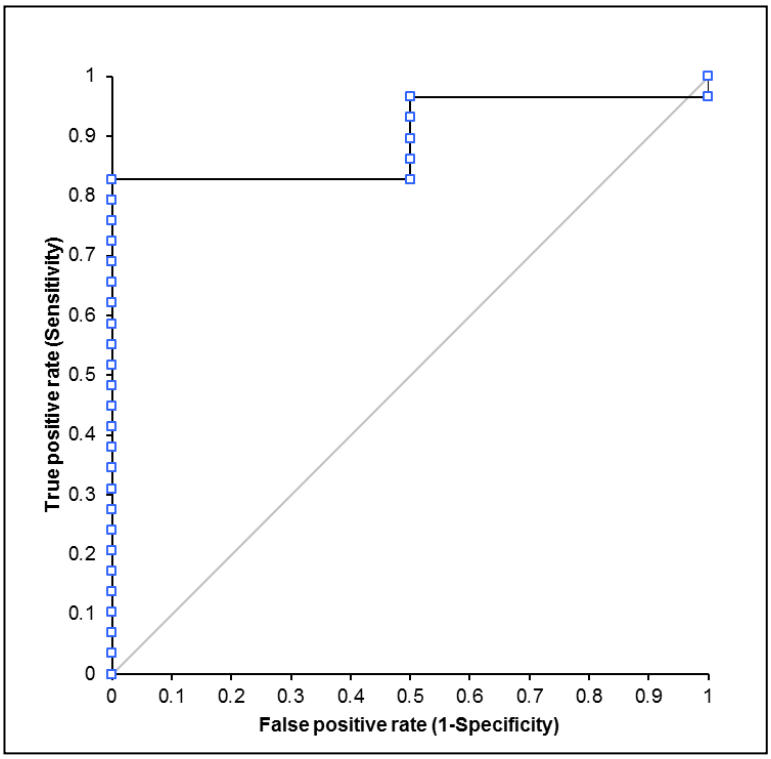

Figure 3: ROC curve for the detection of CSPH as measured by cPDR$_{15_min}$ in Indian data

The Company also conducted a meta-analysis of all accumulated data (in the US and in India) that included in addition six patients from another clinical study which enrolled cirrhotic patients conducted under IDE G080227, who had HVPG done as part of their clinical care. A total of 58 subjects were included in this meta-analysis to assess the correlation between MBT and HVPG as well as the ability of the MBT to identify CSPH (51 with CSPH and 7 without CSPH). The analysis demonstrated a statistically significant negative correlation between HVPG and MBT (r=-0.57) (cPDR$_{15_min}$) as seen in ***Figure 4*** *[Data on File]*.

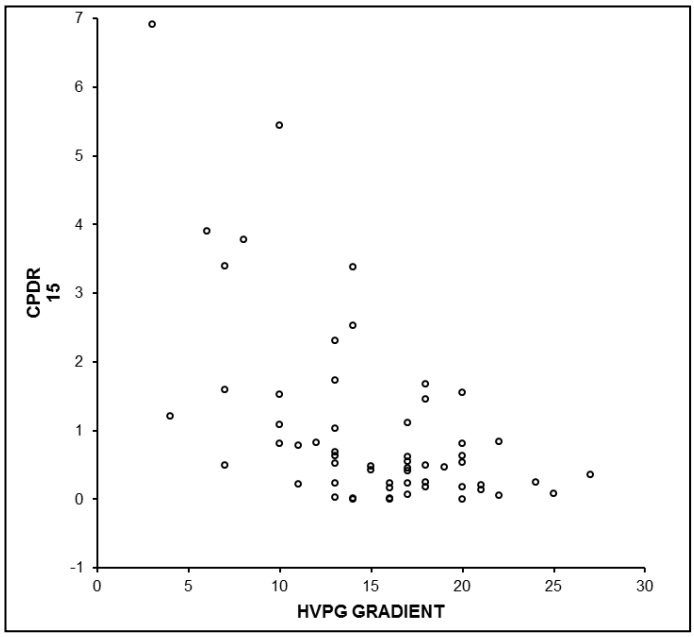

Figure 4: Correlation between HVPG and MBT measure cPDR$_{15_min}$ on 58 patients

The AUC for the detection of CSPH in this meta-analysis remained at 0.88 for cPDR$_{15}$_min. The ability of cPDR$_{15_min}$ to assess CSPH can be seen in a boxplot in ***Figure 5***.

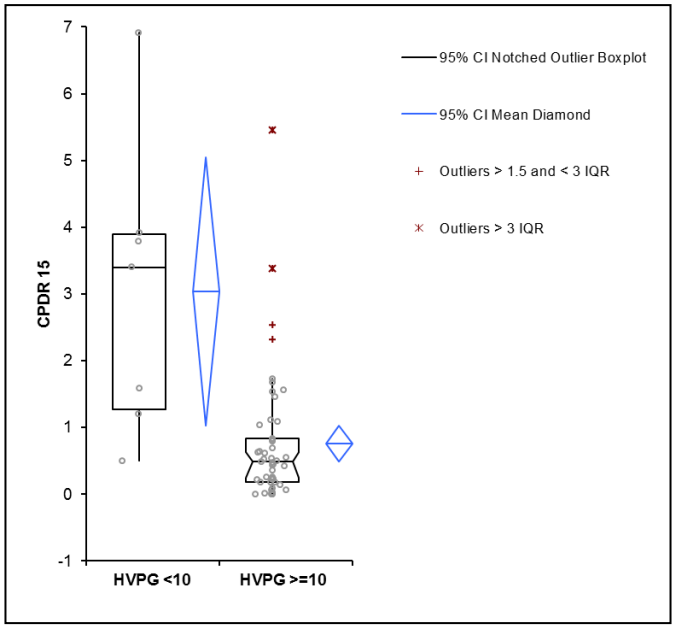

Figure 5: Boxplot showing the ability of cPDR$_{15_min}$ to assess CSPH in 58 patients

The results obtained for $cPDR_{15\_min}$ were very similar to those when using $cPDR_{30\_min}$. The latter is believed to be more informative than $cPDR_{15\_min}$ as it relies on more measurements throughout 30 minutes.

Following these preliminary results, Exalenz conducted the CSPH-EX-0414 training study to develop the BID-CSPH Test algorithm at eight clinical sites; five in Europe and three in the United States (IDE# G140190). This study enrolled 247 patients with compensated advanced chronic liver disease.

An additional training study (to develop the BID-CSPH Algorithm), the GT-EX-0215 study, was conducted as a companion protocol to Galectin Therapeutics Inc. (Galectin's) GT-026 study for evaluating the efficacy of their study drug GR-MD-02 (Galactoarabino-rhamnogalacturonate) for treatment of NASH. This collaborative study was conducted under an IND and IDE; Galectin's IND 115459 and Exalenz' IDE G150125. The MBT was performed during screening, after 26 weeks of treatment, as well as at the end of the study (between weeks 53-55). The HVPG procedure was performed during screening and at the end of the study.

Beyond Galectin's aim in this study, Exalenz' intent was to assess whether the MBT can serve as an aid in identifying changes in portal pressure by measuring performance of the liver before and after treatment with Galectin's GR-MD-02 and to train MBT based algorithms (i.e., for the BID-CSPH Test) using data from screening visits to identify different risk levels of portal hypertension as defined by HVPG $\geq$ 6, 10, 12, 20 mmHg in adult patients with portal hypertension and cirrhosis due to NASH, without a history of clinical decompensation.

Both training studies (CSPH-EX-0414 and GT-EX-0215) contributed data to the building of the algorithm of the BID-CSPH Test to identify CSPH (HVPG $\geq$ 10 mmHg) in NASH patients presenting with ACLD.

The current validation and companion study's primary aim is to validate the BID-CSPH Algorithm to identify CSPH (defined as HVPG $\geq$ 10mmHg) in screening/pre-treatment subjects (the Validation Population). Additionally it will help in the assessment in these subjects of the ability of the MBT to identify severe portal hypertension (defined as HVPG $\geq$ 12 mmHg), to assess the correlation of MBT results to HVPG and assess the effect of frequently used medications and confounding factors on the MBT results.

Additionally, assessing the data of randomized subjects, this study will serve to determine the effect of Conatus' study drug Emricasan on the metabolic capacity of the liver as determined by the MBT after 24 and 48 weeks of treatment (versus pre-treatment) at different treatment doses compared to placebo, and show correlation of changes in the

MBT results compared to changes in HVPG after 24 weeks of treatment (versus pre-treatment) in patients with and without treatment for nonalcoholic steatohepatitis.

4 INTENDED USE / INDICATION FOR USE

The Exalenz ^{13}C-Methacetin Breath Test (MBT) is intended to non-invasively measure changes in the $^{13}CO_2/^{12}CO_2$ ratio of exhaled breath, which is indicative of the ability of the liver to metabolize a set dose of ^{13}C-Methacetin over time.

The Exalenz BID-CSPH Test is indicated for use as an aid in identifying clinically significant portal hypertension (CSPH) in adult patients with clinically diagnosis of Non-alcoholic Steatohepatitis (NASH) who present with advanced chronic liver disease (ACLD).[a] The Test utilizes the ^{13}C-Methacetin Solution, the BreathID® MCS System and the BID-CSPH Software Application.

The MBT and its BID-CSPH Test are for use by trained health care professionals. To be administered under a physician's supervision.

5 STUDY DESIGN

This companion protocol is a validation study for the BID-CSPH Test with its BID-CSPH Algorithm for identification of CSPH (defined as HVPG ≥ 10 mmHg) that will analyze the data generated by Conatus' study of Emricasan under protocol IDN-6556-14. This data will be sequestered from Exalenz until the BID-CSPH Algorithm is fully developed and locked. The IDN-6556-14 study is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-response study to evaluate the safety and efficacy of Emricasan in improving portal hypertension in subjects with NASH cirrhosis and severe portal hypertension. The Conatus study IDN-6556-14 randomizes subjects into 4 parallel treatment arms (5 mg, 25 mg, 50 mg Emricasan or placebo).

As part of the IDN-6556-14 study, MBT will be performed during a screening visit.
The screening data, including data from screen failed subjects, generated by the Conatus study IDN-6556-14 will be used to validate the BID-CSPH Test.

In addition the MBT will be performed at treatment week 24 and at the end of treatment (week 48), in randomized subjects who had MBT at screening to assess whether Emricasan compared to placebo improves liver metabolic function as assessed by the MBT. It will be assessed once the data from treatment week 24 and treatment week 48, respectively,

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[a] - Although Conatus study IDN-6556-14 randomizes only 'NASH patients with cirrhosis and severe portal hypertension', this validation study, as part of the companion protocol to the Conatus IDN-6556-14 study, enrolls patients from the screening phase where the ^{13}C-Methacetin Breath Test is performed, thereby also including screen failed patients without severe portal hypertension (HVPG <12 mmHg).
- Since in this study cirrhosis does not have to be biopsy proven, the terminology used is 'advanced chronic liver disease' - ACLD.

become available. All analyses using only screening data for the Validation Population may be performed prior to week 24.
All sites in the US, Spain and France that will participate in the Conatus IDN-6556-14 study will be offered the opportunity to perform the MBT for all of their subjects meeting the study criteria. Sites in Switzerland and Germany will not have the opportunity to perform the MBT as part of the study.

Sites who elect to participate in the MBT measurements will perform the test at the specified visits for all subjects enrolled at their site. As described in the Conatus' study IDN-6556-14 protocol (Appendix B) section 8.2.6, the MBT will be performed at select sites at screening, treatment week 24, and treatment week 48. MBT should be performed within 1 week of HVPG but not within 24 hours after HVPG. If MBT is performed on the same day as the HVPG test, it should be performed before the HVPG test. For the treatment week 24 and treatment week 48 MBT, subjects should take their morning dose of study drug prior to the test.

A graphical summary of the study schema is included in ***Figure 6***, below. Further details can be found in the Conatus study protocol IDN-6556-14 included in Appendix B.

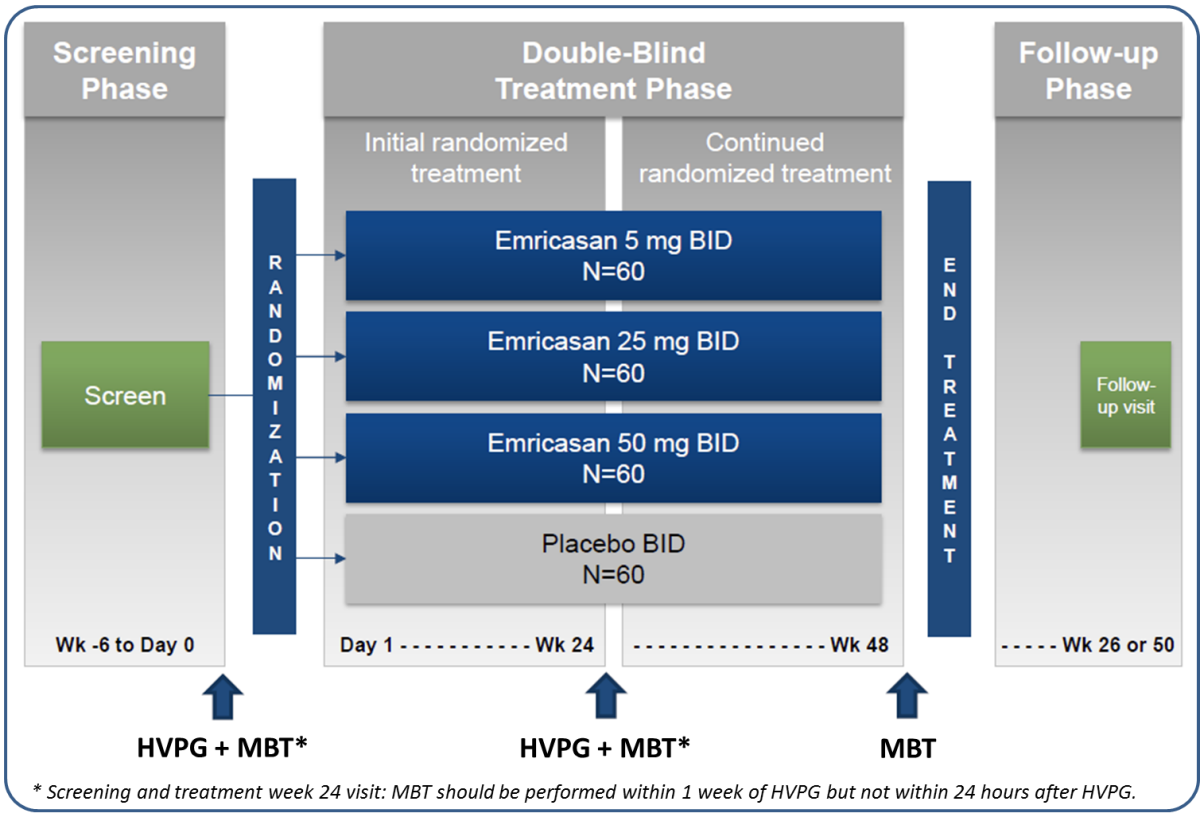

Figure 6: Study Schema

6 STUDY OBJECTIVES AND ENDPOINTS

The data generated in this study will primarily be used to validate the BID-CSPH Test, which uses an MBT based algorithm developed under the Exalenz study CSPH-EX-0414, IDE# G140190 and Companion Protocol to Galectin's study GT26 (GT-EX-0215), conducted in collaboration with Galectin Therapeutics Inc. under their IND 115459 and Exalenz' IDE G150125.

6.1 Study Objectives

6.1.1 Primary Performance Objective

To validate the ability of the BID-CSPH Test to identify clinically significant portal hypertension (CSPH) defined as HVPG ≥ 10mmHg in the Validation Population using the BID-CSPH Algorithm with a predefined cutoff in terms of PPV and NPV.

6.1.2 Secondary Performance Objective

1. To assess additional performance measures for the ability of the BID-CSPH Test to identify clinically significant portal hypertension (CSPH) defined as HVPG ≥ 10mmHg in the Validation Population using the BID-CSPH Algorithm with a predefined cutoff in terms of sensitivity and specificity.
2. To assess the ability of the BID-CSPH Test to identify severe portal hypertension defined as HVPG ≥ 12mmHg in the Validation Population using the BID-CSPH Algorithm with a second predefined cut-off.

6.1.3 Exploratory Performance Objectives

1. To assess the correlation between MBT result parameters (see Appendix A, item 7) and HVPG results in the Validation Population.
2. To assess the effect of frequently used medications or other confounding factors on the correlation of MBT result parameters (see Appendix A, item 7) with HVPG readings in the Validation Population.
3. To show the ability of the MBT to measure the effect of Emricasan on the metabolic capacity of the liver at treatment week 24 of treatment (versus pre-treatment), as compared to changes in placebo treated subjects in the Treated Sub-Population.
4. To show correlation of changes in the MBT results with changes in HVPG at week 24 (versus pre-treatment), in subjects with and without treatment with Emricasan for nonalcoholic steatohepatitis (NASH) in the Treated Sub-Population.

5. To show the ability of the MBT to measure the effect of Emricasan on the metabolic capacity of the liver at treatment week 48 of treatment (versus pre-treatment), as compared to changes in placebo treated subjects in the Treated Sub-Population.

6.1.4 MBT Safety Objective

To evaluate safety events related to the BreathID MCS System or the MBT/BID-CSPH Test.

6.2 Study Endpoints

6.2.1 Primary Endpoint

The primary endpoints are the positive and negative predictive value (PPV and NPV, respectively) of the binary response for clinically significant portal hypertension (CSPH) as determined by HVPG, defined as HVPG ≥ 10mmHg in the Validation Population.

6.2.2 Secondary Endpoints

The secondary endpoints are:

1. Sensitivity and specificity of the BID-CSPH Test binary response for clinically significant portal hypertension (CSPH) as determined by HVPG, defined as HVPG ≥ 10 mmHg in the Validation Population.
2. Positive and negative predictive value (PPV and NPV, respectively) of the BID-CSPH Test binary response for severe portal hypertension as determined by HVPG, defined as HVPG ≥ 12mmHg in the Validation Population.

   The cut-off value of the BID-CSPH Algorithm for identifying severe portal hypertension is different from the one used to identify CSPH.

6.2.3 Exploratory Endpoints

1. Correlation between MBT result parameters (see Appendix A, item 7) and HVPG readings in the Validation Population.
2. Comparison of correlation between MBT result parameters (see Appendix A, item 7) and HVPG readings between frequently used medications or other confounding factors in the Validation Population.
3. Change in MBT result parameters (see Appendix A, item 7) at treatment week 24. Change is measured as the difference between pre-treatment and treatment week 24 MBT measurements in each of the four treatment arms.
4. Correlation between changes in the MBT result parameters (see Appendix A, item 7) and changes in HVPG to treatment week 24, both measured as the difference between pre-treatment and treatment week 24 values.

5. Change in MBT result parameters (see Appendix A, item 7) at treatment week 48. Change is measured as the difference between pre-treatment and treatment week 48 MBT measurements in each of the four treatment arms.

6.2.4 Safety Endpoints

The cumulative incidence of 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 BreathID MCS System and its substrates or related to the procedure.

7 SUBJECT SELECTION

This companion protocol includes all randomized AND all screen failed subjects from the Conatus IDN-6556-14 study that performed an MBT. Only subjects that meet the companion study inclusion/exclusion criteria (sections 7.1, 7.2 and 7.3) will be considered for the performance analyses.

7.1 Inclusion Criteria

Subjects must meet all of the following criteria for this validation study:

1. Male or female subjects 18 years or older, able to provide written informed consent and able to understand and willing to comply with the requirements of the study.
2. Cirrhosis due to NASH with exclusion of other causes of cirrhosis (e.g. chronic viral hepatitis, alcoholic liver disease, etc.)
   - Diagnosis of cirrhosis is based on:
     - Biopsy OR
     - Clinical evidence: platelet count <150,000, AST > ALT, and either nodular liver surface on imaging or splenomegaly
   - NASH is based on at least 1 of the following:
     - Prior or current biopsy showing steatohepatitis (fat, ballooning degeneration, inflammation) consistent with NASH
     - At least 2 metabolic risk factors for at least 5 years preceding the diagnosis of cirrhosis: diabetes mellitus, impaired fasting glucose, obesity (Body Mass Index (BMI) ≥30 kg/m2 or central obesity), hypertension, dyslipidemia (See Appendix IV of Conatus IDN-6556-14 protocol)
     - Prior or current biopsy showing some but not all diagnostic features of NASH (e.g. only fat or ballooning degeneration or inflammation) but with no evidence for viral hepatitis or other liver disease AND either fatty liver disease on prior imaging or at least 1 metabolic risk factor (as above) for at least 5 years preceding the diagnosis of cirrhosis

Note: Previous viral hepatitis that was curatively treated (with sustained viral response) is not an exclusion as long as: 1) viral eradication was achieved at least 3 years prior to the diagnosis of cirrhosis and 2) all other criteria are met for NASH as the etiology of cirrhosis

3. Compensated cirrhosis (no history of or presence of clinically evident ascites, variceal hemorrhage, or encephalopathy, and on no medications to treat these complications)
   OR
   Decompensated cirrhosis with no more than 1 prior significant decompensating event:
   a) If a prior decompensating event was variceal hemorrhage, event must have occurred at least 3 months prior to MBT and HVPG
   b) If a prior decompensating event was ascites requiring chronic diuretics, ascites should be well controlled (not clinically evident, i.e. no ascites or ascites only detectable by ultrasound examination) on a stable dose of diuretics for at least 3 months prior to MBT and HVPG
   c) If a prior decompensating event was hepatic encephalopathy ≥ grade II or requiring hospitalization, encephalopathy should be well-controlled (Stage 0 or 1) on stable medication for at least 3 months prior to MBT and HVPG

   Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count as a prior significant decompensating event

4. Subjects who are on NSBB or statins must be on a stable dose for at least 1 month prior to MBT and HVPG.
5. Subjects must have an initial MBT test performed during screening.

7.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this validation study:

1. Evidence of severe decompensation, defined as:
   - Presence or history of more than one type of significant decompensating event (clinically evident ascites requiring chronic diuretics, variceal hemorrhage, and/or overt encephalopathy)

     Note: Previous transient ascites or hepatic encephalopathy in a subject who is currently stable without clinically evident ascites or encephalopathy and on no medications for these conditions does not count towards this exclusion.

   - One type of decompensating event with the following characteristics:

- More than 1 episode of variceal hemorrhage or bleeding from a portal hypertensive source (e.g. portal hypertensive gastropathy)
- Ascites that has required more than 1 large-volume paracentesis (>5 L) for treatment or that has been complicated by spontaneous bacterial peritonitis, hyponatremia (serum Na <130), and/or hepatorenal syndrome
- More than 1 episode of overt hepatic encephalopathy requiring hospitalization

2. Estimated creatinine clearance <30 mL/min
3. Prior transjugular intrahepatic portosystemic shunt or other porto-systemic bypass procedure
4. Known portal vein thrombosis
5. Symptoms of biliary colic, e.g. due to symptomatic gallstones, within the last 6 months, unless resolved following cholecystectomy, other definitive treatment (e.g., sphincterotomy), or medical management (e.g., ursodeoxycholic acid)
6. Current use of medications that are considered inhibitors of OATP1B1 and OATP1B3 transporters: atazanavir, cyclosporine, eltrombopag, gemfibrozil, indinavir, lopinavir, ritonavir, rifampin, saquinavir, simeprevir, telaprevir, tipranovir, or some combination of these medications
7. Alpha-fetoprotein >50 ng/mL
8. History or presence of clinically concerning cardiac arrhythmias, or prolongation of screening (pre-treatment) QT Interval Corrected by the Fridericia Correction Formula (QTcF) interval of >500 msec
9. History of or active malignancies, other than those successfully treated with curative intent and believed to be cured
10. Significant systemic or major illness other than liver disease that in the opinion of the investigator would preclude the subject from participating in and completing the study, including but not limited to acute coronary syndrome or stroke within 6 months of screening or major surgery within 3 months of screening
11. Prior liver transplant
12. Previous restrictive bariatric surgery or bariatric device or prior malabsorptive bariatric surgery
13. Known human immunodeficiency virus infection
14. Use of controlled substances (including inhaled or injected drugs) or non-prescribed use of prescription drugs within 1 year of screening to the point of interfering with the subject's ability to comply with study procedures and study drug administration in the investigator's judgement
15. History of significant alcohol consumption (>20 g/day for females and >30 g/day for males on average) within the past 5 years

16. If female: planned or known pregnancy, positive urine or serum pregnancy test, or lactating/breastfeeding
17. Previous treatment with Emricasan or active investigational medication (except Methacetin) in a clinical trial within 3 months prior to MBT and HVPG
18. Known allergy to acetaminophen (paracetamol)
19. Known hypotension (systolic pressure < 100mmHg),
20. Known pulmonary hypertension (right ventricular systolic pressure > 45mmHg)
21. Uncontrolled malabsorption or diarrhea

7.3 Restriction 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 randomized subjects), 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 consume any alcohol or caffeine within 24 hours prior to the test
7. Subject should not have general anesthesia or sedation within 24 hours prior to the test
8. Subjects on beta-blockers or statins should be on 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-6556-14 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-6556-14.

8.1 Expected Study Duration

Conatus' protocol IDN-6556-14 is designed to have subjects remain on study therapy for a total of 48 weeks unless intolerable side effects develop, or the subject is withdrawn from study participation. In addition, subjects will have up to a 6 week screening period and a 2 week post-treatment follow-up visit for a total duration of up to 56 weeks.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design and Aim

This companion protocol is a validation study for the BID-CSPH Test with its MBT based algorithm for identification of CSPH (defined as HVPG ≥ 10 mmHg) that will analyze the data generated by Conatus' study of Emricasan under protocol IDN-6556-14. The Conatus study IDN-6556-14 randomizes subjects into 4 parallel treatment arms (5 mg, 25 mg, 50 mg Emricasan or placebo) (see Section 5).

As part of the IDN-6556-14 study, MBT will be performed during a screening visit.

The screening data, including data from screen failed subjects, generated by the Conatus study IDN-6556-14 will be used to validate the BID-CSPH Test.

In addition the MBT will be performed at treatment week 24 and at the end of treatment (week 48), in randomized subjects who had MBT at screening to assess whether Emricasan compared to placebo improves liver metabolic function as assessed by the MBT.

9.2 Endpoint Measures

9.2.1 Primary endpoints

The primary endpoints are the positive and negative predictive value (PPV and NPV, respectively) of the BID-CSPH Test binary response for clinically significant portal hypertension (CSPH) as determined by HVPG, defined as HVPG ≥ 10mmHg in the Validation Population.

9.2.2 Secondary endpoints

The secondary endpoints are:

1. Sensitivity and specificity of the BID-CSPH Test binary response for clinically significant portal hypertension (CSPH) as determined by HVPG, defined as HVPG ≥ 10 mmHg in the Validation Population (prior to any investigational treatment).
2. Positive and negative predictive value (PPV and NPV, respectively) of the BID-CSPH Test binary response for severe portal hypertension (defined as HVPG ≥ 12mmHg) in the Validation Population (prior to any investigational treatment).

   The cut-off value of the BID-CSPH Algorithm for identifying severe portal hypertension is different from the one used to identify CSPH.

9.2.3 Exploratory endpoints

1. Correlation between MBT result parameters (see Appendix A, item 7) and HVPG readings in the Validation Population.

2. Comparison of correlation between MBT result parameters (see Appendix A, item 7) and HVPG readings between frequently used medications or other confounding factors in the Validation Population.
3. Change in MBT result parameters (see Appendix A, item 7) at treatment week 24. Change is measured as the difference between pre-treatment and treatment week 24 MBT measurements in each of the four treatment arms.
4. Correlation between changes in the MBT result parameters (see Appendix A, item 7) and changes in HVPG to treatment week 24, both measured as the difference between pre-treatment and treatment week 24 values.
5. Change in MBT result parameters (see Appendix A, item 7) at treatment week 48. Change is measured as the difference between pre-treatment and treatment week 48 MBT measurements in each of the four treatment arms.

9.2.4 Safety endpoints

The cumulative incidence of 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 BreathID MCS System and its substrates or related to the procedure.

9.3 Acceptance Criteria and Performance Goals

One predefined cut-off to identify CSPH, determined by the BID-CSPH Test with its BID-CSPH Algorithm will be validated in this study.

The study will be deemed successful if:

- the PPV is statistically significantly higher than the observed prevalence + 5% in the Validation Population, in other words if the lower two-sided 95% confidence bound is 5% higher than the prevalence.

and

- the NPV is statistically significantly higher than one minus the observed prevalence (1-prevalence) in the Validation Population, in other words if the lower two-sided 95% confidence bound is higher than 1-prevalence.

9.4 Sample Size

The plan is to enroll a subset of subjects that will be screened under Conatus' IDN-6556-14 study. It is expected that up to 510 subjects will perform the MBT during the screening visit of the Conatus study.

It should be noted that HVPG results (a primary endpoint in this companion protocol) may not be available for all subjects tested with MBT prior to the HVPG procedure (for screen failure subjects as part of the Conatus study). Thus, for the primary endpoint there will be

fewer subjects with pairs of MBT and HVPG measurements. It is expected that approximately 250 subjects will have valid MBT and HVPG results during screening, prior to randomization and any treatment visit.

A sample size of approximately 250 subjects will enable confirmation that the lower two-sided 95% exact confidence limit of the PPV is 5% higher than the observed prevalence if the observed PPV is at least 11% higher than the prevalence (assuming a prevalence of 70%-80%).

A sample size of approximately 250 subjects will enable confirmation that the lower two-sided 95% exact confidence limit of the NPV is higher than one minus the observed prevalence if the observed NPV is at least 7% higher than the 1-prevalence (assuming a prevalence of 70%-80%).

9.5 Randomization

Subjects enrolled into the Conatus' IDN-6556-14 study, were randomized to one of the four treatment arms (5 mg, 25 mg, 50 mg of Emricasan or placebo) for the CON-EX-0616 validation study, this is not relevant for the primary and secondary study endpoints.

9.6 Blinding

The Sponsor, the investigators and study sites personnel and the study statistician are blinded to the BID-CSPH Test results.

9.7 Analysis sets

9.7.1 Safety Analysis Set

All subjects screened under Conatus' IDN-6556-14 study and for whom the MBT test was initiated.

9.7.2 Performance Analysis Set

All subjects screened under Conatus' IDN-6556-14 study who have performed the MBT test and have met the inclusion and exclusion criteria for this companion protocol and have valid measurements of MBT and HVPG at the screening visit. Subjects not randomized in the Conatus study IDN-6556-14, or with missing valid MBT or HVPG results at the treatment weeks 24 or 48 visits will not be part of the corresponding analysis.

The study population for the primary and secondary as well as first two exploratory endpoints will be screened subjects with valid MBT and HVPG results prior to any investigational treatment. This population is referred to as the ***Validation Population***.

Those subjects from the ***Validation Population*** that were randomized into the Conatus IDN-6556-14 study and have at least one MBT on treatment are defined as the ***Treated Sub-Population***.

9.7.3 Per-Protocol Analysis Set

All subjects from the performance analysis set without any major protocol violation.

9.7.4 Statistical Analyses of Analysis Sets

Safety analyses will be performed on the safety analysis set.

The per-protocol analysis set will be the main analysis set for the performance analyses. Performance analyses will also be presented for the performance analysis set.

9.8 Statistical Analysis

9.8.1 General Considerations

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, US).
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.

9.8.2 Significance levels and handling of type I error

9.8.2.1 Type I Error

The overall significance level for this study is 5% using two-tailed tests, except for the treatment by site interaction that will be tested at a significance level of 10%.

9.8.2.2 Hierarchy Approach for Endpoints Analysis

There are two primary endpoints. The study will be deemed successful only if both acceptance criteria are met.

The hierarchy approach will be adopted for the primary and secondary endpoints to control the type I error due to multiple endpoint testing. Thus, the primary endpoints will first be analyzed and only if both primary endpoints will be found significant, will the secondary endpoints be analyzed. The first set of secondary endpoints will be presented descriptively

with confidence intervals. The second set of secondary endpoints of identification of severe portal hypertension will be analyzed together and will be considered met only if both PPV and NPV are found significant. This approach will maintain the overall study type I error.

9.8.3 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.

Demographic information and disease characteristics for subjects that were screened for the Conatus study, but not enrolled into the MBT validation study will be compared to those enrolled into the MBT validation study.

9.8.4 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 performance analysis will be provided as well. Any subject with missing primary endpoint data will be accounted for, including the reason for missing data. Demographic and other baseline characteristics of the subjects with and without HVPG results will be presented in tabular format.

9.8.5 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, which will be coded according to MedDRA, will include incidence tables and will include analyses by severity, relationship to device or drug and baseline (pre-treatment) variables.

9.8.6 Primary Performance Analysis

A 2x2 table of the results comparing the positive /negative results obtained from the BID-CSPH Algorithm compared to HVPG ≥ 10mmHg / < 10mmHg at baseline (screening) will be presented.

The primary performance analysis will present the estimation of the PPV and NPV of the diagnosis together with their respective Wilson' score two-sided 95% confidence intervals (CI).

The study will be deemed successful if:

- The lower limit of the Wilson' score two-sided 95% CI for the PPV is 5% higher than the observed prevalence; ***and***
- The lower limit of the Wilson' score two-sided 95% CI for the NPV is higher than 1 - the observed prevalence.

PPV and NPV will be presented for the prevalence of 65%, 70%, 75% and 80% in addition to the prevalence observed in the study.

9.8.7 Secondary Performance Analysis

1. Secondary performance analysis will present the estimation of the sensitivity and specificity of the BID-CSPH Algorithm to identify CSPH, HVPG ≥ 10mmHg, together with their respective Wilson' score two-sided 95% confidence intervals (CI).
2. A 2x2 table of the results comparing the positive /negative results obtained from the BID-CSPH Algorithm (with a second cut-off for the detection of severe portal hypertension) compared to HVPG ≥ 12mmHg / < 12mmHg at baseline (screening) will be presented.

   This secondary performance analysis of the detection of severe portal hypertension will present the estimation of the PPV and NPV as well as of the sensitivity and specificity of the diagnosis together with their respective Wilson' score two-sided 95% confidence intervals (CI).

   The secondary endpoints will be deemed successful if:

- The lower limit of the Wilson' score two-sided 95% CI for the PPV is higher than the observed prevalence; ***and***
- The lower limit of the Wilson' score two-sided 95% CI for the NPV is higher than 1 - the observed prevalence.

9.8.8 Exploratory Performance Analyses

The Spearman's and Pearson's correlation coefficient of the MBT result parameters (Appendix A, item 7) with the HVPG (as a continuous variable) at baseline (screening) will be presented in a tabular form along with their respective two-sided 95% CI's.

The Spearman's and Pearson's correlation coefficient of the MBT result parameters (Appendix A, item 7) with the HVPG (as a continuous variable) at baseline (screening) by subgroups of frequently used medications and other confounding factors, will be presented in a tabular form along with their respective two-sided 95% CI's as well.

The changes from baseline (screening) to treatment week 24 of the MBT result parameters (Appendix A, item 7) will be presented by descriptive statistic by Conatus' IDN-6556-14 study arm for randomized subjects.

The change from baseline (screening) to treatment week 24 visit in selected MBT result parameters (PDR_{peak}, $cPDR_{30\_min}$, PDR_{45_min}) will be modeled and compared between the Conatus' IDN-6556-14 study arms with regression models. The models will include treatment arm and screening HVPG (as a continuous value). Adjusted means of the change in MBT parameters for each treatment arm will be extracted from the regression model and compared between the treatments arms.

The Spearman's and Pearson's correlation coefficient of the change from baseline (screening) to week 24 in MBT result parameters (Appendix A, item 7) with the change from baseline (screening) to treatment week 24 in HVPG (as a continuous variable) at baseline (screening) will be presented in a tabular form by Conatus' IDN-6556-14 study arm for randomized subjects along with their respective two-sided 95% CI's.

The changes from baseline (screening) to treatment week 48 of the MBT result parameters will be presented by descriptive statistic by Conatus' IDN-6556-14 study arm for randomized subjects.

The change from baseline (screening) to treatment week 48 visit in selected MBT result parameters (PDR_{peak}, $cPDR_{30\_min}$, PDR_{45_min}) will be modeled and compared between the Conatus' IDN-6556-14 study arms with regression models. The models will include treatment arm and baseline HVPG (as a continuous value). Adjusted means of the change in MBT parameters for each treatment arm will be extracted from the regression model and compared between the treatments arms.

9.8.9 Timing of Analyses

After the last subject has completed the screening visits and the BID-CSPH Algorithm has been locked including its respective cut-off, all data for all subjects across all screening visits will be cleaned, locked, and considered as the main analysis set for this validation study. This validation analysis will include all primary, secondary, and exploratory endpoint analyses that require only screening data (Validation Population). This analysis may be performed prior to or together with the assessment from treatment week 24.

For the Conatus phase 2 study, after the last randomized subject has completed its treatment week 24 visit, all data for all subjects across all visits will be cleaned, locked, and considered as the main analysis for this study to assess treatment efficacy. This treatment week 24 analysis will include all primary, secondary, and exploratory endpoint analyses that require treatment week 24 data. Although Conatus will be unblinded for the treatment

week 24 analysis, the investigative sites will remain blinded throughout the study. The purpose of the treatment week 24 analysis is for Conatus' internal decision making.

The final analysis of the study (i.e., treatment week 48 analysis) will be conducted after all randomized subjects have completed all study visits up to and including the follow-up visit. All study data across all subjects and visits will be cleaned and locked for this final analysis.

9.8.10 Pooling

Poolability will be tested in the primary analysis at a significance level of 10%.

Poolability across centers, for the two primary endpoints, will be assessed using Fisher's exact test. The Cochran-Mantel-Haenszel odds ratio estimator or logistic regression will be used to adjust for site effects, as appropriate. Forest plots will be presented for further visual assessment.

Centers with less than 10 subjects will be grouped together by geographical area (In US: West, Mid-West, North-East, South, and OUS: Spain and France together), a table of the sites and their location within the USA will be attached to the statistical report to justify the grouping. If found significant, the reason for the significance will be further explored and rationalized. This evaluation may include demographic features, symptoms at presentation, clinical and treatment history, and site comparability in the features found to be associated with the primary performance variables. In addition, detailed information about each site, including patient enrollment and performance data will be presented.

Pooling analysis will be repeated with US centers combined, and Out of US (OUS) centers combined.

9.8.11 Sub-Group Analyses

Primary and secondary performance analyses will be performed on the following subsets:

1. Subjects with biopsy proven NASH
2. Subjects classified as compensated ACLD

9.8.12 Handling of Missing Data

The study variables cannot be evaluated for subjects for whom BreathID® MCS System MBT results are not available and therefore these subjects will be left out of the performance analysis. Subjects missing HVPG results will be excluded from the relevant analyses.

Measurements with unknown values or unavailable estimates will be treated as missing values and excluded from the analysis. No imputation for missing data is planned for the primary, secondary and exploratory endpoints.

Missing data will be reported as such in the data listings.

10 STUDY PROCEDURES

10.1 General

The schedule of the breath tests is based on the schedule of the IDN-6556-14 protocol. The first MBT will be performed during the screening period (week -6 to Day 0), usually before the HVPG. The second MBT will be performed at treatment week 24 and the third MBT at treatment week 48 (end of treatment).

10.2 Breath Test Procedure

Preparation of the study subject

In preparation for each breath test the patient will be asked to comply with the following restrictions:

1. Subject should be fasting, including all oral morning medications (except for betablockers and study drug [Emricasan or placebo] for randomized subjects), 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 consume any alcohol or caffeine within 24 hours prior to the test
7. Subject should not have general anesthesia or sedation within 24 hours prior to the test
8. Subjects on beta-blockers or statins should be on 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 another qualified medical staff member 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. In these cases, attempts will be made to reschedule a MBT at the earliest convenience and at least 24 hours later.

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 US 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.

This companion protocol will obtain 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, assessed and reported according to local regulations.

Safety assessments of the Conatus study drug will be performed as described in Conatus protocol IDN-6556-14 (Appendix B) section 8.1 - *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-6556-14. 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 investigator prior to signing of the conduct.

16 FINANCIAL ASPECTS

The BreathID® MCS device and test kits 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-6556-14. Conatus will be responsible for study termination procedures, when applicable.

18 REFERENCES

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APPENDIX A – METHACETIN BREATH TEST PARAMETERS

The BreathID MCS System measures the change of the $^{13}CO_2/^{12}CO_2$ ratio in exhaled breath following ingestion of ^{13}C-Methacetin compared to the $^{13}CO_2/^{12}CO_2$ ratio before ingestion. This measure is called 'Delta Over Baseline' (DOB) and is automatically measured every 2-3 minutes, resulting in approximately 23 DOB's and corresponding time points over one hour. Subjects visit height and weight as well as all available DOB measures with corresponding time point (T) will be retrieved from the completed eCRFs.

1. DOB values must be sorted by time before any calculation, while a first pair of data points should always be added with time T_0=0 min and DOB_0 =0.
2. The DOBs will be transformed into percentage dose recovery rates (PDRs) by normalizing the DOB using patient body weight and height at each observed time point (i) by using the following formula:

$$PDR_i = 0.01817853 \cdot DOB_i \cdot Weight^{0.5378} \cdot Height^{0.3963}$$

While Weight is in kg, and Height is in cm
The units of PDR is %/hour

3. The maximum rate at which metabolism occurs results in a peak value of the breath test called DOB_{Peak} and PDR_{Peak}, respectively. Both occur at the same time, which is called the Peak time.
   a. **DOB_{peak}**: DOB_{peak} is defined as the maximum DOB.

$$DOB_{peak} = \max(DOB_0, DOB_1, DOB_2, \dots, DOB_{24})$$

   b. **PDR_{peak}**: PDR_{peak} is defined as the maximum PDR.

$$PDR_{peak} = \max(PDR_0, PDR_1, PDR_2, \dots, PDR_{24})$$

4. The area under the DOB curve will be calculated for each time point. This area represents the cumulative DOB (cDOB) at any given time point.
   a. **DOB_{x_min} and $cDOB_{x\_min}$**: The following steps will be followed to obtain the DOB and cDOB at 5 minutes intervals (e.g. 5, 10, 15,…,60 min), where 'x' is 05, 10, 15, …, 60 respectively. For each 'x' the following steps shall be followed:

   b. Find 'a', the index for which:

$$T_{a-1} < x \leq T_a$$

c. Calculate $\mathbf{DOB_{x\_min}}$ using the following formula:

$$DOB_{x\_min} = DOB_{a-1} + \frac{DOB_a - DOB_{a-1}}{T_a - T_{a-1}} \cdot (x - T_{a-1})$$

d. Calculate $\mathbf{cDOB_{x\_min}}$ using the following formula:

$$cDOB_{x\_min} = \sum_{i=1}^{a-1} \left(\frac{\frac{T_i - T_{i-1}}{60} \cdot (DOB_i + DOB_{i-1})}{2} \right) + \frac{\frac{x - T_{a-1}}{60} \cdot (DOB_{x\_min} + DOB_{a-1})}{2}$$

MBT parameters results that do not have data points for at least 'x' minutes cannot be calculated

5. The PDR as well as the area under the PDR curve will be calculated for each time point. This area represents the cumulative PDR (cPDR) at any given time point in units of %.
   a. $\mathbf{PDR_{x\_min}}$ **and** $\mathbf{cPDR_{x\_min}}$: The following steps will be followed to obtain the PDR and cPDR at 5 minutes intervals (e.g. 5, 10, 15,…,60 min), where 'x' is 05, 10, 15, …, 60 respectively. For each 'x' the following steps shall be followed:

   b. Find 'a', the index for which:

$$T_{a-1} < x \leq T_a$$

   c. Calculate $\mathbf{PDR_{x\_min}}$ using the following formula:

$$PDR_{x\_min} = PDR_{a-1} + \frac{PDR_a - PDR_{a-1}}{T_a - T_{a-1}} \cdot (x - T_{a-1})$$

   d. Calculate $\mathbf{cPDR_{x\_min}}$ using the following formula:

$$cPDR_{x\_min} = \sum_{i=1}^{a-1} \left(\frac{\frac{T_i - T_{i-1}}{60} \cdot (PDR_i + PDR_{i-1})}{2} \right) + \frac{\frac{30 - T_{a-1}}{60} \cdot (PDR_{x\_min} + PDR_{a-1})}{2}$$

MBT parameters results that do not have data points for at least 'n' minutes cannot be calculated

6. The cDOB and cPDR at the peak time are called $cDOB_{peak}$ and $cPDR_{peak}$, respectively. They are calculated as described in steps 4 and 5, respectively, while 'x' is the actual time 'T' of the observed peak value. The $cPDR_{peak}$ divided by Peak time is named cPDRpeak_div_Peaktime.
7. The following list of MBT result parameters will thus be used in the statistical analysis: DOB_{peak}, $cDOB_{peak}$, PDR_{peak}, $cPDR_{peak}$, cPDRpeak_div_Peaktime, Time to Peak, DOB_{5_min}, DOB_{10_min}, DOB_{15_min}, DOB_{20_min}, DOB_{25_min}, DOB_{30_min},

DOB_{35_min}, DOB_{40_min}, DOB_{45_min}, DOB_{50_min}, DOB_{55_min}, DOB_{60_min}, $cDOB_{5\_min}$, $cDOB_{10\_min}$, $cDOB_{15\_min}$, $cDOB_{20\_min}$, $cDOB_{25\_min}$, $cDOB_{30\_min}$, $cDOB_{35\_min}$, $cDOB_{40\_min}$, $cDOB_{45\_min}$, $cDOB_{50\_min}$, $cDOB_{55\_min}$, $cDOB_{60\_min}$, PDR_{5_min}, PDR_{10_min}, PDR_{15_min}, PDR_{20_min}, PDR_{25_min}, PDR_{30_min}, PDR_{35_min}, PDR_{40_min}, PDR_{45_min}, PDR_{50_min}, PDR_{55_min}, PDR_{60_min}, $cPDR_{5\_min}$, $cPDR_{10\_min}$, $cPDR_{15\_min}$, $cPDR_{20\_min}$, $cPDR_{25\_min}$, $cPDR_{30\_min}$, $cPDR_{35\_min}$, $cPDR_{40\_min}$, $cPDR_{45\_min}$, $cPDR_{50\_min}$, $cPDR_{55\_min}$, $cPDR_{60\_min}$.

8. Additional breath test result parameters will be extracted based on the features developed under the Exalenz algorithm training study CSPH-EX-0414, IDE# G140190 and Companion Protocol to Galectin's study GT26 (GT-EX-0215), conducted in collaboration with Galectin Therapeutics Inc. under their IND 115459 and Exalenz' IDE G150125.

APPENDIX B – CONATUS PROTOCOL IDN-6556-14

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Emricasan, an Oral Caspase Inhibitor, in Subjects with Non-Alcoholic Steatohepatitis (NASH) Cirrhosis and Severe Portal Hypertension

Protocol Number: IDN-6556-14

Protocol Version: Version 9.0 (14 March 2018)