CLINICAL TRIAL PROTOCOL

A Multicenter, Double-Blind, Randomized Trial of IDN-6556 in Subjects Who had Hepatitis C Virus (HCV) Reinfection and Liver Fibrosis or Cirrhosis following Orthotopic Liver Transplantation for Chronic HCV Infection and Who Subsequently Achieved a Sustained Virologic Response Following anti-HCV Therapy

Protocol Number: IDN-6556-07

Date: 03 August 2015

Developmental Phase: 2

Sponsor: Conatus Pharmaceuticals
16745 W. Bernardo Drive, Suite 200
San Diego, CA 92127
United States of America

LIST OF KEY PERSONNEL

Sponsor

Conatus Pharmaceuticals
16745 W. Bernardo Drive, Suite 200
San Diego, CA 92127
USA

Medical Monitor

Jean L. Chan, MD
VP, Clinical Development
Phone: 1 858-376-2632
Mobile: 1 617-407-5689
jchan@conatuspharma.com

Serious Adverse Event Reporting

Synteract HCR Safety
Safety Fax: +1-760-268-6500
safetyfax@synteracthcr.com

OR if not available

Mason Yamashita, MD
VP, Pharmacovigilance
Phone: 1 858-376-2617
Mobile: 1 619 306 2125
myamashita@conatuspharma.com

Clinical Operations

Beth Sheedy
Associate Director, Clinical Operations
Office: 1 858 376 2643
Fax: 1 858 432 7721
Mobile: 1 619 980 2126
bsheedy@conatuspharma.com

OR if not available

Lisa Grubbs
VP, Clinical Operations and Data Management
Office: 1 858 376 2627
Fax: 1 858 432 7721
Mobile: 1 858 336 7540
lgrubbs@conatuspharma.com

TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF TABLES

1.0 STUDY SYNOPSIS

Protocol:
IDN-6556-07

Title:
A Multicenter, Double-Blind, Randomized Trial of IDN-6556 in Subjects Who had Hepatitis C Virus (HCV) Reinfection and Liver Fibrosis or Cirrhosis Following Orthotopic Liver Transplantation for Chronic HCV Infection and Who Subsequently Achieved a Sustained Virologic Response Following anti-HCV Therapy

Phase of Trial:
Phase 2

Objectives:
Primary

- To assess the effect of oral IDN-6556 on fibrosis or cirrhosis using the Ishak Fibrosis Score, in subjects with HCV reinfection and liver fibrosis or cirrhosis following orthotopic liver transplantation for chronic HCV who subsequently achieved a sustained virologic response following anti-HCV therapy

Secondary

- To determine the effects of oral IDN-6556 on necro-inflammatory sub-score of the modified Histological Activity Index
- To determine the effects of oral IDN-6556 on markers of mechanism of action and inflammation
- To assess the safety and tolerability of oral IDN-6556 in subjects status post orthotopic liver transplantation

Centers:
Multicenter, approximately 35 sites in the US.

Number of Subjects:
Approximately 60 subjects (40 subjects on IDN-6556: 20 on placebo) will be assigned in a 2:1 ratio to IDN-6556 25 mg BID or placebo. Up to 15 subjects with an Ishak score of F6 can be enrolled.

Design:
This is a double-blind, randomized, multicenter study involving subjects with chronic HCV who underwent liver transplantation; developed HCV-related liver fibrosis or cirrhosis; achieved a sustained virologic response (SVR) following anti-HCV therapy;

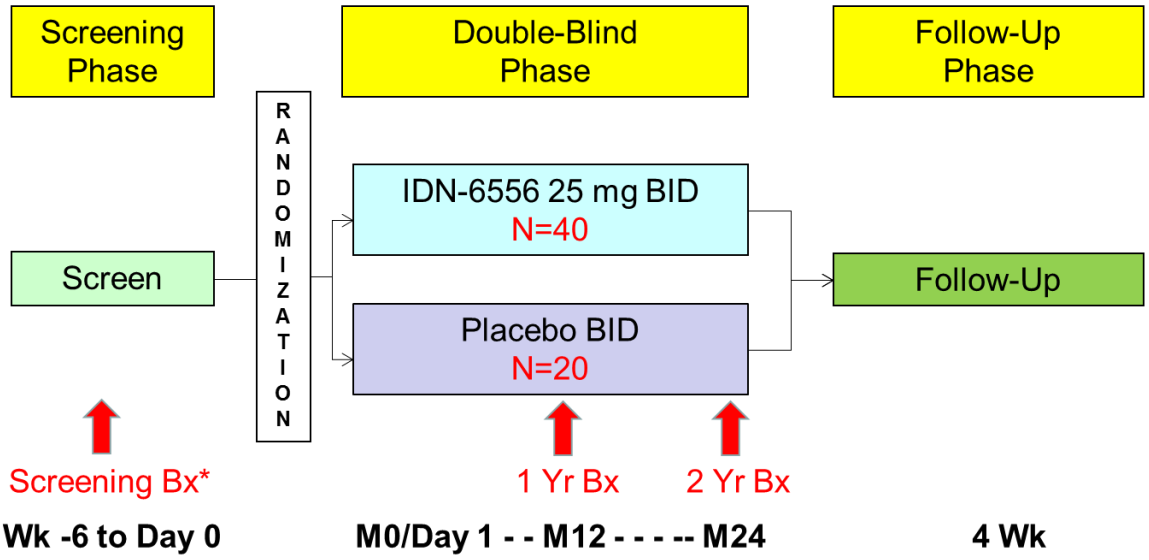
and still show demonstrable fibrosis or cirrhosis on liver biopsy. Upon successful screening, subjects will be randomized to receive 25 mg BID of IDN-6556 or placebo in a 2:1 ratio.

The randomization will be stratified based on the stage of fibrosis or cirrhosis at Baseline:

1. Ishak F2
2. Ishak F3 – F5
3. Ishak 6

The study treatment duration will be two years. All subjects who complete or discontinue from the study, for any reason, will have a follow-up visit four weeks after the end of treatment visit. Subjects who complete the study will have a liver biopsy performed at M24. Subjects who discontinue the study prematurely will be contacted and asked to sign a separate consent to return for a Month 24 liver biopsy (primary endpoint).

Schema:



*A biopsy must be conducted if previous biopsy (bx) was >3 months prior to Day 1 or if tissue is not available.

Dosage and Administration:
IDN-6556 will be double-blind with matching placebo. 25 mg of IDN-6556 or placebo will be administered orally twice a day, preferably with food.

Drug Supply:
IDN-6556 will be supplied in bottles containing 60 capsules, each containing 25 mg of IDN-6556. Matching placebo will be supplied in bottles containing 60 capsules.

Subject Entry Criteria (Refer to protocol **Sections 7.1 and 7.2** for full entry criteria)

Key Inclusion Criteria:

1. Male or female subjects of minimum adult legal age (according to local laws for signing the informed consent document), able to provide written informed consent, and able to understand and willing to comply with the requirements of the study
2. History of orthotopic liver transplantation for HCV-induced liver disease
   Note: Living donor or cadaveric transplantation will be permitted into the study. HCV positive donor livers will also be permitted into the study.
3. Diagnosis of HCV infection (HCV-RNA detectable in serum) and liver fibrosis or cirrhosis status post liver transplantation, and achieved a sustained virologic response (SVR) with anti-viral HCV treatment within 18 months of Day 1
   Note: For the purposes of this study, subjects must meet the definition of SVR as defined by the anti-HCV regimen used.
4. Liver fibrosis or cirrhosis on liver histology as read by central histopathologist of Ishak F2 to F6 within three months of Day 1
   Note: Baseline liver histology in close approximation of the three month window may be permitted on a case by case basis after discussion with the Medical Monitor.
5. Willingness to utilize two reliable forms of contraception (for both males and females of childbearing potential) from Screening to one month after the last dose of study drug

Key Exclusion Criteria:

1. Known active infection with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV)
2. History of renal transplant and/or severe renal impairment defined as eGFR (estimated glomerular filtration rate) of less than 30 mL/min/1.73 m^2
3. Evidence of tumor burden >Milan criteria, or evidence of micro- or macrovascular invasion in explanted liver
4. Hepatocellular carcinoma (HCC) at entry into the study
5. Concurrent sirolimus (rapamycin) use

6. History or presence of clinically concerning cardiac arrhythmias, or prolongation of Screening (pre-treatment) QTcF interval of > 480 milliseconds (msec)
7. Subjects with diagnosed or suspected systemic lupus erythematosus (SLE) and/or rheumatoid arthritis (RA)
8. If female: known pregnancy, positive urine or serum pregnancy test, or lactating/breastfeeding.

Criteria for Evaluation:

Safety Variables:
Safety evaluations will be based on adverse event (AE) reports. These will be coded using MedDRA to preferred terms, sorted by body system, and compared between the two treatment groups.

1. Serious adverse events will be analyzed separately
2. Clinical laboratory variables will be evaluated in the context of coinciding clinical adverse events when necessary

Efficacy Variables:
Efficacy Endpoints:
- Ishak Fibrosis Score
- Necro-inflammatory sub-score of the modified Histological Activity Index
- Biomarkers of apoptosis
- Liver function (e.g., ALT, AST, bilirubin)
- Transient elastography (to be performed at select centers only)

Exploratory Endpoint:
- Morphometric image analysis to quantify collagen deposition

Statistical Methods:
All endpoints will be tested at a two-sided statistical significance level of 0.05.

For the comparison of Ishak Fibrosis Scores at 24 months, subjects will be classified into one of the following three categories:

- Category 1. Regression at 24 months defined as a greater than or equal to a one point improvement in Ishak Fibrosis Score from Baseline.
- Category 2. Stable disease at 24 months defined as no change from Baseline in the Ishak Fibrosis Score from Baseline.

- Category 3. Progression at 24 months defined as a greater than or equal to a one point worsening from Baseline in the Ishak Fibrosis Score from Baseline or death/re-transplantation

Changes in the Ishak Fibrosis Score at 24 months will be analyzed by a logistic regression model, appropriate for the analysis of ordinal categorical data, to derive the odds ratio and associated 95% confidence interval for IDN-6556 against placebo. The model will allow adjustment for the following variables:

- Baseline Ishak Fibrosis Score
- Immunosuppression regimen (classified into one of five groups: tacrolimus with/without steroids; cyclosporine with/without steroids; other)
- Age of the transplant donor
- Age of the recipient

Adverse events, vital signs, ECGs, liver and abdominal ultrasounds, and routine laboratory test data will be explored through the use of standard presentations of descriptive statistics.

2.0 LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE(s)	adverse event(s)
AFP	α-fetoprotein
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	*bis in die,* twice daily
BMI	body mass index
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
C-G	Cockcroft-Gault
CIOMS	Council for International Organization of Medical Sciences
cCK18	caspase cleaved cytokeratin 18
Cl	chloride
CO_2	carbon dioxide
CRA	Clinical Research Associate
CRF	case report form
CRP	c-reactive protein
CS	clinically significant
CT	computed tomography
dL	deciliter
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
e.g.	*exempli gratia,* for example
eGFR	estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
EOT	end of treatment
ET	early termination
FAS	full analysis set

FDA	US Food and Drug Administration
flCK18	full length cytokeratin 18
g	gram(s)
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GMP	good manufacturing practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
Hct	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	investigator's brochure
IBC	iron binding capacity
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
i.e.	*id est,* that is
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intention-to-treat
IWRS	Interactive Web Randomization System
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MedDRA	Medical Dictionary for Regulatory Activities

MDRD	Modification of Diet in Renal Disease
Mg	magnesium
mL	milliliter
mm	millimeter
MPV	mean platelet volume
MRI	magnetic resonance imaging
msec(s)	millisecond(s)
Na	sodium
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NCS	not clinically significant
OTC	over-the-counter
pH	hydrogen ion concentration
POLT	post orthotopic liver transplantation
PP	per-protocol
QD	*quaque die,* once daily
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
sec(s)	second(s)
SLE	systemic lupus erythematosus
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
SVR4	sustained virologic response 4 weeks after therapy
SVR24	sustained virologic response 24 weeks after therapy
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell

3.0 ETHICS

The study will be conducted in accordance with Conatus standards that comply with regulations relating to Good Clinical Practice (GCP). These include the EU Clinical Trials Directives (2001/20/EC, 2005/28/EC, and subsequent amendments), International Conference on Harmonisation Guideline for Good Clinical Practice E6, 21CFR Part 312, and applicable regulatory requirements.

The ethical requirements of Institutional Review Boards/Independent Ethics Committees (IRB/IECs) and the Informed Consent Forms (ICFs) are discussed in **Section 14, Administrative Aspects**.

4.0 INTRODUCTION

4.1 Background

Chronic liver disease is associated with increased rates of hepatic lobular inflammation and hepatocyte apoptosis. While the etiology of liver diseases differs considerably (viral, alcohol, autoimmune, etc.), the pathological disease patterns across chronic liver diseases have similar tissue responses to injury. Chronic insults cause chronic necro-inflammation with increased apoptotic rates and may induce hepatic fibrosis, which typically progresses to cirrhosis. Subjects with cirrhosis may develop liver failure and/or hepatocellular carcinoma.

Hepatitis C virus (HCV)-associated liver disease continues to be the most common indication for liver transplantation in the US, accounting for nearly 25% of all liver transplants[1]. In the HCV-infected, HCV recurrence and reinfection of the liver graft status post orthotopic liver transplantation (POLT) is almost universal and characterized by accelerated progression of liver disease.

The absence of a preventative strategy for HCV reinfection after transplant is a major challenge for the HCV-infected recipients undergoing liver transplantation. Clinicians have successfully treated HCV-infected POLT population with interferon, ribavirin, and/or protease inhibitor-containing regimens, although these regimens were complicated by the necessity of close subject monitoring and by enhanced adverse effects of the combination treatments[2,3,4]. Data presented at the 2013 annual meeting of the American Association for the Study of Liver Diseases (AASLD) showed that an interferon-free combination of sofosbuvir plus ribavirin led to early viral clearance (SVR4) in about 75% of those subjects treated after transplantation[5]. Although it is too early to determine the sustained virologic response at Week 24 (SVR24) with this regimen, it is anticipated that a large number

of post-transplant subjects may be treated with this interferon-free, all-oral therapy once sofosbuvir is readily available.

There are data to suggest that with eradication of the HCV virus, improvements in liver fibrosis can be seen in the post-transplant population[6,7,8]. However, amelioration of inflammatory activity, and deceleration of fibrosis progression is a gradual process over the course of many years[9]. This placebo-controlled study is designed to evaluate the effects of IDN-6556, compared to placebo, on markers of apoptosis and inflammation, and liver histology.

4.2 Study Rationale

The Investigator's Brochure (IB) contains a summary of the data and information collected about IDN-6556 (including principal data and findings from preclinical, toxicological, and clinical studies conducted to date).

IDN-6556 is a novel small molecule irreversible caspase inhibitor. Caspases are enzymes responsible for executing apoptotic pathways, or programmed cell death, and activating cytokines such as IL-1β and IL-18. The apoptotic pathway has been previously shown to play an important role in the formation and progression of hepatic fibrosis, leading to the hypothesis that inhibition of caspases may have significant therapeutic benefit for the treatment of liver fibrosis, independent of the underlying disease state (e.g., viral infection, fatty liver, etc.). Activation of pro-inflammatory cytokines such as IL-1β has also been shown to play a role in hepatic injury. IDN-6556 has shown specificity in assays measuring caspase inhibition, and prevented apoptosis in a variety of cellular assays. IDN-6556 demonstrated efficacy in a number of animal models of liver disease, as well as in models of damage to other organ systems. Human studies have demonstrated that IDN-6556 can lower serum transaminases after intravenous or oral administration. Treatment with IDN-6556 was also associated with statistically significant reductions in elevated activated serum caspases and cCK18, a caspase cleaved substrate, indicating that IDN-6556 works by the presumed mechanism of action of inhibiting caspases.

In subjects who received a liver transplant and were successfully treated and achieved an SVR, fibrosis and inflammation were still present up to 5 years after treatment[9,10,11]. In general, fibrosis stabilized or regressed in most subjects with increases in fibrosis in only a small subset of subjects. In general, inflammation/ necro-inflammation was still present, but reduced as compared to pre-treatment. A caspase inhibitor, such as IDN-6556, could have clinical utility by reducing apoptosis rates and inflammation, which would also reduce the stimulus for fibrogenesis. Given this rationale, this study will evaluate the efficacy and safety of IDN-6556 in subjects with chronic hepatitis C virus (HCV) infection who have undergone

orthotopic liver transplantation, achieved an SVR, and still show demonstrable fibrosis or cirrhosis on liver histology.

5.0 STUDY OBJECTIVES

The objectives of the study are as follows:

Primary

- To assess the effect of oral IDN-6556 on fibrosis or cirrhosis using the Ishak Fibrosis Score, in subjects with HCV reinfection and liver fibrosis or cirrhosis following orthotopic liver transplantation for chronic HCV who subsequently achieved a sustained virologic response following anti-HCV therapy

Secondary

- To determine the effects of oral IDN-6556 on necro-inflammatory sub-score of the modified Histological Activity Index
- To determine the effects of oral IDN-6556 on markers of mechanism of action and inflammation
- To assess the safety and tolerability of oral IDN-6556 in subjects status post orthotopic liver transplantation

6.0 STUDY DESIGN

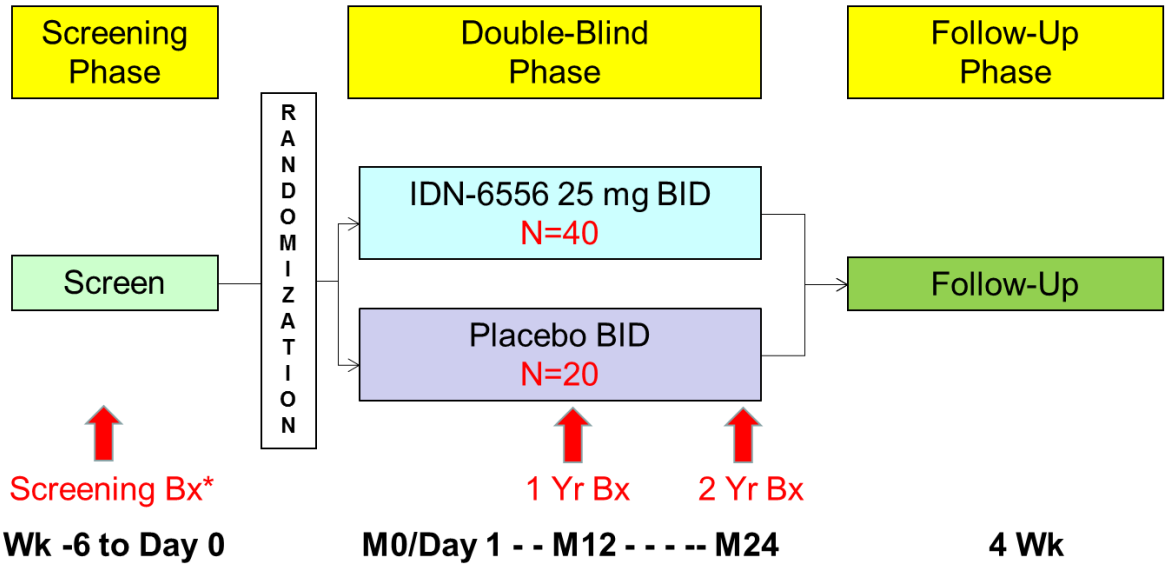
This is a double-blind, randomized, multicenter study involving subjects with chronic HCV who underwent liver transplantation; developed HCV-related liver fibrosis or cirrhosis; achieved a sustained virologic response (SVR) following anti-HCV therapy; and still show demonstrable fibrosis or cirrhosis on liver biopsy. Upon successful screening, subjects will be randomized to receive 25 mg BID of IDN-6556 or placebo in a 2:1 ratio.

The subjects will be stratified based on the stage of fibrosis or cirrhosis at Baseline:

1. Ishak F2
2. Ishak F3 – F5
3. Ishak 6

The study schema is outlined is Figure 6.1.

Figure 6.1 Study Schema



*A biopsy must be conducted if previous biopsy (bx) was >3 months prior to Day 1 or if tissue is not available.

Appendix I, the Schedule of Events Table*, indicates which procedures and evaluations will be performed throughout the study. An overview of key events is described below.

Screening Phase (Week -6 to Day 0): Subjects will sign an informed consent form (ICF) before any study-related procedures are performed. Subjects will be screened to determine their eligibility. Medical history and medication record (prior and concomitant medications) will be obtained for all subjects. A physical examination and a series of laboratory and diagnostic tests will be performed as described in the Schedule of Events. After confirming initial eligibility criteria, availability of prior liver biopsy will be assessed and a liver biopsy conducted if needed. The liver biopsy slides must be submitted to the central histopathologist who will confirm subject's eligibility prior to randomization.

* If any discrepancies should be found between the text of the protocol and the Schedule of Events Table, the table will predominate.

Double-Blind Phase (Month 0/Day 1 through to Month 24):
During treatment, for safety and efficacy, all subjects will be evaluated frequently through a series of physical examinations, laboratory tests, and diagnostic tests as described in the Schedule of Events.

All subjects who prematurely discontinue the study during the Double-Blind Phase, regardless of the cause, will be contacted and asked to sign a separate consent to return for a Month 24 liver biopsy. If premature discontinuation is within approximately 42 days of the originally scheduled Month 24 visit, the liver biopsy may be performed at the time of premature discontinuation. All liver biopsy slides must be submitted to the central histopathologist.

However, all subjects who discontinue prematurely **s**hould also undergo all other assessments, as outlined for End of Treatment (see **Section 8.3.2** and **Appendix I**).

Follow-up Phase (4 Weeks after End of Treatment):
All subjects will return for a follow-up visit four weeks after completion of treatment. The visit will include a physical examination, updating of medication records, reporting of any adverse events, and laboratory tests. (i.e., four weeks after early termination) should occur.

7.0 STUDY POPULATION

Approximately 60 subjects who underwent orthotopic liver transplantation for chronic HCV, developed HCV-related liver fibrosis or cirrhosis, achieved a sustained virologic response with anti-viral treatment, and still have demonstrable fibrosis or cirrhosis on liver histology will be enrolled. Up to 15 subjects with an Ishak score of F6 can be enrolled.

Table 7.1 Treatment Arm Allocation

Treatment Arm	N
IDN-6556 25 mg BID	40
Placebo BID	20
TOTAL	60

Subjects will be enrolled at approximately 35 clinical sites in the US. Expected duration of subject participation is as follows:

Table 7.2 Duration of Subject Participation

Time expected for all subjects to be enrolled:	Approximately 12 months
Duration of individual subject participation:	Approximately 2.2 years (6 weeks Screening, 2 years treatment, and 4 weeks for follow-up)

7.1 Inclusion Criteria

To participate in this study, subjects must meet **all** of the following criteria:

1. Male or female subjects of minimum adult legal age (according to local laws for signing the informed consent document), able to provide written informed consent, and able to understand and willing to comply with the requirements of the study
2. History of orthotopic liver transplantation for HCV-induced liver disease
   Note: Living donor or cadaveric transplantation will be permitted into the study. HCV positive donor livers will also be permitted into the study.
3. Diagnosis of HCV infection (HCV-RNA detectable in serum) and liver fibrosis or cirrhosis status post liver transplantation, and achieved a sustained virologic response (SVR) with anti-viral HCV treatment within 18 months of Day 1
   Note: For the purposes of this study, subjects must meet the definition of SVR as defined by the anti-HCV regimen used.
4. Liver fibrosis or cirrhosis on liver histology as read by central histopathologist of Ishak F2 to F6 within three months of Day 1
   Note: Baseline liver histology in close approximation of the three month window may be permitted on a case by case basis after discussion with the Medical Monitor.
5. Available liver tissue for central read (ten, 4-microns-thick, unstained liver sections)
6. Willing to undergo protocol-determined liver biopsies during the study
7. Hemoglobin ≥ 11 g/dL, platelet count ≥ 75 x 10^9/L, WBC ≥ 2.0 x 10^9/L
   Note: As these parameters may be influenced by immunosuppressive therapy, small variances may be permitted on a case by case basis after discussion with the Medical Monitor.
8. On stable doses of immunosuppressant therapy for ≥ 3 months prior to Day 1
9. Willingness to utilize two reliable forms of contraception (for both males and females of childbearing potential) from Screening to one month after the last dose of study drug

7.2 Exclusion Criteria

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

1. Known active infection with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV)
2. History of renal transplant and/or severe renal impairment defined as eGFR (estimated glomerular filtration rate) of less than 30 mL/min/1.73 m^2
3. Subjects with post-transplant liver fibrosis of any etiology other than chronic HCV infection
4. History of autoimmune hepatitis
5. History of autoimmune cholestatic disease
6. Wilson's disease, defined by ceruloplasmin below the limits of normal and liver histology consistent with Wilson's disease
7. Alpha-1-antitrypsin deficiency defined by serum alpha-1-antitrypsin level less than normal and liver histology consistent with alpha-1-antitrypsin deficiency
8. Hemochromatosis or secondary iron overload as defined by the following:
   a. Presence of 3+ or 4+ iron on liver biopsy stain or a history of previous phlebotomy for iron overload, or
   b. Iron saturation (serum iron/IBCx100%) of greater than 50%
9. Subjects with diagnosed or suspected systemic lupus erythematosus (SLE) and/or rheumatoid arthritis (RA)
10. Drug induced liver disease defined on the basis of typical exposure and history of ingestion of drugs known to produce hepatic injury (including but not limited to high dose estrogens, tetracycline or amiodarone) in the previous six months
11. Cholestatic liver disease
12. Inflammatory bowel disease
13. Bile duct obstruction as shown by imaging studies
14. Alpha-fetoprotein levels > 200 ng/mL
15. Evidence of tumor burden > Milan criteria, or evidence of micro- or macrovascular invasion in explanted liver
16. Hepatocellular carcinoma (HCC) at entry into the study
17. Subjects with active or history of non-liver malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas)
18. History of alcohol abuse within the last year
19. History of pancreatitis
20. Concurrent sirolimus (rapamycin) use
21. Evidence of rejection of implanted liver within three months of Day 1, unless adequately treated and resolved prior to Day 1
22. Any drugs known to cause fibrosis, with the exception of immunosuppressive therapy, six months prior to dosing and throughout the study

23. History or presence of clinically concerning cardiac arrhythmias, or prolongation of Screening (pre-treatment) QTcF interval of > 480 milliseconds (msec)
24. Any subject who has received any investigational drug or device within 30 days of dosing or who is scheduled to receive another investigational drug or device in the course of the study
25. Active or latent tuberculosis on chest x-ray at study entry
26. Significant systemic or major illness other than liver disease, including coronary artery disease, cerebrovascular disease, pulmonary disease, renal failure, serious psychiatric disease, that, in the opinion of the Investigator would preclude the subject from participating in and completing the study
27. Spontaneous bacterial peritonitis or any other active systemic infection at the time of entry into the study unless adequately treated with antibiotics
28. Decompensated or severe liver disease defined by one or more of the following criteria:
    a. INR > 1.6
    b. Total bilirubin ≥ 1.5 x ULN
    c. Serum albumin below normal
    d. AST or ALT > 10 x ULN during the Screening Phase
    e. Diuretic-resistant ascites. (Ascites that is well-controlled on stable medication is NOT exclusionary)
    f. Encephalopathy grade 2-4 according to the Child-Turcotte-Pugh score. (Encephalopathy that is well-controlled on stable medication is NOT exclusionary)
    g. Untreated esophageal varices that are – in the opinion of the investigator – at high risk for bleeding
    h. History of variceal hemorrhage
29. If female: known pregnancy, positive urine or serum pregnancy test, or lactating/breastfeeding.

7.3 Subject Identification

During the Screening period, subjects will be identified by a unique screening number and by either their initials (first, middle, last) or de-identified initials (e.g., AAA, BBB, etc.). On Month 0/Day 1, subjects will be identified by a unique four-digit subject number and initials. Only qualified subjects will be assigned a subject number.

7.4 Randomization Procedure

The assignment to IDN-6556 or placebo will be performed randomly. The randomization schedule will be generated using a validated randomization program and verified for accuracy using strict quality control procedures.

The assignment of subject number and treatment assignment will be centrally coordinated through the study's Interactive Web Randomization System (IWRS) to ensure that appropriate stratification, based on stage of Baseline Ishak Fibrosis score (Ishak F2, F3 – F5 or F6), occurs at randomization. Subject numbers will be assigned by the IWRS.

7.5 Blinding/Unblinding Procedures

The Investigators and the Medical Monitor(s) will be able to unblind subjects through the IWRS when it is medically imperative to know whether a subject is receiving IDN-6556 or placebo. The emergency unblinding should only be instituted by the Investigator or the Medical Monitor(s). Each Investigator will make arrangements to ensure that access to the secure internet site (i.e., individual user name and password) is maintained in strict confidence to prevent a compromise of subject blinding by non-study or unauthorized individuals.

Only in the event of an adverse event (AE) that the Investigator feels cannot be adequately treated without knowing the identity of the study drug should the medication code be broken for an individual subject. Every effort must be made to contact Conatus and/or the Medical Monitor before breaking the blind, or if in an emergency, as soon as possible thereafter (no later than 24 hours after emergency unblinding). Similarly, if the Medical Monitor breaks the blind for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within study correspondence the rationale, circumstances, and the person or persons being informed about the unblinding.

If the blind is broken, an entry must be made in the case report form (CRF) that contains the reason that the blind was broken and the name of the person contacted at Conatus or designee.

Access to randomization codes and corresponding treatment assignment will also be made available through the IWRS to the appropriate Conatus designee(s) and individual(s) who are responsible for reporting serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities and should be accessed only in the event of a medical emergency or as needed for regulatory agency notifications. No other Conatus personnel will have access to blinded subject treatment codes until all study data have been entered onto the study database and validated, and the database locked.

8.0 STUDY ASSESSMENTS AND CONDUCT

8.1 Efficacy and Safety Assessments

8.1.1 Liver Biopsy

A screening liver biopsy must be performed prior to randomization if the prior biopsy was done more than 3 months prior to Day 1, or if tissue from the previous biopsy is not available. Ten (10) unstained liver biopsy sections, cut 4-microns-thick, must be submitted to the central histopathologist who will confirm subject's eligibility prior to randomization. Generally, the liver biopsy should be the last assessment performed during the Screening Phase prior to randomization and should only be performed in subjects who fulfill all other inclusion criteria.

After randomization, yearly (12 months ± 42 day window) liver biopsies will be performed during the Double-Blind Phase of the study. In the event that a subject is withdrawn from the study prior to the 24 Month visit. The subject will be contacted and asked to sign a separate consent to return for the Month 24 liver biopsy. If premature discontinuation is within approximately 42 days of the originally scheduled Month 24 visit, the liver biopsy may be performed at the time of premature discontinuation. All reasonable attempts should be made to continue to follow the subject for the duration of the study follow-up period.

For all liver biopsies conducted during the Double-Blind Phase, 10 unstained sections, cut 4-microns-thick, must be available for analysis by the central histopathologist. In addition, all liver biopsies performed during the study should be of adequate quality to enable morphometric quantification of fibrosis and smooth muscle actin as well as meaningful interpretation of the histology by the central histopathologist.

Lastly, all liver biopsies taken during the course of the study, regardless of the indication (i.e., both protocol-defined and those performed for other clinical indications) must be assessed at the local institution and forwarded to the central histopathologist for assessment as well as being assessed at the local institution. In the event of any discrepancy between the local and central histopathology reports, the latter shall prevail.

Additional liver biopsies should be performed for subjects who show signs and symptoms of clinical worsening. Criteria for additional liver biopsy include:

- If the ALT at Baseline is ≤ 60 IU/L and it is raised to ≥ 3X ULN on two separate occasions separated by at least one week

- If the ALT is >60 IU/L at Baseline and it is raised to ≥ 2X Baseline value on two separate occasions separated by at least one week
- Any sustained rise in ALT above either ULN (if Baseline was below ULN) or above Baseline (if Baseline was above ULN) together with sustained increases in neutrophil count and/or C-reactive protein (CRP) and/or α-fetoprotein on at least two occasions separated by at least one week
- Any clinical concerns that the Investigator may have that, in their opinion, requires an additional biopsy

8.1.2 Medical History and Physical Examinations

Medical history will be taken at Screening. A comprehensive physical examination will be performed at the Screening visit and on-study visits as specified in the Schedule of Events. The physical examination will include the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen (including liver examination), extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes off, and height (Screening visit only) will be recorded at the specified visits. Each subject's body mass index (BMI) will be calculated. If additional physical examinations are performed during the study, the results will be captured as study data.

Given that the subjects enrolled in the study are on long-term immunosuppression with drugs such as cyclosporine and/or tacrolimus, they have an increased risk of development of lymphoma and other malignancies, particularly of the skin, due to prolonged immunosuppression. Thorough clinical evaluations, e.g., assessment of symptoms and physical examinations, etc., must be performed during the study and at follow-up visits in order to assess for any potential malignancies.

8.1.3 Vital Sign Measurements

Evaluation of the respiratory rate will be measured by counting the inhalations for one minute. Heart rate, systolic and diastolic blood pressure, and temperature measurements ('vital signs') will be performed. If clinically significant findings occur, as determined by the Investigator, then that measurement will be repeated at medically appropriate intervals until the value returns to within an acceptable range.

8.1.4 Liver and Abdominal Ultrasound, and Other Imaging

A comprehensive liver and abdominal ultrasound (including the examination of the biliary tree) will be performed at the Screening visit and on-study visits as specified in the Schedule of Events. If the subject had a liver and abdominal ultrasound performed within three months of Screening, the prior ultrasound results can be

used for study entry. If the subject had an abdominal MRI or CT scan within three months of Screening, it can be utilized in lieu of the ultrasound at Screening.

If the Investigator deems it medically necessary, additional liver and abdominal ultrasounds (or higher resolution imaging), other than those specified by the protocol, may be performed during the study. If additional ultrasounds (or other imaging) are performed during the study, the reasons for and results of the additional imaging will be captured as study data.

In addition, if any abnormalities are found during on-treatment ultrasounds, the Investigator should utilize normal clinical practice for additional subject follow-up and discuss treatment (dis)continuation with the Conatus Medical Monitor.

8.1.5 Transient Elastography (FibroScan®)

FibroScan® is a novel, non-invasive, reproducible method for measuring liver stiffness. An ultrasound transducer probe is mounted on the axis of a vibrator; vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing a wave that propagates through the underlying tissue. The propagation velocity of the wave is then measured. The velocity is directly related to tissue stiffness; the stiffer the tissue, the faster the wave propagates. Preliminary reports suggest that FibroScan® accurately predicts hepatic fibrosis in chronic HCV subjects.

FibroScan® measurements will be performed at select centers every six months as indicated in the Schedule of Events (see **Appendix I**), and the results will be evaluated against liver biopsy and other biomarkers of disease severity. The protocol for the FibroScan® procedure is provided in **Appendix IV**. Centers who elect to participate in the FibroScan® measurements will make every effort to collect the Screening and post-Screening measurements as indicated in the Schedule of Events.

8.1.6 Chest X-Ray

A chest x-ray will be performed at Screening to rule out entry of subjects who have radiological evidence of active or latent pulmonary tuberculosis. If additional chest x-rays are medically required and performed during the study, the reasons for and results of the additional chest x-rays will be captured as study data.

8.1.7 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at Screening and at subsequent visits, as specified in the Schedule of Events. **Original** ECGs with interval printouts and rhythm strips run at 25 mm/sec must be provided as source documentation.

Automatically calculated QTc intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the automatically calculated QTc interval is greater than 480 msec, or has increased by 50 msec or more over the Baseline value, it will be manually over-read by the Investigator or designated ECG reviewer. The ECG parameters that will be assessed include heart rate, PR interval, QRS interval, and QTc interval. If QTc interval prolongation exceeding these limits is verified during treatment, the subject's medical background should be examined closely for risk factors that may have contributed to the event, including genotyping for hereditary long QTc syndromes, if appropriate.

Any sign of arrhythmia should be noted. During treatment, any indication of QTc prolongation or Torsade de Pointes, a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline, must be recorded as an adverse event and reported to the Conatus Medical Monitor.

The decision to continue the treatment of any subject with prolonged QTc interval must be discussed and agreed upon by the Investigator and the Conatus Medical Monitor. All such subjects, including subjects with cardiac arrhythmias, should be monitored closely. If appropriate, ECG monitoring should be performed until the QTc intervals and waveform morphology have returned to normal. If the QTc interval prolongation or abnormal rhythm persists, the Conatus Medical Monitor must be contacted.

8.1.8 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood and urine sample volumes will meet the laboratory's specification.

Table 8.1 Clinical Laboratory Tests

Hematology	Coagulation	Chemistry		Urinalysis	Other
		Liver Enzymes & Other Function Tests	Other Chemistry		
Hgb, Hct, RBC count, WBC count and differential, Platelet count, MCV, MCH, MCHC, MPV	INR, PT, PTT	AST, ALT, GGT, Total bilirubin, Direct bilirubin, AP	Na^+, K^+, Cl^-, Total CO_2 (bicarbonate), Ca^{++}, Mg^{++}, Phosphate, Creatinine, Serum creatinine clearance (calculated), BUN, Uric acid, Glucose, Total protein, Albumin, Globulin, LDH, CRP	Specific gravity, pH, Blood, Protein, Glucose, Ketones, Bilirubin	α-fetoprotein CA-19-9 β-HCG serum pregnancy test* Urine pregnancy test* Immunosuppressant concentration

*For women of childbearing potential

Table 8.2 Serum Biomarkers

Serum Biomarkers#
cCK18/M30, Caspase 3/7, flCK18/M65, ELF (component scores also to be reported), IL-18

#Proposed biomarkers to be studied. Additional biomarkers may be evaluated.

8.1.9 Additional Laboratory and Clinical Assessments for Safety

Additional laboratory and clinical assessments should be performed for subjects who show the following signs and symptoms of potential drug induced liver injury. The following laboratory and clinical assessments should be performed:

- If ALT or AST is > ULN at Baseline and an increase of ≥ 2X Baseline occurs in ALT, AST and/or total bilirubin, prompt repeat testing within 48 to 72 hours must be performed. In addition, the subject must be evaluated for any adverse events, including symptoms suggestive of worsening liver disease (e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, etc.). Subsequent close observation is required.

- If ALT, AST and total bilirubin are < ULN at Baseline and there is an increase of > 3X Baseline in any of these parameters, prompt repeat testing within 48 to 72 hours must be performed. In addition, the subject must be evaluated for any adverse events including symptoms suggestive of worsening liver disease (e.g., anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, etc.). Subsequent close observation is required.

The need for prompt repeat testing is especially critical if ALT or AST is much greater than 3X ULN and/or total bilirubin is greater than 2X ULN. If symptoms persist or repeat testing shows ALT or AST >3X ULN for subjects with normal Baseline values or 2-fold increases above Baseline values for subjects with elevated values before study drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening. If close observation and monitoring is not possible, the study drug must be discontinued.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin)
- Considering further gastroenterology and/or hepatology consultations if appropriate

8.1.10 Pharmacokinetic Sampling

8.1.10.1 IDN-6556 Pharmacokinetic Sampling

Up to 5 mL of whole blood will be collected at each sampling time point by using tubes provided by the central laboratory. Samples will be obtained according to the Schedule of Events and processed according to the instructions provided by the

central laboratory. After processing, each sample is to be harvested, equally divided into two aliquots, and transferred into cryotubes. Aliquots are to be frozen at less than or equal to (≤) -70°C.

Samples are to be shipped to a central laboratory specified by Conatus. The samples will be assayed at the laboratory using validated methods.

8.1.10.2 Immunosuppression Pharmacokinetic Sampling

Up to 10 mL of whole blood will be collected at each sampling time point by using tubes provided by the central laboratory. Samples will be obtained according to the Schedule of Events and processed according to the instructions provided by the central laboratory. After processing, each sample is to be harvested, equally divided into two aliquots, and transferred into cryotubes. Aliquots are to be frozen at less than or equal to (≤) -20°C.

Samples are to be shipped to a central laboratory specified by Conatus. The samples will be assayed at the laboratory using validated methods.

8.1.11 Biomarker Sampling

Up to 12 mL of whole blood will be collected at specified visits by using tubes provided by the central laboratory. Samples will be obtained according to the Schedule of Events. After processing, each sample is to be harvested, divided into multiple aliquots as specified by the central laboratory, and transferred into cryotubes. Aliquots are to be frozen at less than or equal to (≤) -70°C.

Samples are to be shipped to a central laboratory specified by Conatus. The samples will be assayed at the laboratory using validated methods.

8.1.12 Blood Volume

Table 8.3 summarizes the total blood to be collected over the course of the Screening, Double-Blind, and the Follow-up Phases of the study.

Table 8.3 Total Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples Per Study Phase			Total Volume (mL)
		Screening	Double-Blind	Follow-Up	
Hematology	5	1	10	1	60
Chemistry	5	1	11	1	65
Coagulation	5	1	6	1	40
Immunosuppression concentration	10	0	2	0	20
Immunosuppression PK	80	0	1	0	80
α-fetoprotein	5	1	4	0	25
CA 19-9	5	0	2	0	10
Biomarkers	12	0	7	1	96
Population IDN-6556 PK	5	0	2	0	10
IDN-6556 PK	40	0	1	0	40
IDN-6556 PK if ALT, AST or bilirubin increase*	5	0	1	0	5
Serum pregnancy test**	5	1	9	1	55
TOTAL					**506**

*Assumes a single case requiring PK sampling.
**For women of childbearing potential only

Note: Total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters. Additional blood samples may be taken at times specified by Conatus (or due to sample/test repeat) or if clinically indicated for safety.

8.2 Efficacy Assessments

8.2.1 Primary

The primary efficacy endpoint of the study will be change from Baseline in liver histology as defined as ≥1 point change in the Ishak Fibrosis Score at 24 months.

8.2.2 Secondary

The secondary efficacy endpoint will be the effects on liver inflammation measured by the difference in responder rates in the necro-inflammatory sub-score of the modified Histological Activity Index between the two treatment groups (change defined as a movement by at least 2 points at 24 months compared with Baseline).

8.2.3 Additional

Effects on biomarkers of mechanism of action and inflammation, and liver function will be evaluated as additional endpoints.

8.2.4 Exploratory

An assessment of morphometric image analysis to quantify collagen deposition will be performed on liver histology.

8.3 Specific Study Visit Information

The following sections provide specific details of the assessments to be performed at each study visit. After a subject is entered into the study, the visit window from Day 1 to Month 6 will be ± seven days. After Month 6, the visit window will be ± 14 days. However, every effort should be made to maintain the nominal visit schedules of subjects as predicated by the date of the Month 0/Day 1 visit.

Except at Screening, the liver biopsy window will be ± 42 days. In the event that a subject is withdrawn from the study prior to the 24 month visit, the subject will be contacted and asked to sign a separate consent to return for a Month 24 liver biopsy unless a biopsy was performed within 42 days of the Month 24 visit.

8.3.1 Screening Phase (Week -6 to Day 0)

The following study evaluations will be performed during the course of the Screening period:

- Signed informed consent
- Inclusion and exclusion criteria
- Complete medical and surgical histories
- Record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin, mineral, and/or herbal supplements/therapies
- Subject demographics
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Complete physical examination, including height and weight
- Liver and abdominal ultrasound (prior ultrasound, or superior imaging, may be utilized if performed within 3 months of Screening)
- 12-Lead ECG
- Chest X-ray
- Liver biopsy (refer to the biopsy window in **Section 8.1.1**)
- Transient elastography (at select centers only)
- Clinical chemistry, hematology, and coagulation
- Urinalysis
- α-fetoprotein

- Serum pregnancy test (for women of childbearing potential)

Since the Screening Phase can last up to 6 weeks, it is highly recommended that only key assessments and laboratory tests initially be conducted to confirm a subject's eligibility after signing of the informed consent document. The remainder of the screening assessments should only be performed for those subjects who pass the initial screening assessments.

Clinically meaningful, unexpected findings in the laboratory or clinical tests that may interfere with the study conduct need to be discussed with the Medical Monitor prior to entry into the study.

Once the subject's eligibility is confirmed, including confirmation of the fibrosis score by the central histopathologist, the subject will be randomized by IWRS to either IDN-6556 or placebo, and stratified by degree of Baseline Ishak Fibrosis Score (F2, F3-F5 or F6).

Subjects who initially fail screening may be re-screened after discussion with the Conatus Medical Monitor. Reasons for initial screen failure and eligibility for re-screening will be clearly documented.

8.3.2 Double-Blind Phase (Month 0/Day 1 through to Month 24/ Early Termination/ End of Treatment)

The following study evaluations will be performed during Double-Blind Phase as noted on the Schedule of Events:

- Record concomitant medications and therapies
- Vital signs (blood pressure, respiratory rate, pulse, and temperature)
- Physical examination, including weight, at yearly intervals
- 12-lead ECG at yearly intervals
- Liver and abdominal ultrasound every 6 months
- Transient elastography every 6 months (at select centers only)
- Liver biopsy at yearly intervals – refer to **Section 8.1.1** for requirements for additional biopsies
- Study drug administration and dispensation
- Compliance assessment (capsule count)
- Record adverse events
- Clinical chemistry and hematology. On Day 14, only clinical chemistry will be performed – refer to **Section 8.1.9** for requirements for additional laboratory and clinical assessments for safety

- Coagulation at Month 0/Day 1, Month 1, Month 6, and every 6 months thereafter
- Urinalysis at Month 0/Day 1 and every 6 months thereafter
- Blood sample for immunosuppressant concentration monitoring (Month 0/Day 1 and Day 14)
- Collection of up to 10 mL of blood for immunosuppressant pharmacokinetic analysis at predose, and at 0.5, 1, 2, 3, 4, 5, and 8 hours post dose at Month 1
- α-fetoprotein every 6 months♠
- CA 19-9 at Month 0/Day 1 and Month 24
- Collection of 12 mL of blood for serum biomarkers at Month 0/Day 1, Day 14, Months 1, 3, 6, 12, and 24 (Note: ELF test to be conducted every 6 months only)
- Collection of 5 mL of blood for population pharmacokinetic analysis at Months 12 and 24
- Collection of 5 mL of blood for pharmacokinetic analysis at predose, and at 0.5, 1, 2, 3, 4, 5, and 8 hours post dose at Month 1
- Collection of 5 mL of blood for pharmacokinetic analysis if repeat laboratory testing is required for elevated ALT, AST, and/or total bilirubin values
- Serum pregnancy test (for women of childbearing potential); except Month 0/Day 1, and Day 14
- Urine pregnancy test (for women of childbearing potential) at Month 0/Day 1 prior to study drug administration

The study procedures specified for Month 0/Day 1 should be performed prior to dosing with study drug.

In the event that a subject is withdrawn from the study prior to the 24 Month visit, the subject will be contacted and asked to sign a separate consent to return for the Month 24 liver biopsy. If premature discontinuation is within approximately 42 days of the originally scheduled Month 24 visit, the liver biopsy may be performed at the time of premature discontinuation.

♠ If elevations occur during the Double-Blind Phase of the study, Investigators should utilize normal clinical practice for follow-up of subjects and discuss treatment (dis)continuation with the Conatus Medical Monitor.

8.3.3 Follow-Up Phase (Month 25, 4 Weeks after Early Termination/End of Treatment)

All subjects will be seen four weeks after end of treatment. Follow-up procedures will consist of the following:

- Update of concomitant medications and therapies
- Vital signs (blood pressure, respiratory rate, pulse, and temperature)
- Physical examination, including weight
- Update of adverse events
- Clinical chemistry, hematology, and coagulation
- Urinalysis
- Collection of 12 mL of blood for serum biomarkers
- Serum pregnancy test (for women of childbearing potential)

If the subject discontinues the study early, all reasonable attempts should be made to complete the final follow-up phase, which may or may not coincide with the M24 liver biopsy.

8.4 Prior and Concomitant Medications

All prescription and 'over-the-counter' (OTC) medications, including supplements, taken by the subject during the 30 days before Screening will be recorded on the Concomitant Medications case report form. The generic drug name, indication, total daily dose, and dates of drug administration will be recorded. Any additions, deletions, or changes in the dose of these medications should be entered on the case report form.

Any current ongoing medications, including OTC drugs, will be allowed if not prohibited by the protocol and approved by the Investigator. Subjects must be instructed not to take any new OTC drugs during the study without first obtaining approval from the Investigator. Subjects should also be instructed to contact the Investigator if they develop any illnesses or any new medications.

Subjects should not take the following:

- Potentially hepatotoxic drugs (starting 30 days prior to dosing and throughout the study)
- Any drugs known to cause fibrosis, with the exception of immunosuppressive therapy (for six months prior to dosing and throughout the study)

It is expected that all subjects will be receiving immunosuppressant therapy during the course of the study. This should be tailored to the specific subject's

requirements. The reasons for any changes in background immunosuppressant therapy should be documented in the case report forms and the subject should continue with all study related procedures. In the event that a subject develops liver transplant rejection during the study, decisions about a subject's treatment regimen, including whether or not the subject will continue in the study, will be completely at the discretion of the Investigator.

8.5 Other Precautions, Restrictions, Drugs, and Alcohol

All subjects must take appropriate precautions to avoid excessive sun exposure due to the increased risk of malignancies, especially skin malignancies, with their requisite, long-term use of immunosuppressants. Subjects should also be advised that illicit drugs, drugs of abuse and excessive alcohol use will not be allowed from the start of the Screening to the end of the follow-up visits. If there is clear evidence of use of illicit drugs, drugs of abuse, or excessive alcohol use during study drug treatment, the Investigator must counsel the subject and determine whether continued study participation is appropriate.

8.6 Subject and Study Termination

8.6.1 Reasons and Procedures for Early Termination

Subjects may be withdrawn from the study at their own request, upon request of the Investigator, or by the Sponsor at any time and for any reason. Reasons for removing a subject from the study may include:

- the subject does not adhere to study rules and procedures;
- the subject wishes to withdraw from the study ;
- the subject develops an AE necessitating withdrawal, or requires an unacceptable concomitant medication;
- continuation of the subject is in violation of the inclusion and/or exclusion criteria;
- the Investigator feels it is in the subject's best interest to terminate participation;
- the study is terminated by the Sponsor.

All subjects who discontinue the study because of adverse events (AEs) will be followed up at suitable intervals in order to evaluate the course of the AE and to ensure the resolution or stabilization of the abnormality.

All subjects who prematurely discontinue the study, regardless of the cause, will be contacted and asked to sign a separate consent to return for a Month 24 liver biopsy. If premature discontinuation is within approximately 42 days of the originally scheduled Month 24 visit, the liver biopsy may be performed at the time of premature discontinuation.

However, subjects should undergo all other assessments during the final visit, scheduled for End of Treatment on the date of discontinuation (see **Sections 8.3.2** and **Appendix I**). A follow-up visit should be scheduled to occur 4 weeks following the early termination visit.

Female subjects who are discontinued prematurely due to a pregnancy should be followed as outlined in **Section 10.0**.

If a subject is lost to follow up (i.e., fails to return for study visits), reasonable efforts should be made to contact the subject and complete study termination procedures, in addition to the long-term follow-up of the subject.

8.6.2 Completion of the Study

The Investigator will document the completion or the reason for early withdrawal by a subject in the case report form. The following categories should be used to describe the early withdrawal reasons in the case report form:

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject (document reason)
- Adverse event(s)
- Administrative reasons (e.g., early termination of the study)
- Subject lost to follow-up
- Major protocol violation (with approval by the Sponsor)
- Death

If the study is prematurely terminated by Conatus, all reasonable attempts should be made to complete the final follow-up phase for all remaining subjects.

8.6.3 Termination of the Study

The study may be terminated prematurely, for any reason, by the Investigator with sufficient advance notice, per the terms of the contract with the Sponsor. The reason should be communicated in writing to the Sponsor.

Conatus reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the Investigator, if instructed to do so by Conatus, in a time frame that is compatible with each subjects' well-being.

9.0 INVESTIGATIONAL MEDICINAL PRODUCT

For the purpose of this protocol the term 'investigational medicinal product (IMP)' is interchangeable with the term 'study medication' and/or 'study drug'.

All study medication (IDN-6556 and matching placebo) will be manufactured according to Good Manufacturing Practice (GMP).

9.1 IDN-6556 and Placebo Supplies

The double-blind supplies of IDN-6556 will be in bottles containing 60 capsules, with each capsule containing 25 mg of IDN-6556. Matching placebo will also be supplied in bottles containing 60 capsules. Therefore, each bottle will contain a 30-day supply of study drug (IDN-6556 or placebo).

Subjects should be instructed to take one capsule in the morning and one capsule in the evening, preferably with food.

IDN-6556 and placebo supplies must be stored in a secure, lockable area. Subjects should be instructed to store their study drug bottles with the caps tightly closed in a safe area at room temperature. Study drug bottles should not be stored near heating devices, at high temperatures or humidity, or where children or pets have access to them.

9.2 Investigational Medicinal Product Packaging and Labeling

The packaging and labeling of study medication supplies will be performed according to GMP standards by a designated, qualified vendor.

IDN-6556 and placebo capsules will be dispensed to subjects in the provided bottles in sufficient quantities for continuation of treatment to at least the next scheduled visit, along with instructions for the proper method of taking the study drug.

All study drug bottles will carry a uniquely numbered label which will also contain the drug description and conditions for storage.

9.3 Investigational Medicinal Product Dispensing and Accountability

All study drugs must be dispensed in the original containers in order to assure stability of the drugs. At each visit, subjects must be instructed to return all, original, study-drug containers (even empty containers) and all unused capsules (in partially or completely full bottles) in order to adequately assess each subject's compliance with dosing instructions. The number of capsules remaining in the bottles should be counted at each visit to assess subject compliance with study drug administration. Every effort should be made to obtain all unused capsules and all dispensed bottles.

9.4 Investigational Medicinal Product Administration

Subjects will be instructed to take IDN-6556 or placebo twice daily, about the same time in the morning and evening, preferably with food.

Details of dosing information (e.g., dates of dosing, missed doses and dose adjustment, if any) are to be captured in the case report forms.

10.0 WARNINGS AND PRECAUTIONS

IDN-6556 has potential to be teratogenic (refer to the Investigator's Brochure for further details). There have been no studies with this compound in pregnant women. Teratology studies, conducted in rats and rabbits, demonstrated that IDN-6556 may be teratogenic. Therefore, IDN-6556 should not be used in pregnant women. IDN-6556 has also been found to reduce male and female fertility in rats. There have been no studies on the effect of IDN-6556 on fertility in men and women.

Both male and female subjects of reproductive potential must use two reliable forms of contraception from screening to one month after the last dose of study drug. Effective contraception is defined as abstinence or two reliable forms of contraception, including one barrier method, used simultaneously.

If pregnancy occurs in a female subject taking study drug, the subject should be instructed to immediately stop taking the study drug, and the Investigator should inform the Sponsor within 24 hours of the Investigator's learning of the pregnancy. If the female subject is in the Double-Blind Phase of the study, the treatment arm may be unblinded (after discussion between the Investigator and the Conatus Medical Monitor). If the female subject chooses to terminate the pregnancy, the Investigator should document the termination and contact the Conatus Medical Monitor to discuss whether continued participation of the subject in the study is appropriate. If the female subject chooses to continue the pregnancy, the procedures for withdrawing a subject from the study should be completed, and the

Investigator will attempt to obtain information on the outcome of the pregnancy. If the pregnancy goes to term, then the Investigator should also attempt to obtain information on the health of the infant after delivery and provide the information to the Sponsor.

If pregnancy occurs in a female subject after the Double-Blind Phase of the study but within one month of taking study drug, the Investigator should inform the Sponsor immediately.

If pregnancy occurs in the female partner of a male subject during the Double-Blind Phase of the study or within one month of taking study drug, the Investigator should inform the Sponsor immediately.

11.0 DOCUMENTATION OF DATA

11.1 Source Documentation

All data obtained in this study are source data. The clinical site study staff members will record the data on source documents immediately, except for data that are available on original printouts or as data files.

All clinical work conducted under this protocol will be conducted according to GCP rules. This includes an inspection by the Sponsor or their designee(s) and/or health authority representative(s) at any time. The Investigator will agree to the inspection of study-related records by representatives of the health authority(ies) and/or the Sponsor. If the study is to be audited by a health authority at a given site, the Investigator will agree to immediately notify the Sponsor upon receipt of the audit notification.

11.2 Data Entry in Database

All data will be entered electronically by the study personnel using electronic data capture (EDC) specifically designed for this study.

11.3 Query Checks

The raw data will be checked by appropriate programs for consistency and plausibility according to previously defined query checks documented in a data validation plan.

11.4 Coding of Adverse Events, Drugs, and Diseases

After data entry, the AEs will be coded according to the MedDRA dictionary. Concomitant medications will be coded according to the World Health Organization Drug Reference List.

11.5 Study Language & Translations

The primary study materials (protocol, correspondence, clinical study report) will be prepared in English. However, where the first language of the subject, study personnel, or others involved in the study (such as IRBs/IECs) is not English, appropriate arrangements will be made to have the relevant documents translated into the local language. In this case, the qualified translator will need to provide documentation to attest to the fact that the translated study documents are an accurate reflection of the original, English study documents.

Additional documents may need to be translated into English (e.g., transcripts of necessary additional hospital tests that may occur), and others (e.g., new safety information) may need to be translated into the local language. The Sponsor, or designee, will make arrangements for such translations to occur promptly.

12.0 STATISTICAL METHODS

12.1 Introduction

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol.

Should any of the assumptions of the statistical methods described below not be met, alternative methods will be applied and documented in the Clinical Study Report.

12.2 Parameters of Interest

12.2.1 Safety Variables

The following parameters will be recorded for the safety evaluation:

- Adverse events
- Vital signs (pulse, heart rate, respiration), physical examinations
- Clinical chemistry, hematology, coagulation, and urinalysis

- ECGs
- Liver and abdominal ultrasounds

12.2.2 Efficacy Variables

The following parameters will be recorded for the efficacy evaluation:

- Histologic changes defined as ≥1 point change in the Ishak Fibrosis Score
- Effects on liver inflammation in the necro-inflammatory sub-score of the modified Histological Activity Index. A responder will be defined as a subject who has improved by at least 2 points at 24 months on the necro-inflammatory sub-score of the modified Histological Activity Index from Baseline.
- Clinical outcomes defined as time to clinical worsening. Time to decompensation, re-transplantation, and/or death will be captured as clinical outcomes. (Note: Decompensation is defined as presence of: bleeding varices, encephalopathy, ascites requiring treatment and jaundice.)
- Effects on biomarkers of apoptosis and mechanism of action
- Effects on liver function parameters such as ALT, AST, bilirubin
- Changes in transient elastography (at select centers)

12.2.3 Other Variables

The following parameter will be assessed as an exploratory variable:

- Effects on liver collagen as measured by morphometric image analysis

12.3 Demographics and Baseline Characteristics

All continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum and maximum). Summary statistics for categorical variables will include frequency counts and percentages.

12.4 Analysis Populations

The safety analysis set consists of all randomized subjects who have received at least one dose of study medication, i.e., any dose of IDN-6556 or placebo. If the application of any study medication is not certain, the subject will be included in the safety analysis set. The analyses based on the safety analysis set will be conducted on an “as treated” basis, i.e., all subjects will be analyzed by the treatment they have actually received.

The Full Analysis Set (FAS) population consists of all randomized subjects who have received at least one dose of study medication, i.e., any dose of IDN-6556 or placebo. The analyses based on the FAS population will be conducted on an intention-to-treat (ITT) principle (i.e., all subjects will be analyzed with the group to which they were randomly assigned).

The Per Protocol (PP) population will be used as a sensitivity analysis of the primary endpoint. Criteria for assessing the PP population will be detailed in the Statistical Analysis Plan (SAP).

All safety analyses will be based on the safety analysis set. All efficacy analyses will be based on the intention-to-treat population

12.5 Sample Size

The sample size determination for this study is based on the Phase 2b screening methodology presented in Fleming and Richardson[12].

A total of 60 subjects will be treated in a 2:1 ratio to IDN-6556 or placebo. Treatment duration for all subjects will be two years. The primary outcome variable is change in Ishak Fibrosis Score at 24 months.

The primary analysis of this Phase 2 "screening" study is formally based on a three-category decision guideline. To be specific, the decision guideline for this study is based on whether the proportion of subjects who show a regression (i.e., improvement) of Ishak Fibrosis Score at 24 months for the IDN-6556 arm compared to the placebo arm is less than 5%, is from 5% up to 15%, or is at least 15%.

Note that these categories should not be interpreted as providing strict decision rules but rather as guidelines that will be factored into a broader scientific assessment of the benefit to risk profile of the IDN-6556 regimen. This broader assessment will include consideration of safety, of secondary efficacy endpoints, and of relevant information external to this study. Specifically, the decision guidelines for this study are:

1. If the estimated absolute increase in the proportion of subjects who show regression in Ishak Fibrosis Score is less than 5%, (e.g., less than an estimated increase from 30% to 35%), then the IDN-6556 regimen is not plausibly more efficacious than placebo; the formulation of this IDN-6556 regimen or its utility in this indication will be reconsidered.
2. If the estimated absolute increase in the proportion of subjects who show regression in Ishak Fibrosis Score is from 5% up to 15%, (e.g., an estimated increase from 30% to between 35% and 45%), then the IDN-6556 regimen is

plausibly more efficacious than placebo and if analyses of biomarkers suggest utility of the IDN-6556 regimen, should be evaluated definitively in a subsequent Phase 3 clinical study.

3. If the estimated absolute increase in the proportion of subjects who show regression in Ishak Fibrosis Score is at least 15%, (e.g., an estimated increase from 30% to greater than 45%), then the IDN-6556 regimen will be evaluated definitively in a subsequent Phase 3 study.

The operating characteristics for this three-category decision guideline (based on 100,000 simulated trials) are shown in the table below.

Table 12.1 Probabilities of Study Outcomes According to Various Levels of True Treatment Effect (TE)

	Probability of obtaining an estimated TE (active – placebo)		
TE	<5%	Of >5% but ≤15%	>15%
0	67%	22%	11%
5	52%	26%	22%
10	36%	27%	37%
15	23%	24%	53%
20	13%	19%	68%
25	7%	13%	80%
30	3%	8%	89%

Of note:

1. The false-positive error rate of the screening procedure is low. In particular, if the IDN-6556 regimen truly provides no improvement in the 2-year Ishak Fibrosis Score, then there is only an 11% chance of going forward to a Phase 3 study and only a 2.5% chance of false positive conclusion that the IDN-6556 regimen has statistically significant improvement in efficacy relative to placebo.
2. The false-negative error rate is acceptable. If the IDN-6556 regimen truly provides an absolute increase of 15%, (e.g., an increase from 30% to 45%), then there is only a 23% chance that the combination intervention would be discarded, and thus a 77% chance that it would be evaluated in a subsequent Phase 3 study. If the true absolute increase is 15%, there is a 20% chance that the IDN-6556 regimen will have a statistically significant improvement in efficacy relative to placebo and a 80% chance of a statistically significant difference if the true absolute increase is 37% (at the 2-sided 0.05 level).

12.6 Statistical Analysis

12.6.1 General

Where appropriate, parameters will be analyzed using descriptive methods. Continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, median, minimum and maximum). Summary statistics for categorical variables will include frequency counts and percentages. All subjects within the respective analysis set will be tabulated.

Graphical presentation of data may be performed.

12.6.2 Safety Analysis

Safety will be assessed by adverse events, laboratory tests, vital signs, physical examinations, ECGs, and liver and abdominal ultrasounds.

Adverse events will be tabulated by body system and preferred term. The number of entries, as well as the number of subjects will be reported. The nature, intensity, frequency, and relationship to IDN-6556 or placebo of adverse events will be described for all study subjects.

Results of laboratory tests, vital signs, physical examinations, and ECGs will be analyzed descriptively. Abnormal laboratory and ECG findings will be tabulated against appropriate cut-off points (e.g., ≥ 2 x ULN) using frequency counts and percentages.

Furthermore, any prior and concomitant medication will be described.

Graphical presentation of results will be performed, where appropriate.

12.6.3 Efficacy Analysis

Primary Endpoint: Change from Baseline in Ishak Fibrosis Score at 2-years

The primary analysis of the primary endpoint will test the change in Ishak Fibrosis Scores at 24 months between the treatment groups in the FAS Population using ITT principles.

Subjects will be classified into one of the following 3 categories:

- Category 1. Regression at 24 months defined as a greater than or equal to a one point improvement in Ishak Fibrosis Score from Baseline.

- Category 2. Stable disease at 24 months defined as no change from Baseline in the Ishak Fibrosis Score from Baseline.
- Category 3. Progression at 24 months defined as a greater than or equal to a one point worsening from Baseline in the Ishak Fibrosis Score from Baseline or death/re-transplantation.

Changes in the Ishak Fibrosis Score at 24 months will be analyzed by a logistic regression model, appropriate for the analysis of ordinal categorical data, to derive the odds ratio and associated 95% confidence interval for IDN-6556 against placebo. The model will allow adjustment for the following variables:

- Baseline Ishak Fibrosis Score
- Immunosuppression regimen (classified into one of five groups: tacrolimus with/without steroids; cyclosporine with/without steroids; other)
- Age of the transplant donor
- Age of the recipient

Subgroup analyses of the model covariates, stated above, will also be conducted.

Shift tables of changes in Ishak Fibrosis Score over time will also be presented.

Secondary Endpoint

Estimates of the treatment effect of IDN-6556 versus placebo, and corresponding 95% confidence intervals of the modified Histological Activity Score will be conducted applying the suitable model for ordinal categorical data and detailed in the Statistical Analysis Plan. Shift tables showing changes over time will also be presented.

12.6.4 Interim Analysis

No formal interim analyses are planned for this exploratory study.

12.6.5 Handling of Missing Data

Methods for imputing missing data will be detailed within the Statistical Analysis Plan.

12.7 Analysis Plan

Prior to the analysis, a detailed SAP for the core study will be developed. This plan will be finalized prior to the database lock and/or study unblinding. It is intended that

the database will be locked once the last subject completes the 4 week follow-up visit.

A detailed analysis plan to determine the exposure effect relationship and the population pharmacokinetics will be developed separately. The results of the analysis will be generated as a stand-alone report.

12.8 Statistical Software

Analyses will be done using the validated statistical software of SAS® (version 9 or later).

12.9 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) is planned for this study. The DMC will review safety data at periodic intervals from this and all other IDN-6556 studies conducted by the Sponsor. Members of the DMC will not be allowed to participate as Investigators in this study and will not otherwise consult for the Sponsor.

A charter, which will include a detailed description of the scope and the extent of the DMC's responsibilities and procedures, will be implemented prior to any data review. DMC documents (charter, open and closed meeting minutes, etc.) will be considered part of the study documentation, but not part of this protocol. The DMC will review data within its general remit to oversee subject safety in the study, and provide recommendations and guidance to the Sponsor in accordance with the procedures stated in its charter.

Should the DMC make subject-safety-related recommendations which affect the conduct of this study, all Investigators, responsible IRB/IECs, and applicable regulatory agencies will be informed of any decisions made by the Sponsor in response to such DMC recommendations. The Investigators will inform the subjects of any such decisions, and the protocol and ICF will be revised, as appropriate.

13.0 ADVERSE EVENTS

13.1 Adverse Event Reporting Obligations

The Investigator is responsible for recording adverse events observed during the study. In addition, certain adverse events (as described in **Section 13.2.** below) are classified as "serious" and must be reported within 24 hours to Conatus or its designee.

In the case of certain adverse events, the Investigator and the Medical Monitor, after discussing the details of the adverse events, may decide to temporarily interrupt dosing, or permanently discontinue study drug treatment in a subset of subjects or in entirety.

13.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization and the U.S. Code of Federal Regulations [21 CFR 312.32] and are included herein.

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse events include, but are not limited to:

- Any symptom or condition not previously reported by the subject (medical history).
- An exacerbation of a pre-existing symptom or condition.
- A significant increase in frequency or intensity of a pre-existing episodic event or condition.
- A drug interaction.
- A condition first detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.

An AE does **not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or blood transfusion); the condition that leads to the procedure is an adverse event (e.g., bleeding esophageal varices, dental caries).
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

An adverse reaction is any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An adverse event or suspected adverse reaction is considered 'unexpected' if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. 'Unexpected,' as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The Sponsor will determine if a suspected, unexpected serious adverse reaction (SUSAR) or SAE meets the criteria as being reportable as a 7-day or a 15-day safety report.

13.2.1 Anticipated Serious Adverse Events in HCV POLT SVR Subject Population

Given the chronic HCV subject population who underwent an orthotopic liver transplantation being studied in this protocol, serious adverse events are anticipated to occur, despite having achieved HCV viral clearance. As such, expected events in this patient population, with the exception of Immunologic and Infectious Disorders, if they become serious, will not be reported in an expedited manner because they may occur at some frequency, independent of drug exposure.

The Medical Monitor will review the subject data electronically via the EDC portal on an ongoing basis to ensure prompt review of protocol-specified SAEs. In addition, at minimum, quarterly outputs of all adverse events will be provided to the Medical Monitor to determine if any serious adverse events remain unreported and to establish routine monitoring of all adverse event data. The Medical Monitor will forward a summary of his/her review, if required by the DMC charter, to the DMC for additional safety oversight.

13.2.2 Pre-Treatment-Emergent Adverse Events

Conatus considers adverse events that occur between the time the subject signs the informed consent form for the study and the time when that subject is first administered the study drugs as “pre-treatment-emergent” events. Any pre-treatment-emergent event should not be recorded as an adverse event but should be recorded in the appropriate category of the subject’s medical history case report form.

13.2.3 Laboratory Abnormalities as Adverse Events

Many laboratory abnormalities observed during the course of a study will be included under a reported adverse event describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an adverse event of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an adverse event. However, isolated laboratory abnormalities should be reported as adverse events if they are considered to be

clinically significant by the Investigator. Criteria for a "clinically significant" laboratory abnormality are:

a) A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose suspension or discontinuation), or
b) A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy)

For laboratory abnormalities that do not meet the above criteria but are outside of normal range (e.g., < or > normal reference range), the Investigator should indicate whether the value is clinically significant (CS) or not clinically significant (NCS) for the subject.

13.3 Severity of Adverse Events

The Investigator must categorize the severity of each adverse event according to the following guidelines:

Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

13.4 Classification of Adverse Events by Relationship to Study Drug Administration

The Investigator must assess whether each adverse event is related to either IDN-6556 or placebo. The relationship of each adverse event will be assessed by the Investigator after careful consideration, and according to the following guidelines:

Definitely: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on

cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered.

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

Possibly: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could reasonably have been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.

Unlikely: A reaction that does not follow a reasonable temporal sequence from administration, and/or that can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatments.

Not Related: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

13.5 Recording and Reporting Adverse Events

13.5.1 Recording Adverse Events

All adverse events will be recorded in the appropriate section of the case report form. Subjects withdrawn from the study due to adverse events will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided. The Investigator should attempt, if possible, to establish a diagnosis based on the presenting signs and symptoms.

If the adverse event meets the definition of a serious adverse event, or if the Investigator becomes aware of an unexpected adverse event that places the subject at risk or a pregnancy at any time after the study drug administration up to the end of the study follow-up period, the event must be documented and reported as described in **Section 13.5.2**.

13.5.2 Investigator Reporting of a Serious Adverse Event

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for prompt notification of serious adverse events to the Sponsor's Medical Monitor or designee.

All serious adverse events must be reported to Conatus within 24 hours after the Investigator recognizes/classifies the event as a serious adverse event. At a minimum the following information should be provided at the time of the initial report: subject number and initials, a description of the event, at least one criterion classifying the event as Serious and the name and title of the reporting individual. Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting to regulatory authorities by the Sponsor or designee(s) (e.g., CIOMS forms, FDA MedWatch Form 3500A or other equivalent form). After the initial report, as necessary, the Investigator must provide any additional information on a serious adverse event to the Medical Monitor within 24 hours after he/she receives that information. This follow-up information will be a detailed written report that will include copies of hospital records, case reports, autopsy reports, and other pertinent documents.

Conatus will consider the Investigator's assessment of the causality assessment; however, since Conatus will assess the overall safety of the study medication, Conatus' causality assessment will take precedence, unless the Investigator's assessment must take precedence per country-specific regulations

Contact:

SynteractHCR Safety Safety Fax: +1-760-268-6500 safetyfax@synteracthcr.com	OR if not available	Mason Yamashita, MD VP, Pharmacovigilance Mobile: 1 619 306 2125 Fax: 1 858 432 7720 myamashita@conatuspharma.com

All serious adverse events must be reported to Conatus within 24 hours after the Investigator recognizes/classifies the event as a serious adverse event. At a minimum the following information should be provided at the time of the initial report: subject number and initials, a description of the event, at least one criterion classifying the event as Serious and the name and title of the reporting individual. Additionally, judgment of causality by the Investigator must be provided as soon as possible to ensure timely reporting to regulatory authorities by the Sponsor or designee(s) (e.g., CIOMS forms, FDA MedWatch Form 3500A or other equivalent form). After the initial report, as necessary, the Investigator must provide any additional information on a serious adverse event to the Sponsor or designee within 24 hours after he/she receives that information. This follow-up information will be a

detailed written report that will include copies of hospital records, case reports, autopsy reports, and other pertinent documents.

Conatus will consider the Investigator's assessment of the causality assessment; however, since Conatus will assess the overall safety of the study medication, Conatus' causality assessment will take precedence, unless the Investigator's assessment must take precedence per country-specific regulations

13.6 Additional Investigator Responsibilities on Follow-up of Serious Adverse Events

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of serious adverse events. The results of these additional assessments conducted must be reported to Conatus. If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to Conatus.

13.7 Post-Study Follow-Up of Adverse Events

All adverse events, including a worsening of clinically significant laboratory values, physical examination findings compared with Baseline values, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

Adverse events ongoing at the final visit will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves. If resolved, a resolution date should be documented on the case report form or reported to Conatus if the case report forms have been collected. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the adverse event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals as is practical.

13.8 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigator becomes aware of a serious adverse event, he/she should notify Conatus if such an event is attributable to study drug. The notification to Conatus of a post-study serious adverse event by the Investigator should occur within 24 hours of becoming aware of the serious adverse event.

13.9 IRB/IEC Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his IRB/IEC of all serious adverse events, including any follow-up information, occurring at her/his site. In addition, the Investigator is responsible for submitting information on SUSARs/SAEs received from Conatus to their local IRB/IEC. Documentation of the submissions to IRBs/IECs must be retained in the appropriate study file(s).

However, in some countries, the notification of SUSARs/SAEs to IRB/IEC will be the responsibility of the Sponsor or the Sponsor's designee.

13.10 Health Authority Safety Reports

Conatus, or its representatives, will submit a safety report to the US Food and Drug Administration (FDA) and any other appropriate regulatory agencies in accordance with country specific requirements, for any serious adverse event that is unexpected and related to the study drug within the appropriate time frame. Conatus or its representatives will send copies of each safety report submitted to the FDA and other regulatory agencies to the Investigators who are actively participating in Conatus-sponsored clinical studies. Safety reports must be submitted to the appropriate IRB/IEC as soon as possible. In some countries, submission of the safety reports to IRB/IEC will be made by Conatus or its representatives. Documentation of the submission to the IRB/IEC must be retained for each safety report. As instructed by Conatus or its designee, safety reports should be retained in the appropriate study files, or with the Investigator's Brochure.

14.0 ADMINISTRATIVE ASPECTS

14.1 Investigator Responsibilities for General Study Conduct

It is the Investigator's responsibility to ensure that:

- The protocol, subject information sheet, the proposed informed consent form, trial participation card (if applicable), or any information to the Primary Care Physician and any advertisement for subject recruitment are reviewed and approved by the appropriate IRB/IEC, prior to the start of the study.
- The proposed subject information sheet, informed consent form, trial participation card (if applicable) and any proposed advertisement are agreed to by Conatus.
- A copy of the IRB/IEC approval letters for the protocol, any amendments, subject information sheet, the informed consent form, trial participation card (if

applicable) and any advertisements are supplied to Conatus prior to starting the study.

- During the course of the study, at intervals not exceeding one year, timely and accurate reports are submitted to the IRB/IEC on the progress of the study and any other local IRB/IEC regulations regarding reporting are satisfied.
- Copies of all reports to and correspondence with and from the IRB/IEC are provided to Conatus.
- At the completion or early termination of the study, a final report is made to the IRB/IEC within the applicable IRB/IEC time frames.
- Any significant deviation in the study protocol or any change that may alter subject risk is approved by Conatus (and FDA/other regulatory agency review and/or approval is obtained, if required) and is approved in writing by the IRB/IEC prior to implementation. All protocol amendments will be submitted to the IRB/IEC.
- Acknowledge receipt of administrative amendments that are provided for information only.
- An approval/favorable opinion is obtained from the IRB/IEC on substantial amendments prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants.
- A written notice of approval from Conatus is obtained prior to initiating changes to the study protocol.

A protocol deviation intended to eliminate an apparent immediate hazard may be implemented immediately, provided that Conatus is notified and an amendment is subsequently provided by Conatus and approved by the IRB/IEC. Such deviations, and their rationale, should be documented.

It is the Investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review by representatives of Conatus and applicable regulatory agencies as part of the study monitoring process.

14.2 Informed Consent

Each site's proposed informed consent form must be in compliance with applicable regulations and must be reviewed and approved by Conatus prior to initiation of the study. The proposed informed consent form must contain a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages and risks, alternate treatment options, a statement of confidentiality of subject study records, a statement regarding compensation and availability of treatment in the case of injury, an explanation of whom to contact about the

research, the subject's rights, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits. These requirements are in accordance with the Federal Regulations as detailed in 21 CFR Part 50.25, ICH GCP 4.8.10, and the most current revision of the Declaration of Helsinki. It should also indicate by signature that the subject (or, where appropriate, legal guardian/representative) permits access to relevant medical records by the Sponsor and/or the Sponsor's duly appointed agent and by representatives of the US Food and Drug Administration (FDA) and other applicable regulatory agency and permits their data to be used in publications.

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study specific screening and entry into the study. A copy of the signed document will be provided to the subject. The original will be retained by the Investigator along with the case report forms.

14.3 Subject Confidentiality and Data Protection

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential and confidentiality of all subjects will be maintained. Monitors (e.g., CRA, Medical Monitor), auditors and inspectors will require access to a subject's medical notes for the purpose of source document verification but the subject's confidentiality will be maintained at all times. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent. The study data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the Sponsor. All data shall be secured against unauthorized access.

The Investigator will maintain a list of subject names and identifying information (e.g., subject's hospital number, unique subject number). This list will not be collected by the Sponsor.

The written information sheet will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by the Sponsor or designee will be identified by unique subject number / subject initials / site number only.

When personal data on subjects are stored or processed by computer, the data must be protected to prevent their disclosure to unauthorized third parties. The pertinent sections of the data protection laws in which the country is being conducted will be complied with in full.

The written ICF/subject information sheet will explain that, for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may require direct access to parts of the hospital or practice records relevant to the study, including subject's medical history.

14.4 Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or normal ranges for the test results must be provided to Conatus. Conatus must be notified promptly in writing of any reference value changes during the course of the study.

This protocol will analyze exploratory serum biomarkers of caspase and apoptotic activity. As such, some of the analytes may be tested at a non-accredited research or analytical laboratory. The requirement for adequate licensure or accreditation will not apply to any research or analytical laboratories utilized in this protocol.

14.5 Required Documents

Before the site initiation visit or the enrollment of any subject may occur, the Investigator must provide the Sponsor with the following documents (copies of which should be kept in the Investigator's regulatory document binder):

- Signed copy (original) of the approved protocol
- Completed and signed statement of Investigator (Form FDA 1572) or foreign equivalent
- Financial disclosure of the Investigator and sub-Investigators
- Curriculum vitae and medical licenses (or equivalent) of the Investigator and sub-Investigators
- Composition (names and representation) of IRB/IEC
- Letter of approval from the IRB/IEC for both the protocol and the informed consent form, and other information provided to study participants
- Copy of the stamped IRB/IEC-approved written informed consent form or subject information sheet to be used
- For each clinical laboratory utilized in the study:
  - Relevant laboratory certification(s)
  - List of normal laboratory values
  - Curriculum vitae of the laboratory director

In case a laboratory certification is not available, a written statement as to how the laboratory complies with quality assurance should be provided. The Sponsor must be notified if the laboratory is changed.

14.6 Study Initiation, Monitoring, and Termination

Prior to commencement of the study, representatives of Conatus will visit the study site to verify adequacy of facilities to conduct the protocol, and to review with the Investigator the general obligations regarding studies with investigational new drugs.

Upon satisfactory receipt of all required documentation (see **Section 14.5**), representatives of Conatus will arrange for all study materials to be delivered to the study site and will schedule a study initiation visit at a mutually convenient time. Subject entry must not begin until this initiation visit has been completed. At the initiation visit, site personnel will undergo a study-specific orientation, during which they will receive instruction in the study protocol, case report form completion, drug accountability, study file maintenance, and other study responsibilities.

Throughout the course of the study, the Investigator shall make every reasonable effort to maintain the enrollment rate of appropriate subjects at the level prospectively estimated to Conatus. Should the enrollment rate lag or significant numbers of clearly non-evaluable subjects be enrolled in the study, Conatus may elect to terminate the study at one or more sites. Conatus also has the right to terminate the study at a particular site, at any time, for non-adherence to the protocol, lack of Investigator or site personnel availability (to the Sponsor or its designated monitoring personnel), or administrative reasons. If it is necessary to terminate the study, Investigators will be compensated for reasonable expenses incurred during study termination. Conatus will not compensate the Investigator (or investigative site) for procedures and/or evaluations conducted in a manner other than that specified by the protocol.

Throughout the course of the study, representatives of Conatus will make frequent contacts with the Investigator and investigative site personnel. Contacts will include e-mails, telephone calls, and/or on-site visits at appropriate and necessary intervals. During on-site visits, case report forms will be reviewed for completeness and for adherence to the protocol. As part of the data review, it is expected that source documents (e.g., hospital records, office records, etc.) will be made available for review by the representatives of Conatus. The representatives will also perform drug accountability checks and may periodically review the Investigator's study file to assure completeness of documentation in all aspects of the conduct of the study.

The Investigator (or appointed delegate) will be available to the representatives of Conatus during these on-site visits, will provide necessary study documents for inspection, and will respond to all inquiries that may arise as part of this review. On completion of the study, the representatives of Conatus will arrange for a final review of the study files, after which the study files should be secured for the appropriate time period (specified in **Section 14.9)**. The Investigator will also permit inspection of the study files by the Sponsor's Quality Assurance auditors, IRB/IEC, authorized representatives of the FDA, and/or other applicable regulatory agencies.

14.7 Data Recording and Case Report Forms

Electronic case report forms will be provided by Conatus or its designee for the collection of all study data. Forms should be completed in a timely manner, and appropriate efforts should be made to have forms completed and up-to-date prior to visits by the representatives of Conatus. It is the obligation of the Investigator, as the study's authority, to review each page of the case report forms and to e-sign the designated and appropriate forms. Case report form completion may be formally delegated to other study personnel. However, Conatus must be informed in writing of the name of such persons and the scope of their authority.

14.8 Investigational Medicinal Product Accountability

The investigational drug is to be prescribed only by the Investigator or physician sub-Investigators named on the Form FDA 1572 or foreign equivalent. Under no circumstances will the Investigator(s) allow the investigational drug to be used other than as directed by this protocol.

The Investigator must maintain accurate records accounting for the receipt of the investigational drug supplies and for the disposition of the study drug. Documentation of the disposition of the study drug should consist of a dispensing record including the identification of the person to whom the study drug is dispensed, the quantity and the date of dispensing, and any unused study drug returned. This record is in addition to any drug accountability information recorded on the case report forms. At the termination of the study or at the request of the Sponsor, the Investigator must return any unused study medications and all partially dispensed or empty containers to the Sponsor or its designee according to applicable local and country regulations. If return of study drugs is not feasible, the Sponsor will supply instructions as to how the supplies may be destroyed. Study drug supply destruction must be clearly documented. Any investigational drug return will be documented at Conatus. The Investigator will also provide a written explanation for any missing study drugs.

14.9 Record Retention

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by the Sponsor's Quality Assurance auditors and by US and non-US regulatory authorities. The period of time these documents must be maintained is governed by US and non-US regulations. International requirements specify that these documents are to be maintained for 15 years or longer after a drug is approved for marketing. Conatus or its designee(s) will inform the Investigator when these documents may be destroyed. The Sponsor or its designee(s) must be notified in writing *at least 6 months* prior to the intended date of disposal of any study record related to this protocol to allow the Sponsor to make alternate storage arrangements.

If the Investigator relocates, retires, or for any reason withdraws from the study, Conatus should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Conatus.

14.10 Investigator's Final Report

Each Investigator will submit, shortly after completion of study participation, a final, written report to the Sponsor.

14.11 Publication Policy

Conatus intends to publish the results of all of the clinical studies that it sponsors. Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Conatus-sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study[13]. Thus, it is anticipated that authorship will reflect the contribution made by the Sponsor personnel, the Investigators and others involved such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, Conatus has developed publication guidelines for clinical studies that are appropriate for this study. Key issues include:

- **Responsibility:** Each Investigator is responsible for the accuracy and completeness of all data from his/her site. The Sponsor (or its representatives) is (are) responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.

- **Authorship and Publication Committee:** The Sponsor, in collaboration with the Investigators, will establish the appropriate authorship and responsibility for drafting study documents in accordance with the principles of the ICMJE. It is anticipated that a publication committee will be formed to assume oversight of these activities. All manuscripts will be reviewed and agreed upon before submission for publication by all authors.

- **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted to the Sponsor for review, approval, and to ensure consistency with the policy in this protocol. The Sponsor will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication. Any Investigator who plans to submit material for publication must adhere to the following procedure for Sponsor review and approval:

  (a) The Investigator will notify Conatus of his/her intent to publish and/or present results of the study at least 30 days prior to submission for publication or the scheduled presentation date. The notification should be made in writing to Conatus.
  (b) The Investigator shall provide to Conatus the full details of the proposed publication or presentation in electronic format at minimum 14 (fourteen) days prior to submission for publication of any paper, letter or similar publication, or 7 (seven) days prior to submission for presentation of any abstract, poster, talk or any other presentation.
  (c) The Investigator shall give reasonable consideration to any request by Conatus to make changes within the periods mentioned in (b) above.
  (d) The Investigator shall remove confidential information requested by Conatus before finalizing the publication.
  (e) Upon written request from Conatus, the Investigator agrees not to submit data for publication/presentation for an additional 60 (sixty) days in order to allow for actions to be taken which might be necessary to preserve rights for patent protection. If such written request is not made within the periods mentioned in (b) above, Conatus will be deemed to have waived the right to delay.
  (f) In any case, the Investigator will also provide a final version, in exactly the form that was submitted for publication, to Conatus simultaneously with that submission; this shall also apply to any revised versions that are submitted following review by the journal (etc.) in which publication is projected.

- **Confidentiality:** Investigators will conduct all interactions with the Sponsor and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.

- **Medical Journal Review:** Consistent with the intention of the Sponsor to publish the study in a fair and accurate manner, the Sponsor supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, e.g., protocol and amendments, data tabulations, *etc.* The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and the Sponsor will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.

- **Internet Clinical Study Listing:** In addition, also consistent with the recommendations of the ICMJE, the Sponsor will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical studies.

14.12 Confidentiality

Conatus, its designees, and all clinical site personnel affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified *only* by an identification number and subject initials.

All information concerning this study and Conatus' development of IDN-6556 that is not previously published is considered confidential information. This confidential information shall remain the sole property of Conatus. It shall not be disclosed to others without written consent of Conatus and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by Conatus as they deem necessary. To allow the use of the information derived from this clinical study and to ensure compliance to current federal and international regulations, the Investigator is

obliged to furnish Conatus with complete test results and all data compiled in this study.

15.0 REFERENCES

1. http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/03_%20liver_12.pdf. OPTN & SRTR Annual Data Report 2011. Accessed 27 January 2014.

2. Roche B, Samuel D. Treatment of hepatitis B and C after liver transplantation. Part 2, hepatitis C. Transpl Int 2005;17:759-766.

3. Garg V, van Heeswijk R, Lee JE, et al. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology 2011 Jul; 54(1): 20-27.

4. Hezode C, Dorival C, Zoulim F, et al. Safety of Telaprevir or Boceprevir in combination with Peginterferon alfa/Ribavirin, in Cirrhotic Non Responders (ANRS CO20-CUPIC).

5. MR Charlton, EJ Gane, MP Manns, et al. Sofosbuvir and ribavirin for the treatment of established recurrent hepatitis C infection after liver transplantation: preliminary results of a prospective, multicenter study. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. AbstractLB-2.

6. Abdelmalek MF, Firpi RJ, Soldevila-Pico C, et al. Sustained viral response to interferon and ribavirin in liver transplant recipients with recurrent hepatitis C. Liver Transpl 2004;10:199-207.

7. Walter T, Dumortier J, Guillaud O, et al. Factors influencing the progression of fibrosis in patients with recurrent hepatitis C after liver transplantation under antiviral therapy: a retrospective analysis of 939 liver biopsies in a single center. Liver Transpl 2007;13:294-301.

8. Bixollon T, Ahmed SNS, Radenne S, et al. Long term histological improvement and clearance of intrahepatic hepatitis C virus RNA following sustained response to interferon-ribavirin combination therapy in liver transplanted patients with hepatitis C virus recurrence. Gut 2003;52:283-287.

9. Bahra M, Neumann UP, Jacob D, et al. Fibrosis progression in hepatitis C positive liver recipients after sustained virologic response to antiviral combination therapy (interferon-ribavirin therapy). Transpl 2007;83:351-353.

10. Nair S, Lipscomb J, Eason J. Efficacy of interferon based antiviral therapy for recurrent hepatitis C in patients who received steroid free immunosuppression for liver transplantation. Transpl 2008;86:418-422.

11. Roche B, Sebagh M, Canfora ML, et al. Hepatitis C virus therapy in liver transplant recipients: response predictors, effect on fibrosis progression, and importance of the initial stage of fibrosis. Liver Transpl 2008;14:1766-1777.

12. Fleming T, Richardson B. Some design issues in trials of microbicides for the prevention of HIV infection. J Infectious Diseases 2004;190(4):666-674.

13. Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. N Engl J Med, 2001; 345: 825-827.

14. Pugh R, Murray-Lyon I, Dawson J, et al. Transection of the oesophagus for bleeding oesophageal varices. Brit. J. Surg. **60**: 646-649, 1973.

15. National Kidney Foundation: KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, classification, and stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1).

16. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003; 29(12):1705-1713.

17. Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005; 41(1):48-54.

APPENDIX I: SCHEDULE OF EVENTS

	STUDY VISITS[A]											
	Screening Phase (Week -6 to Day 0)	Double-Label Phase										Follow-Up Phase
		M0/ Day 1	Day 14	M 1	M 3	M 6	M 9	M 12	M 15	M 18	M 21	M24/ ET/EOT	M25/ 4 Wks post ET/EOT
Study Procedures													
Informed Consent	X												
Eligibility Criteria	X												
Medical and Surgical History	X												
Medication/Therapy Record	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (including weight, height at screening only)	X							X				X	X
Chest X-ray	X												
12 Lead ECG	X							X				X	
Liver and Abdominal Ultrasound	X[B]					X[C]		X[C]		X[C]		X	
Liver Biopsy	X[D]					X[E]		X[F]		X[E]		X[F]	
Transient Elastography (at select centers only)	X					X		X		X		X	
Study Drug Administration/Dispense Study Drug		X	X	X	X	X	X	X	X	X	X		
Compliance Assessment (Capsule Count)			X	X	X	X	X	X	X	X	X	X	
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Evaluations													
Hematology	X	X		X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X		X		X		X		X		X	X
Urinalysis	X	X				X		X		X		X	X
Immunosuppressant Concentration Monitoring		X	X										

	STUDY VISITS[A]											
	Screening Phase (Week -6 to Day 0)	Double-Label Phase										Follow-Up Phase
		M0/ Day 1	Day 14	M 1	M 3	M 6	M 9	M 12	M 15	M 18	M 21	M24/ ET/EOT	M25/ 4 Wks post ET/EOT
Blood Samples for Immunosuppressant Pharmacokinetic Analysis				X[G]									
α-fetoprotein	X					X[H]		X[H]		X[H]		X	
CA 19-9		X										X	
Blood Sample for Biomarkers		X[I]	X	X	X	X[I]		X[I]				X[I]	X
Blood Sample for Population Pharmacokinetic Analysis								X				X	
Blood Samples for Pharmacokinetic Analysis				X[J]									
Blood Samples for Pharmacokinetic Analysis (If Repeat Testing is Required for Elevated ALT, AST, and/or Bilirubin)			X[K]	X[K]	X[K]	X[K]	X[K]	X[K]	X[K]	X[K]	X[K]	X[K]	
Serum Pregnancy Test[L]	X			X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[L]		X											

[A] Acceptable variation for actual study visits from Day 1 to Month 6 is ± 7 days from nominally scheduled day, and ± 14 days from nominally scheduled day from Month 6 onward. However, every effort should be made to maintain the nominal visit schedules of subjects as predicated by the date of the Day 1 visit.

[B] If the subject had a liver and abdominal ultrasound performed within three months of Screening, the prior ultrasound results can be used for study entry. If the subject had an abdominal MRI or CT scan within three months of Screening, it can be utilized in lieu of the ultrasound at Screening

[C] If on-treatment abnormalities in liver and abdominal ultrasound occur, Investigators should utilize normal clinical practice for follow-up of subjects and discuss treatment (dis)continuation with the Conatus Medical Monitor.

[D] The biopsy should be within 3 months prior to Day 1.

[E] If clinically indicated. Refer to Section 8.1.1 for further details.

[F] Yearly biopsy window is ± 42 days. In the event that a subject is withdrawn from the study prior to the 24 month visit, the subject will be contacted and asked to sign a separate consent to return for a biopsy at the Month 24 visit

[G] Blood samples will be taken at predose, and at 0.5, 1, 2, 3, 4, 5, and 8 hours post dose for immunosuppressant pharmacokinetic analysis.

[H] If elevations in α-fetoprotein occur during the study, Investigators should utilize normal clinical practice for follow-up of subjects and discuss treatment (dis)continuation with the Conatus Medical Monitor.

[I] ELF test to be run every 6 months only.

[J] Blood samples will be taken at predose, and at 0.5, 1, 2, 3, 4, 5, and 8 hours post dose for pharmacokinetic analysis. The time window for samples will be:

- 0.5 hour ± 5 minutes
- 1 hour ± 5 minutes
- 2 hour ± 5 minutes
- 3 hour ± 10 minutes
- 4 hour ± 10 minutes
- 5 hour ± 10 minutes
- 8 hour ± 10 minutes

[K] If repeat laboratory testing is required for elevated ALT, AST, and/or total bilirubin (refer to Section 8.1.9) a single blood sample will be taken for pharmacokinetic analysis.

[L] For women of childbearing potential only.

APPENDIX II: LIVER BIOPSY SCORING AND ASSESSMENT

Ishak Modified Histological Activity Index (Ishak Fibrosis Score)

Liver biopsy findings are assigned scores for fibrosis as follows:

Table II.1 Ishak Fibrosis Score: Architectural Changes, Fibrosis and Cirrhosis

	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas, with occasional portal to portal bridging	3
Fibrous expansion of portal areas, with marked bridging (portal to portal as well as portal to central)	4
Marked bridging (portal to portal and/or portal to central) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis probable or definite	6

Ishak Modification of Knodell Histological Activity Index

Liver biopsy findings will be assigned scores for necro-inflammation as follows:

Table II.2 Ishak Modification of Knodell Histological Activity Index: Necro-inflammatory Scores

	Score
A Periportal or periseptal interface hepatitis (piecemeal necrosis)	
Absent	0
Mild (focal, few areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continuous around <50% of tracts or septa)	3
Severe (continuous around >50% of tracts or septa)	4
B Confluent necrosis	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis + occasional portal-central bridging	4
Zone 3 necrosis + multiple portal-central bridging	5

Pan acinar or multiacinar necrosis	6
C Focal (spotty) lytic necrosis, apoptosis and focal inflammation	
Absent	0
One focus or less per 10X objective	1
Two – Four foci per 10X objective	2
Five – Ten foci per 10X objective	3
More than ten foci per 10X objective	4
D Portal Inflammation	
None	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4

APPENDIX III: CLASSIFICATION OF HEPATIC AND RENAL IMPAIRMENT

Table III.1 Assessment of Hepatic Impairment: Child-Pugh Scale (adapted from Pugh et al)[14]

	Points Scored for Observed Findings		
	1	2	3
Encephalopathy Grade+	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum Bilirubin (mg/dL)	< 2.0	2.0 - 3.0	> 3.0
Serum Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
Prothrombin Time (sec prolonged)	< 4	4 - 6	> 6
Classification of clinical severity Class A: Score 5-6 (mild) Class B: Score 7-9 (moderate) Class C: Score 10-15 (severe)			

+Hepatic Encephalopathy grading:

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disorientated, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuperous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Determination of Encephalopathy for the Calculation of the Child-Pugh Score

Encephalopathy Test (If needed)
The number connection test will facilitate the diagnosis of hepatic encephalopathy. The test should be performed by the subject after the investigator's verbal instructions. The purpose is to correctly combine numbers with a pencil on a test chart as fast as possible. If the subject needs more than 40 seconds to perform the task, there is a strong indication of a latent hepatic encephalopathy.

Table III.2 Classification of Renal Function Based on GFR (eGFR) or Estimated Creatinine Clearance (CLcr)[a]

Stage	Description[b]	eGFR[c] (mL/min/1.73m^2)	CLcr[d] (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60 - 89	60 - 89
3	Moderate decrease in GFR	30-59	30 - 59
4	Severe decrease in GFR	15 - 29	15 - 29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis	<15 not on dialysis
		Requiring dialysis	Requiring dialysis

a. In some situations, collection of 24-hour urine samples for measurement of creatinine clearance, or measurement of clearance of an exogenous filtration marker, may provide better estimates of GFR than the prediction equations. The situations include determination of GFR for patients in the following scenarios: undergoing kidney replacement therapy; acute renal failure; extremes of age, body size, or muscle mass; conditions of severe malnutrition or obesity; disease of skeletal muscle; or on a vegetarian diet.

b. Stages of renal impairment are based on K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from the National Kidney Foundation in 2002[15]; GFR: glomerular filtration rate

c. eGFR: estimate of GFR based on an MDRD equation

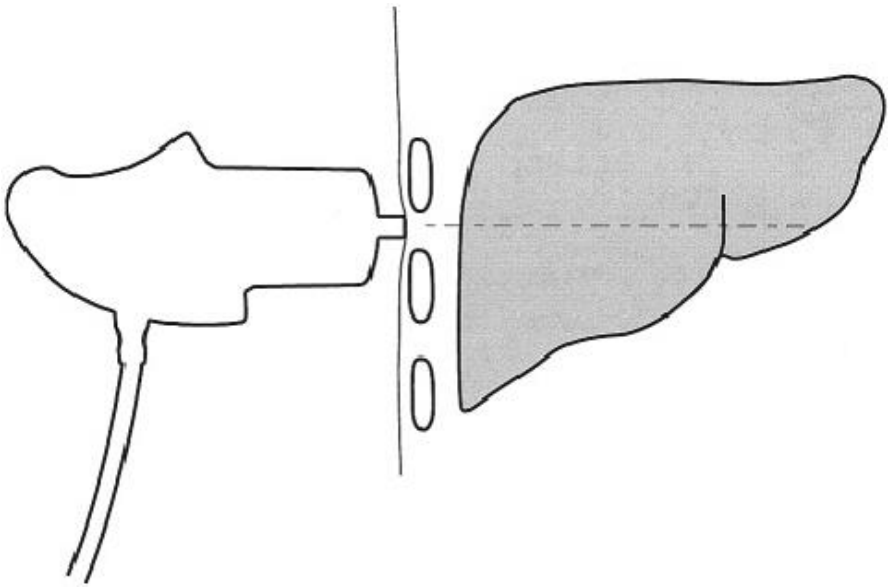
d. CLcr: estimated creatinine clearance based on the C-G equation

APPENDIX IV: FIBROSCAN® PROTOCOL

Background

Transient elastography performed with FibroScan® uses a low frequency vibrator (50Hz) mounted on 1-D US probe (5MHz). The speed of propagation of the shear wave through the liver is proportional to stiffness. The stiffness correlates with the severity of fibrosis[16,17].

Figure IV.1 FibroScan® Probe Placement in Relation to Anatomy of a Subject



Reproduced from Ziol et al 2005[17].

There are three images displayed on the monitor:

1. A-mode image
2. Time movement (TM) image
3. A 2D elastogram

These images are used by the operator to make sure that the area of the liver selected is free of large vascular structures, that lung fields do not encroach on inspiration and that the selected area is not over a rib. The elastogram demonstrates the depth of the shear wave with time. The slope of the resulting line gives speed of propagation.

There are four figures displayed on the monitor:

1. The cumulative median liver stiffness value
2. The current liver stiffness value
3. The inter-quartile range
4. The success rate

Method

1. The subject is asked to lie comfortably in the supine position with his/her right arm fully abducted and resting on a pillow.
2. Cover the tip of the probe with a small amount of coupling gel and place on the skin, on the right lateral wall of the abdomen between the ribs at the level of the right lobe of the liver.
3. The right lobe of the liver is selected to ensure that the area of the liver to be measured is at least 6 cm thick.
4. The probe must be placed perpendicular to the subject's abdominal wall.
5. Pressure should be applied by the operator on the subject and the button is pressed to initiate an acquisition.
   a. It is important to apply enough pressure on the subject so that the pressure bar display is within the green range. Insufficient pressure will be displayed as orange and over pressure will be displayed as red.
   b. Pressure must be released immediately following an acquisition.
   c. When making a measurement, it is also important to ensure that the subject is breathing slowly and not moving or speaking.
6. If a successful reading is not acquired, the probe should be moved up or down by one rib space and, if that is not successful, anteriorly or posteriorly from the initial site by 1cm. Once a successful reading has been obtained, the remaining readings should be taken from the same site.
7. To obtain a reliable and representative evaluation of the stiffness of the liver, 10 valid measurements with a success rate of >60% should be acquired.
8. For each subject the following parameters should be recorded:
   a. The median liver stiffness value (kPa)
   b. The success rate (%)
   c. The inter-quartile range (kPa)

In order to standardize the FibroScan® procedure, the following should be implemented to obtain consistent and reproducible measurements.

1. The subject should be NPO for 4 hours prior to the procedure

2. The operator should be seated next to the subject, with the hand holding the probe, stabilized by the other. This will improve the stability of the probe as it is held up against the subject yielding an improved result with a low IQR.
3. The measurement should be taken during expiration.

Signature Page for CTS-CTD-0604 v1.0

Approved	Lisa Grubbs Document Owner 14-Aug-2015 00:50:06 GMT+0000

Approved	Cindy Luchetti RA/QA Approval 14-Aug-2015 16:00:58 GMT+0000

Approved	Jean Chan Monitoring 14-Aug-2015 16:03:37 GMT+0000

Approved	David Hagerty Clinical Operations 17-Aug-2015 17:22:01 GMT+0000

Signature Page for CTS-CTD-0604 v1.0