CLINICAL STUDY PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY TO ASSESS THE SAFETY AND EFFICACY OF IFETROBAN FOR THE TREATMENT OF PORTAL HYPERTENSION IN CIRRHOTIC PATIENTS

Study Number: CPI-IFE-005

Protocol Version

Version Number: Amendment 02
Final: 24 JULY 2017

CONFIDENTIALITY STATEMENT

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1 INVESTIGATOR'S STATEMENT

I have read and agree to Amendment 02, dated 24Jul2017, of Protocol CPI-IFE-005, "A randomized, double-blind, placebo-controlled pilot study to assess the safety and efficacy of ifetroban for the treatment of portal hypertension in cirrhotic patients". I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

Principal Investigator

Signature:

<<name>> <<address>>	Date of Signature

<<phone>>

Sponsor Signature

Signature:

[redacted] Director, Medical Affairs	Date of Signature

Signature:

[redacted] Executive Vice President, Operations & Chief Development Officer	Date of Signature

2 SYNOPSIS

Name of Sponsor: Cumberland Pharmaceuticals Inc.	**Finished Product:** Ifetroban Sodium Injection and Oral Capsule	**Active Ingredient:** Ifetroban Sodium
Title of Study: A randomized, double-blind, placebo-controlled pilot study to assess the safety and efficacy of ifetroban for the treatment of portal hypertension in cirrhotic patients		
Coordinating Center: [redacted]		
[redacted]	**Phase of Development:** II	
Objectives: To evaluate the following in cirrhotic patients with portal hypertension that are treated with ifetroban: • Safety • Portal pressure • Serum liver enzymes • Surrogate markers of liver fibrosis and inflammation • Occurrence of variceal bleeds		
Methodology: This is a multicenter, double-blind randomized study to evaluate the efficacy and safety of ifetroban treatment in patients with cirrhosis.		
Number of subjects (planned): Thirty patients: 20 assigned to ifetroban; 10 on placebo		

Diagnosis and main criteria for inclusion:

1. Cirrhosis defined by histology or historical mean HVPG > 7 mm Hg, or confirmed by liver stiffness measurement (LSM) above diagnostic threshold (15 kPa for Vibration Controlled Transient Elastography (VCTE) or 6.7 kPa for Magnetic Resonance Elastography (MRE) AND evidence of splenomegaly or collaterals OR platelet count below 150 x 10^3 with AST>ALT
2. At least two stable baseline values for AST, ALT, ALP and bilirubin taken at screening and between 15 and 90 days prior. Stable is defined as values having a difference $\leq$ 40 U/L for AST and ALT, $\leq$ 60 U/L for ALP and $\leq$ 3.0 mg/dL for total serum bilirubin
3. Baseline mean hepatic venous pressure gradient between 8 and 18 mmHg, inclusive

Main criteria for exclusion:

4. Less than 18 or more than 70 years of age
5. Portal or splenic thrombosis
6. Transjugular intrahepatic shunt (TIPS)
7. Active GI/variceal hemorrhage within the last 60 days
8. Hemodialysis
9. Child-Pugh score $\geq$ 12, calculated within 30 days of enrollment
10. MELD-Na score $\geq$ 20
11. Platelet count < 60 x $10^3/\mu L$
12. History of bleeding diathesis or risk factors based on patient or familial history, other than cirrhosis and its sequelae
13. Current acute kidney injury (AKI), chronic kidney disease (CKD) or hepatorenal syndrome (HRS) or a baseline SCr $\geq$ 2.0 mg/dL
14. MI in the 90 days prior to enrollment
15. Current need for endothelin receptor antagonists, somatostatin analogues or prostanoids, treatment for viral hepatitis, anticoagulant or antiplatelet drugs.

Investigational Medicinal Product (IMP), dose and mode of administration: Loading IV infusion of 150 mg ifetroban or placebo, followed by 250 mg ifetroban or placebo taken orally each day for 90 days

Duration of treatment: 90 days

Criteria for evaluation:

SAFETY EVALUATION

- Incidence and severity of adverse events

EFFICACY EVALUATION

- Hepatic Venous Pressure Gradient
- AST/ALT levels
- Aspartate Aminotransferase/Platelet Ratio Index (APRI)
- measurements of fibrosis and inflammatory biomarkers
- incidence and severity of variceal bleeds

Statistical methods: Statistics will be descriptive. Continuous safety and efficacy data will be summarized in tables comparing proportions or percentages of patients in the active treatment group with those of the placebo patients. Standard deviation or standard error will also be calculated. All treated patients will be included in the safety analysis population.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event/experience
AERD	aspirin exacerbated respiratory disease
AKI	acute kidney injury
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
APRI	aspartate aminotransferase/platelet ratio
AST	aspartate aminotransferase
AUC	area under the curve
AUC-ROC	area under the curve of the receiver operator characteristics
BUN	blood urea nitrogen
C	celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CKD	chronic kidney disease
cm	centimeter
C_{max}	maximum concentration
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
D5W	5% dextrose in water
DILI	Drug-induced liver injury
dL	deciliter
EGD	esophagogastroduodenoscopy
ET	early termination
EU	European Union
F	fahrenheit
FDA	Food and Drug Administration
FHVP	free hepatic venous pressure
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
Hg	mercury
HRS	hepatorenal syndrome
HSC	hepatic stellate cells
HVPG	hepatic venous pressure gradient
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IV	intravenous
kPa	kilopascal
LSM	Liver stiffness measurement
MedDRA	medical dictionary for regulatory activities
MELD	model end stage liver disease
mg	milligram
mL	milliliter
mm	millimeter
mm Hg	millimeter mercury
MRE	Magnetic Resonance Elastography
PT-INR	Prothrombin time – international normalized ratio
RNA	ribonucleic acid
ROTEM	rotational thromboelastometry
SAE	serious adverse event
SBP	systolic blood pressure
SCr	serum creatinine
TEG	thromboelastography
TIPS	transjugular intrahepatic portosystemic shunt
T_{max}	time to maximum concentration
TPr	thromboxane prostanoid receptor
TxA_2	thromboxane A_2
US	United States of America
USP	United States Pharmacopeia
VCTE	Vibration Controlled Transient Elastography
WHVP	wedged hepatic venous pressure

5 INTRODUCTION

This study is to be performed in accordance with Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations Parts 50, 56 and 312, and the International Conference on Harmonization E6.

5.1 Background Information

Cirrhosis is a potentially life-threatening condition that occurs when the liver is damaged by fibrotic scarring. Fibrosis can impair the flow of portal blood through the hepatic sinusoids and result in hypertension in the portal vasculature. One of the major complications from portal hypertension is the development of gastrointestinal varices. Bleeding due to varices specifically in the esophagus accounts for one third of the deaths related to portal hypertension. The median survival period in humans following diagnosis of cirrhosis is six years (La Vecchia 1994; Pagliaro 1994). Currently little effective therapy is commercially available for treatment of portal hypertension.

[redacted]

[redacted] liver (Yokoyama 2005). However, in the cirrhotic liver, studies in rats have revealed an increase in the hepatic production of TxA_2 which would then further increase portal hypertension via vasoconstriction (Graupera 2003; Rodriguez-Vilarruplas 2012). Also, the compensatory feedback between TxA_2 as a vasoconstrictor and nitric oxide as the inhibitory vasodilator seems to disappear in the cirrhotic liver (Yokoyama 2005).

Blockade of thromboxane-mediated signaling in the TPr has revealed an anti-fibrotic effect in two rat models of cirrhotic disease (Rosado 2013). Additionally, interrupting this signaling pathway lowered portal pressure suggesting a reduction in h[redacted]

[redacted]

[redacted]

5.2 Stage of Development

This is a Phase II exploratory study to determine the safety of oral ifetroban compared to placebo in patients with portal hypertension. The efficacy of oral ifetroban compared to placebo in reducing portal pressure and liver fibrosis will also be explored.

5.3 Patient Population

Adult patients with liver cirrhosis, confirmed by liver biopsy, laboratory features, and/or elastography findings will be considered for study participation. Portal pressures are measured by the hepatic venous pressure gradient (HVPG) method during screening. A HVPG reading greater than 5 mm Hg defines portal hypertension, while higher HVPG values $\geq$ 10 mm Hg suggest patients that are at a significant risk of developing gastrointestinal varices. This study will select patients with a baseline mean HVPG of $\geq$ 8 mm Hg as they will have significant disease progression to be candidates for the study of an effect to the investigational treatment. Patients with baseline mean HVPG values over 18 mm Hg will be excluded as a surgical intervention may be indicated at this severity of disease.

5.4 Trial Rationale

[redacted] The current standard of care for treatment of portal hypertension focuses on management of symptoms, including mechanical hemostasis of varices, pharmacologic support with B-blockers and surgical relief of the increased portal pressure with the transjugular intrahepatic portosystemic shunt (TIPS) procedure. [redacted]

5.5 Risk-Benefit Assessment

Clinical history with the use of ifetroban [redacted] has not identified any major risks with ifetroban use. [redacted]

[redacted]

6 STUDY OBJECTIVES

The exploratory objectives of this study are to evaluate the following in cirrhotic patients with portal hypertension that are treated with ifetroban:

- Safety
- Portal pressure
- Serum liver enzymes
- Surrogate markers of liver fibrosis and inflammation
- Occurrence of variceal bleeds

6.1 Study Endpoints

The study objectives will be assessed utilizing the following endpoints; see 8.2.1 for details of the assessments:

- To evaluate the safety of ifetroban treatment in this population, the incidence and severity of adverse events will be compared between the ifetroban and the placebo groups.
- To evaluate the effect of ifetroban treatment on portal pressure in this population, the change from baseline in the mean HVPG will be calculated at 15 minutes, 30 minutes and Day 90 following the completion of the first investigational medicinal product (IMP) dose and compared to placebo patients.

- To evaluate the effect of ifetroban treatment on serum liver enzymes in this population, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values on Day 45 and Day 90 will be compared to baseline for ifetroban and placebo patients.

- To evaluate the effect of ifetroban treatment on liver fibrosis and inflammation in this population, the change from baseline to Day 45 and Day 90 will be calculated for ifetroban and placebo patients in the following assessments:

  - Aspartate aminotransferase/platelet ratio (APRI)

  - Specified serum biomarkers

- To evaluate the occurrence of variceal bleeds in this population, the incidence and severity of any variceal bleeds will be documented.

7 STUDY DESCRIPTION

7.1 Study Design

- Phase II, randomized, double-blind, and placebo-controlled pilot study.

- Thirty patients will be enrolled; twenty patients will be allocated to ifetroban and ten will receive placebo.

- Each qualified subject will remain in the study for 90 days. Enrollment for the entire study is expected to take twelve months.

- A schedule of assessments is summarized in Table 8.1-1.

7.2 Randomization and Blinding Conditions and Methods

7.2.1 Randomization

[redacted] The aim is to include twenty patients treated with ifetroban and ten patients with placebo. There is no stratification of patient sub-populations. [redacted]

7.2.2 Unblinding Conditions and Procedures

Breaking the blind for a subject should be considered only when knowledge of the treatment assignment is deemed essential by the subject's physician for the subject's care. Given that there are no antidotes for ifetroban, unblinding is not likely to lead to a change in treatment of the patient beyond holding or discontinuing the IMP. As such, unblinding should be a rare occurrence.

If time permits, and if significant risk is not introduced to the patient, the investigator will contact the medical monitor at the sponsor to discuss the desire to unblind the treatment assignment. If agreement is reached that unblinding should occur, the blinded clinical monitor will mediate contact between the investigator and the unblinded sponsor contact, as needed, to disclose the treatment assignment. All discussions on this topic, including the treatment disclosure, if applicable, will be documented and filed in the study files.

In emergency scenarios, the Investigator may contact the blinded clinical monitor directly who will then mediate communication with the unblinded sponsor contact.

Any intentional or unintentional breaking of the blind at an investigative site must be reported to the Sponsor immediately.

7.3 Drugs and Dosages

7.3.1 Identification and Description of Test Agents

7.3.1.1 Ifetroban Injection

[redacted]

[redacted]

Ifetroban injection, 50 mg (10 mg/mL)
Lot number: 1-FIN-1122 Volume: 5 mL
Store at room temperature.
Instructions: Use as directed.
Caution: New Drug—Limited by United States Law to Investigational Use
Cumberland Pharmaceuticals Inc., Nashville, TN 37203

7.3.1.2 Oral Ifetroban Capsules

[redacted]

7.3.1.3 Oral Placebo Capsules

[redacted]

PLACEBO OR IFETROBAN CAPSULES 50MG
Quantity: 75 Capsules
Instruction: Take capsules by mouth as directed.
Store at controlled room temperature, 20ºC – 25ºC (68ºF – 77ºF)
Caution: New Drug-Limited by Federal law to investigational use
Cumberland Pharmaceuticals Inc.

[redacted]

7.3.2 IMP Preparation and Dosing Instructions

[redacted]

7.3.2.1 Ifetroban or Placebo Injection

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.3.2.2 Oral Ifetroban or Placebo

[redacted]

[redacted] 7.3.2.1 [redacted]

[redacted]

Dosing Instructions

The subject is prescribed to begin taking their oral dose on Day 2, the day following their intravenous dose. Ifetroban and placebo should be taken at least 30 minutes before a meal or 6 hours after a meal. Therefore, it is advisable to recommend the subject dose themselves each day soon after waking up.

All subjects are to take five capsules once daily throughout the 90-day treatment period. All capsules are taken in the same episode. In a double-blinded manner, ifetroban subjects will take five capsules of 50 mg ifetroban daily; placebo subjects will take five capsules of matched placebo per day.

7.3.3 Drug Accountability Procedures

Ifetroban and placebo labeled for investigational use will be provided without charge by Cumberland Pharmaceuticals Inc. The investigator is required to keep complete and accurate records of the receipt, dispensation, disposal and return of all clinical trial drugs provided during the conduct of the study. Cumberland Pharmaceuticals will ensure maintenance of complete and accurate records of the receipt, dispensation, disposal or return of all trial drugs.

Additional details regarding the monitoring of drug accountability and patient compliance with at-home dosing is covered in 8.2.4.

7.4 Selection of Study Population

Determination of study eligibility will be made by the Investigator on the basis of the inclusion and exclusion criteria listed below.

7.4.1 Inclusion Criteria

To be considered eligible to participate in this study, a patient must meet the following inclusions criteria:

1) Adults with cirrhosis, defined as meeting at least one of the following:
   a) Histopathological diagnosis of liver cirrhosis
   b) Historical HVPG value $\geq$ 7 mm Hg
   c) Liver stiffness measurement (LSM) greater than
      - 15 kPa, if measured by Vibration Controlled Transient Elastography (VCTE), or
      - 6.7 kPa, if measured by Magnetic Resonance Elastography (MRE) with at least one of the two following criteria:
        i) Evidence of splenomegaly or collateral portal-venous anastomoses on imaging or endoscopy without portal vein thrombosis
        ii) Platelet count below 150 x $10^3/\mu L$ and AST value greater than ALT

2) At least two stable baseline values for each of the following variables: AST, ALT, ALP and bilirubin. One value will be from the study screening period, and the other value(s) taken between 15 and 90 days prior to the screening labs. Stable is defined as values having a difference $\leq$ 40 U/L for AST and ALT, $\leq$ 60 U/L for ALP and $\leq$ 3.0 mg/dL for total serum bilirubin

3) Baseline mean HVPG measurement $\geq$ 8 and $\leq$ 18 mm Hg

7.4.2 Exclusion Criteria

To be considered eligible to participate in this study, a patient must not meet any of the following exclusion criteria:

1. Be less than 18 years of age or greater than 70 years of age.

2. Be pregnant, nursing, or planning to become pregnant.

3. Have portal or splenic vein thrombosis. Patients with portal or splenic vein thrombosis in their history may participate if there is more recent confirmation that there is no occlusion or that no thrombosis is detectable.

4. Previous transjugular intrahepatic shunt (TIPS) or portocaval shunt.

5. Variceal or other gastrointestinal bleed in the two months prior to enrollment.

6. Current or scheduled hemodialysis.

7. Most recent Child-Pugh Score $\geq$ 12, within 30 days of enrollment.

8. Most recent MELD-Na score $\geq$ 20, within 30 days of enrollment.

9. Current acute kidney injury, chronic kidney disease, or most-recent baseline serum creatinine $\geq$ 2.0 mg/dL.

10. Active alcohol consumption (greater than an average of two drinks per day).

11. Active hepatitis B virus (HBV) or hepatitis C (HCV) infection; current treatment, except suppression treatment for HBV, or plans to initiate treatment for HBV or HCV during study involvement; or eradication of HCV within previous 3 months.

12. Platelet count < 60 x $10^3/\mu L$

13. Confirmed or suspected diagnoses of Vitamin A toxicity, extramedullary hematopoiesis, or Budd Chiari Syndrome.

14. Use of endothelin receptor antagonists, somatostatin analogues or prostanoids in the last seven days or planned use during the study.

15. Myocardial infarction in the 90 days prior to enrollment.

16. History of bleeding diathesis OR any risk factors for bleeding based on patient or familial history, other than cirrhosis and its sequelae, or use of anticoagulant or antiplatelet drugs, including aspirin, in the last 14 days or planned use during the study.

17. History of allergy or hypersensitivity to ifetroban.

18. Have taken investigational drugs within 30 days before IMP administration.

19. Inability to understand the requirements of the study, spoken English, or the need to abide by the study restrictions and to return for the required treatments and assessments.

20. Be otherwise unsuitable for the study, in the opinion of the investigator.

7.5 Prior and Concomitant Therapy

Patients may enter the study while on a beta blocker but the patient must be on a stable dose for at least 30 days prior to enrollment, and the dose may not be altered or stopped during the Treatment Period. Beta-blocker-naïve patients may not initiate beta blocker therapy during the Treatment Period.

Drugs from the statin class are allowed if the patient has been on a stable dose for three months and will continue on that dose throughout the study.

7.5.1 Excluded Medications/Procedures/Therapy

Some concomitant medications are prohibited during study involvement as detailed below. As applicable, some medications must undergo a sufficient wash-out period before a subject can begin study treatment.

The following drugs are not allowed to be taken between Day -14 and the end of study treatment:

- Aspirin, other anti-platelet drugs, and anticoagulants

The following drugs are not allowed to be taken between Day -7 and the end of study treatment:

- Endothelin receptor antagonists, somatostatin analogues and prostanoids
- Drugs from the nitrate class
- Treatment protocols for HBV or HCV

[redacted]

8 EXPERIMENTAL PROCEDURES

8.1 Overview – Schedule of Time and Events

The study consists of a 14-day screening period, a 90-day treatment period [redacted]

A 7-day follow-up completes the study. The schedule of events for the study, including allowable time windows appears in Table 8.1-1 below.

Table 8.1-1 Schedule of Events

Study Phase	**Screening**	**Baseline**	**Day 1**	**Day 10**	**Day 45**	**Day 90 / Early Term**	**Follow-up**
Allowable Windows	Day -14 to Hour 0	Hour -6 to Hour 0		+/- 3 days	+/- 5 days	From -5 to +0 days (Day 85-90)	6 to 8 days following Day 90/ET visit
Demographic Data	X						
Medical History	X						
Review of Inclusion/Exclusion	X	X					
Pregnancy Test	X						
Physical Exam	X			X	X	X	
Hepatic Venous Pressure Gradient Measurements		X	[redacted]			X	
[redacted]	[redacted]				[redacted]	[redacted]	
Safety Labs	X*			X	X	X	
[redacted]	[redacted]			[redacted]	[redacted] Section 8.2.1.2		
HBV and/or HCV testing, if needed	X						
VCTE, if needed	X						
Vital Signs		X	after IV IMP completion	X	X	X	
IMP dosing – intravenous			Start of IV dose defines Hour 0				
IMP dosing - oral			Once daily oral IMP dosing begins on Study Day 2 and continues through Day 90				
Review of Drug Accountability				X	X	X	
Con Med monitoring	Continual						
Adverse Event monitoring			Continual				Phone Call

* Per Inclusion Criterion #2, if historical ALT, AST, ALKP, and bilirubin are not available from between 15- and 90-days prior to the safety labs drawn during screening, an initial set of labs, reporting ALT, AST, ALKP, and bilirubin, will be required by the study prior to screening but following the subject's consent. In such a case, full safety labs per 8.2.1.5 will be assessed 15-90 days later during the 14-day screening window shown above.

8.2 Measurements and Evaluations

8.2.1 Description of Key Study Assessments

8.2.1.1 Hepatic Venous Pressure Gradient (HVPG) Measurement

A recorder capable of generating permanent tracings (paper and/or electronic) must be used for this study. Following standard medical process regarding sedation, aseptic preparation of the venous access site and catheter care, initial venous access is established through a route and method chosen by the Investigator or qualified designee. Ultimately, a balloon-tipped catheter is placed in the main right hepatic vein under fluoroscopic guidance until the tip is approximately 5 cm from the vena cava. The succeeding steps are then followed to record the hepatic venous pressure gradient:

1. The balloon is inflated and dye is injected to confirm complete occlusion of the catheterized vein. Dye that circumvents the balloon or is shunted to other venous return will require the catheter to be repositioned.

2. The inflated catheter is left in place for approximately 45 seconds while pressure is recorded and stabilized [wedged hepatic venous pressure (WHVP)].

3. The balloon is completely deflated and the catheter is retrieved proximally until the tip is approximately 2 cm from the vena cava.

4. Pressure recordings continue for approximately 45 seconds [free hepatic venous pressure (FHVP)].

5. After 1 minute, the catheter is advanced distally to its original position and the balloon inflated.

6. Steps 2-4 are repeated at least two additional times.

7. The hepatic venous pressure gradient is measured as the difference between the stable WHVP reading and the subsequent stable FHVP reading. At the Baseline and Day 90 time points, pressure gradients will be recorded until three HVPG values are all within 1 mm Hg of each other. . [redacted]

The three valid HVPG values, plus the mean, are recorded in the study case report form for each time point.

[redacted]

8.2.1.4 Incidence of Variceal Bleeds

The occurrence and details of any variceal bleeds during the treatment period will be captured in a dedicated module of the Case Report Form (CRF) and occurrences will be reported as endpoints in the study results. If the bleed meets the criteria of an adverse event, it will also be captured as an adverse event according to standard GCP reporting processes.

Variceal bleeding is defined for this study as the presence of either reported or witnessed hematemesis, melenemesis, melena, or bright red blood per rectum and a concomitant drop in hemoglobin of 1 gm/dL compared to baseline and no other source of bleeding.

Additional diagnostics, including upper gastrointestinal endoscopy, will not be ordered by the study protocol; however, results from any standard of care procedures should be captured in the study records.

Treatment for any bleeding will be ordered at the Investigator's discretion according to standard of care.

8.2.1.5 Safety Labs

Blood sample collection for safety laboratory assessments will be performed within protocol-specified time periods and according to the site's standard practices for drawing and processing samples. The following analytes are measured by the site's local laboratory and evaluated by the investigator with respect to reference ranges provided by that lab:

- Hematology and coagulation
    - Complete blood count (CBC) with differential
        - Total white blood cell count
        - absolute counts for
            - neutrophils
            - lymphocytes
            - monocytes
            - eosinophils
            - basophils
        - platelet count
        - hematocrit
        - hemoglobin
    - PT-INR (International Normalized Ratio of Prothrombin Time)
    - aPTT (activated Partial Thromboplastin Time)
- Clinical biochemistry with electrolytes

- Sodium
- Potassium
- Chloride
- Total carbon dioxide
- Glucose
- Blood urea nitrogen (BUN)
- Serum creatinine (SCr)
- Total bilirubin
- Albumin
- Total protein
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)

8.2.2 Description of Screening/Baseline Period

Before the initiation of study-specific screening assessments, the patient or legal authorized representative must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the patient or legal authorized representative must sign and receive a copy of an Informed Consent Form that was approved by the center's governing Institutional Review Board (IRB). Once informed consent has been obtained, the eligibility of the patient to participate in this study will be determined by the Investigator on the basis of the inclusion and exclusion criteria. Screening/Baseline Period assessments will also be performed according to the protocol to determine eligibility. Only eligible patients will be randomized to receive IMP.

During the Screening/Baseline Period, the following evaluations will be performed to determine the patient's eligibility for this study and document their baseline disease state; allowable time windows are described in Table 8.1-1:

- Demographic data
- Review and documentation of medical history. Subjects must be asked about patient or familial history of bleeding diathesis and any known risk factors for bleeding. Resolved diseases or past procedures that are not significant to the disease under study should be captured if they occurred in the previous five years. Other history should be captured regardless of time reference.
- A serum or urine pregnancy test will be performed on all women of child-bearing potential.

- A baseline physical examination will be performed for all significant body systems.

- Safety labs will be drawn and processed according to standard local processes. Analytes to be measured are listed above in 8.2.1.4. Per inclusion criterion #2 (See Section 7.4.1), historical lab values for ALT, AST, ALKP and bilirubin are required from between 15 and 90 days prior to the safety lab values drawn during screening for comparison and confirmation of disease-state stability. If no such lab values are available to the Investigator, an initial panel will be drawn following the obtaining of subject consent, and the screening assessments, including a full safety lab panel (See Section 8.2.1.5) will be performed 15 to 90 days later, within the defined screening period.

- Additional serum will be collected for submission to the central lab for biomarker analysis as per the laboratory manual.

- Active HBV and HCV must be ruled out prior to enrollment. If the patient's HBV status is unknown, a Hepatitis B surface antigen (HBsAg) test will be performed. If the patient's HCV status is unknown, an HCV antibody test and/or, if needed, an HCV RNA test will be performed.

- Baseline HVPG measurements are performed within the 6 hours prior to first IMP administration. However, as detailed in 8.2.3 below, this screening measurement will likely be performed immediately prior to IMP administration.

- Baseline vital signs are taken in the six hours prior to first IMP treatment: heart rate; respiration rate; body temperature; and indirect blood pressure.

- If the subject has been diagnosed with cirrhosis, but by a method other than those listed in inclusion criterion #1 (See Section 7.4.1), a VCTE will be performed to confirm a diagnosis of cirrhosis as defined in this protocol.

[redacted]

7.3.2.1

[redacted]

[redacted]

8.2.4 Description of Treatment Period

8.2.4.1 Day 1

Hour 0 of the treatment period is defined as the time when the intravenous infusion of IMP is first initiated. According to the site's standard procedures, the 100 mL infusion volume will be administered over a 15-minute period. As soon as allowable after the completion of the infusion, an assessment of the mean HVPG will be made according to the procedure detailed in 8.2.1.1. [redacted]

[redacted]

[redacted]

8.2.4.2 Day 10

Subject will have a clinic visit on Day 10 (+/- 3 days) for a safety follow-up evaluation. The visit will consist of a physical examination, [redacted] vital sign measurement, and local lab assessment of safety labs, [redacted]. Consistent with the entire treatment period, changes in concomitant medications and any spontaneously-reported adverse events will be recorded.

[redacted]

[redacted]

8.2.4.3 Day 45

At Day 45 (+/- 5 days), an interim treatment-period visit is performed for the standard safety evaluations (physical exam [redacted] vital signs, and safety labs) [redacted]

[redacted]

[redacted]

8.2.4.4 Day 90 / Early withdrawal

[redacted] Safety assessments (physical exam [redacted] vital signs, and safety labs) are performed [redacted] The subject is again prepared for hepatic vein pressure measurements and HVPG measurements are recorded during the visit. [redacted]

8.2.4.5 Follow-up

A phone call is made by the study staff between 6 and 8 days following the Day 90/Early termination visit. The subject is asked about their medical status to assess for any spontaneously reported adverse events.

8.2.5 Potential Drug-induced Liver Injury

Subjects in this study are enrolled with confirmed pre-existing hepatic disease; therefore, published guidelines (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf) for monitoring potential drug-induced liver injury (DILI) are available but do not apply to the same degree.

A modified protocol is followed when patients in the treatment or follow-up phases show evidence of possible DILI and need to be monitored or have their study treatment modified accordingly.

8.2.5.1 Criteria for Initiating Protocol for Potential DILI Cases

Any subject meeting any one of the following criteria during the treatment or follow-up phase will enter the protocol (See Section 8.2.5.2 below) for potential DILI cases:

- An elevation of ALT or AST greater than 2 X the baseline value for that patient
- An elevation of total bilirubin greater than 1.5 X the baseline value for that patient
- Any increase in bilirubin seen in conjunction with suspect hypersensitivity signs or symptoms such as fever, rash, eosinophilia, nausea, vomiting, or right upper quadrant pain mandates that the subject enter the monitoring protocol, but also **discontinue study drug immediately**.

8.2.5.2 Protocol for Potential DILI Cases

All assessments made during the monitoring of potential DILI cases will be captured in the CRF.

Initial Evaluation

Any subject that meets a criterion in Section 8.2.5.1 should have liver enzymes and bilirubin levels repeated within 48 hours to confirm the abnormalities and detect if they are increasing or decreasing. At that unscheduled visit, the following assessments will be performed and additional information collected:

- Physical Exam with detailed assessment of symptoms
- History of concomitant drug use (including nonprescription medications and supplements), alcohol use, recreational drug use, and special diets.

- History of exposure to environmental chemical agents

A diagnostic plan should be formulated and initiated by the Investigator, if appropriate based on history, physical exam findings and laboratory results, to rule out additional potential causes of liver disease such as acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.

Monitoring

At a minimum, liver enzyme and serum bilirubin testing should be performed initially 2-3 times weekly until abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. The scope and frequency of monitoring can then be modified as appropriate.

Decision to Stop Study Drug

There is no strict guidance on when to stop study drug in a patient with pre-existing liver disease that is demonstrating some possible signs of drug-induced liver injury. Section IV.A.5 of the following guidance may be used for reference and assistance:
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

The Medical Monitor should be consulted as well in the decision to continue or discontinue study drug.

The decision to discontinue or temporarily interrupt study drug treatment should generally be based on the following factors:

- Stability or directional changes of ALT, AST, and bilirubin
- Elapsed time during which values have remained higher than baseline
- The degree to which the baseline ALT, AST and bilirubin were high relative to the upper limit of normal

Please note that Section 8.2.5.1 directs the study drug to be stopped for cases of elevated bilirubin with concurrent symptoms such as fever, rash, eosinophilia, nausea, vomiting, or right upper quadrant pain.

Follow-up

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the expected baseline state given the pre-existing liver disease.

9 SUBJECT DISCONTINUATION

9.1 Subject Discontinuation - General

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time and for any reason. The Investigator will describe in the CRF the reason for the subject's choice to discontinue.

A subject may be removed from the study for the following reasons; in each case, the decision to discontinue should be confirmed following consultation between the Investigator and Sponsor:

- Adverse event (AE): If a subject experiences an AE for which continued study participation presents an unacceptable consequence or risk to the subject, the subject may be discontinued under the Investigator's judgement. See also Section 9.2.

- Subject non-compliance: A subject's past, current, or anticipated inability to comply with study visits, clinical trial medication or other processes required by the protocol may lead to the decision to discontinue the subject from the study. The subject's compliance in taking oral medication at home should be within 90 and 110% at all visits.

- Enrollment violation: If it is realized after the initiation of investigational treatment (or placebo) that a subject did not meet all eligibility requirements, the Sponsor and Investigator will discuss whether it is safe, ethical, and scientifically sound to keep the subject in the study or to discontinue the subject.

- Concurrent Treatment: If a subject initiates a procedure or medication that may interfere with their study conduct or for which study involvement may pose a significant risk to the prescribed therapy, the subject may be discontinued. This also includes the use of therapies restricted by the protocol in Section 7.5.

- TIPS or shunt procedure during the treatment period.

- Liver transplant during the treatment period.

- Other reasons: Following discussion between the Sponsor and Investigator, subjects may be discontinued from the study for reasons other than those listed above.

9.2 Subject Discontinuation - Protocol-specified Common Terminology Criteria for Adverse Events (CTCAE)

Subjects encountering adverse events meeting either of the criteria below will be discontinued from study drug but continued to be monitored for safety. The Investigator will plan to remain blinded and consult with the sponsor's Medical Monitor and a decision will be made and documented regarding continued patient monitoring and criteria under which study drug would be re-initiated or additional efficacy assessments would be performed.

- Any grade 4 or higher adverse event defined by CTCAE (See Section 10.1.2 for guidance)
- Any grade 3 adverse event that is classified by the Investigator as possibly or probably related to study drug

See also Section 10.4 regarding the unblinded review of safety data if multiple subjects have significant AEs.

9.3 Procedures for Subject Discontinuation

If a subject is permanently withdrawn from study drug prior to completion of the full treatment period, a Day 90 visit, as described above should be performed if the subject consents and there is no additional risk to the patient by performing the assessments. Following the visit, reasonable efforts should be made to monitor the subject for AEs, as appropriate.

Subjects that are discontinued may be replaced, as needed. The decision will be made on a case-by-case basis by the study sponsor.

9.4 Study or Site Termination

If conditions arise during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, Medical Monitor, and Study Monitor.

Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product

- See also Section 10.4 regarding enrollment termination due to AEs.

A study conducted at a single study site or a single study site in a multicenter study may also warrant termination under the following conditions:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonization (ICH) sixth efficacy publication (E6) on Good Clinical Practice, Section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

10 ADVERSE EVENTS

Information about AEs, whether spontaneously reported by the subject, discovered by the Investigator by questioning/review of diary records or detected through physical examination, laboratory test or other means, will be collected and recorded on the adverse event form and followed-up as appropriate. Information about serious adverse events should be reported to the Sponsor within 24 hours of obtaining knowledge of the event.

10.1 Definitions

10.1.1 Adverse Event Definitions

Adverse events are defined according to ICH Harmonized Tripartite Guideline E2A.

Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a trial product whether it has a causal relationship with the study treatment or not.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following are not considered an AE:

- Pre-planned procedure (documented as concomitant illness on the CRF at screening) unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent form.

- Pre-existing conditions found during and as a result of screening procedures.

Serious adverse event (SAE)

An AE that meets any of the following criteria:

- results in death

- is immediately life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)

- requires in-patient hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability or incapacity

- is a congenital anomaly or birth defect

- is judged medically important in the opinion of the Investigator (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed.

Non-serious adverse event

Any adverse event that does not meet the definition of an SAE.

Unexpected adverse event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator 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.

10.1.2 Adverse Event Assessment Definitions

Anticipated

Anticipated events include known consequences of an underlying disease or the condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pretreatment baseline.

Severity

The reported event terms and severity grading of each event reported in this study adhere to the Common Terminology Criteria for Adverse Events (CTCAE) grading criteria, which is coordinated by the National Cancer Institute of the National Institutes of Health.

Resources including quick references, governance documents and data files of adverse events can be found here: http://evs.nci nci.nih.gov/ftp1/CTCAE/About.html

The Investigator, with support from the study monitor, will report adverse events using the lowest level terms, as identified by the Medical Dictionary for Regulatory Activities (MedDRA) http://www.meddra.org/, whenever possible.

The severity of each event adheres to the severity grades established by CTCAE:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

The investigator will determine the severity for each individual event utilizing the following guidance; listed here http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf:

Relationship/Relatedness

The causal relationship between an adverse event and the trial product is assessed by the investigator using the following definitions:

Probable: Good reasons and sufficient documentation to assume a causal relationship.

Possible: A causal relationship is conceivable and cannot be dismissed

Unlikely: The event is most likely related to an etiology other than the trial product.

An adverse event is considered causally related to the use of the trial product when the relationship assessment is probable or possible. Events assessed as unlikely related to the use of trial product will be considered as having no relationship to treatment.

Outcome

The outcome of an adverse event is assessed by the investigator using the following definitions:

Recovered: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.

Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial.

Recovered with sequelae: As a result of the AE the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be classified as an SAE.

Not recovered: The subject's condition has not improved and the symptoms are unchanged

Unknown: The subject's condition is unknown. This term should only be used when no other definition is possible e.g., the subject is lost to follow-up.

10.2 Collection, Recording and Reporting of Adverse Events

All events meeting the definition of an adverse event must be collected and reported from the first trial-related activity after the subject signs the informed consent and until, for example, last subject contact/visit/end of post-treatment follow-up period.

At each contact with the trial center, the subject must be asked about adverse events in an objective manner like: "Have you experienced any problems since the last contact?"

Adverse events according to the definition, either observed by the investigator or reported by the subject, must be recorded by the investigator and evaluated. Adverse events must be recorded in the case report forms. For serious adverse events, the SAE form must also be filled in.

The investigator should record the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual adverse events.

Serious Adverse Events

The investigator must report initial information on all serious adverse events within 24 hours of obtaining knowledge of the event.

Furthermore, the investigator must complete and transmit, as applicable, the adverse event and SAE forms within five days of obtaining knowledge of the SAE. The monitor must be informed accordingly.

The Investigator will inform the health authorities and independent ethics committees (IECs)/IRBs in accordance with local requirements in force and the International Conference on Harmonization (ICH) guidelines for GCP and the European Union (EU) Directive 2001/20/EC / Food and Drug Administration (FDA) Title 21 Code of Federal Regulations, Part 312.32 (5).

Adverse Events Starting after Trial Completion

Adverse events occurring after trial completion, which the investigator considers to be related to the investigational medicinal product must be reported to the sponsor.

10.3 Study-Specific Guidance Pertaining to Adverse Events

Patient interactions, including examinations, tests, procedures and treatments that are ordered based on the occurrence of cirrhosis decompensation or hemorrhagic events are captured in the CRF in the Concomitant Treatment, [redacted] Unscheduled Visits, and/or Comments Modules.

10.3.1 Variceal Bleeding

In most cases, an occurrence of a gastrointestinal hemorrhage during the treatment phase will meet the definition of an adverse event. Since variceal bleeds are an endpoint of the study, specific details surrounding such an occurrence are collected on a dedicated module of the CRF. However, the same event is also added to the Adverse Event module of the CRF so that safety listings for the study are complete.

Incidences of variceal bleeds will also follow the protocol for general bleeding as directed below in Section 10.3.3.

10.3.2 Cirrhosis Decompensation

All events that are considered decompensation events related to cirrhosis meet the definition of an adverse event and are captured accordingly. The following are recognized decompensation events:

- Ascites
- Hepatorenal syndrome (HRS)
- Spontaneous bacterial peritonitis (SBP)
- Hepatic encephalopathy (HE)
- Gastric or esophageal variceal bleeding

Of these events, only the occurrence of variceal bleeding is an endpoint of the study and is captured in a dedicated CRF module in addition to the AE module. All other decompensation events will be captured in the AE module and monitored closely.

[redacted]

[redacted]

As noted in 10.3.1, variceal bleeding will also be reported in a dedicated CRF module.

10.4 Subject or Study Discontinuation Due to Adverse Event

In the event that three or more patients experience a grade 3 (CTCAE) or above from one system organ class, regardless of the events' relative attribution to study drug by the Investigator, additional enrollment will be halted immediately and an unblinded safety review of patient data will be initiated according to the study's safety plan. The outcome of this review will be documented and communicated to the Investigators. Potential outcome may include termination of the study, modification of the protocol, or resuming of the protocol without modification.

10.5 Follow-up of Adverse Events

Follow-up of Non-Serious Adverse Events

All adverse events classified as non-serious adverse events that are both severe and possibly or probably related to the investigational medicinal product should be followed until the subject has recovered.

For cases of chronic conditions, follow-up until "recovered" is not required. After the subject has completed the trial, these cases can be closed with the outcome "recovering" or "not recovered".

All other non-serious adverse events must be followed until the outcome of the event is "recovering" (for chronic conditions), "recovered" or until, for example, last subject contact/visit/end of post-treatment follow-up period, whichever comes first, and until all queries related to the adverse event have been resolved.

Follow-up of Serious Adverse Events

All adverse events classified as serious should be followed until the outcome of the event is "recovered", "recovered with sequelae", "death" and until all queries have been resolved. For cases of chronic conditions and cancer, follow-up until "recovered", "recovered with sequelae" or "death" is not required. After the subject has completed the trial, these cases can be closed with the outcome "recovering" or "not recovered".

11 STATISTICAL METHODS AND DATA ANALYSIS

There is no statistical analysis plan for this study [redacted] Results will be analyzed and reported descriptively.

11.1 Sample Size Determination

Formal sample size calculations were not performed. Twenty active, and ten placebo subjects will be enrolled in this study and results will be presented descriptively.

11.2 Subject Population(s) for Analysis

All data will be listed by subject. Continuous data will be summarized in tables comparing proportions or percentages of patients in each treatment group. Standard deviation or standard error will also be calculated. The safety population consists of all subjects who were enrolled and received at least a partial dose of IMP; no treated subjects will be excluded from the safety analysis population. For the efficacy analyses on this pilot study, patients will be evaluated according to the treatment they received.

11.3 Statistical Methods

In presenting data from this trial, continuous data will be summarized in tables listing the mean, standard deviation or standard error, median, and number of subjects in a group. Categorical data will be summarized in tables listing the frequency and the percentage of subjects in a group. These summaries will be presented separately for subjects in the Ifetroban and placebo treatment arms.

11.4 Interim Analysis

No interim analyses are planned.

12 STUDY MANAGEMENT AND DATA COLLECTION

12.1 Confidentiality

All information regarding the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on CRFs and other study documents submitted to the Study Monitor. Documents that will not be submitted to the Study Monitor and that identify the subject (e.g., the signed informed consent document) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

12.2 Source Documents

Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, tracings from the HVPG measurements, copies or transcriptions certified after verification as being accurate and complete, magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. The Monitor, representatives of the Sponsor and the applicable regulatory authority will be allowed access to source documentation.

12.3 Case Report Forms

CRF forms will be available for data entry by the site [redacted]. Cases will be monitored remotely and on-site by the sponsor

according to a written Monitoring Plan and data will be retrieved by the monitor for data analysis at the sponsor.

12.4 Records Retention

According to 21CFR312.62, all CRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of two years following notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed upon designee, such as the Study Monitor, another Investigator, or the institution where the study was conducted.

13 STUDY MONITORING, AUDITING, AND INSPECTING

13.1 Study Monitoring Plan

The investigator will permit study-related monitoring, audits and inspections by the IRB, the Sponsor and any applicable regulatory authority.

The sponsor will adhere to a written Monitoring Plan in fulfilling the requirements of ICH/GCP guidelines and the CFR to monitor the execution of the study and the collection of data. In general, the progress of the study will be monitored by using the following methods:

- Periodic onsite visit(s) by the sponsor representative
- Telephone communications among the Investigator, Clinical Monitor and/or Medical Monitor, as needed
- Remote and on-site review by the sponsor representative of CRFs, clinical records and regulatory documents

Details are described in the written monitoring plan.

14 ETHICAL CONSIDERATIONS

This study will be conducted according to the standards of ICH, GCP Guidelines, IRB regulations, any applicable government regulations and procedures. This protocol and any amendments will be submitted to a properly constituted IRB for approval of the study conduct.

14.1 Informed Consent

Written informed consent must be obtained from each subject (or the subject's legal guardian/representative) before performing any Screening/Baseline Period evaluations. The signed informed consent document will be retained by the Investigator, and a signed copy will be given to the subject or subject's legal guardian/representative. The informed consent document, which is prepared by the Investigator, must have been reviewed and approved by the Sponsor and the Investigator's IRB before the initiation of the study. The document must contain the 20 elements of informed consent described in 21CFR50.25 and ICH E6 4.8. In addition, subjects of appropriate intellectual maturity should provide written informed assent, as determined by the institution's IRB or local legal requirement.

14.2 Protocol Compliance

Investigators must follow the IRB-approved protocol. If the Investigator intends to deviate from the protocol, the IRB and Sponsor should be informed prior to the deviation.

In cases where the Investigator decides to deviate from the protocol in order to avoid an apparent immediate risk to a specific subject, the Investigator may proceed with emergency and appropriate treatment at his discretion and the IRB and Sponsor will be notified as soon as possible afterward. In addition, the Investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria. Such changes must be prepared as a protocol amendment by the Sponsor. A protocol amendment must receive IRB approval before implementation.

In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the informed consent document, the revised informed consent document prepared by the Investigator must be approved by the Sponsor, Study Monitor, and the IRB.

14.3 Financial Disclosure

Each clinical site investigator will provide the Sponsor with sufficient, accurate financial information in accordance with local and federal regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory

health authorities. Investigators are responsible for providing information on financial interest during the study and for one year after completion of the study in accordance with FDA policy (Title 21 CFR – PART 54 FINANCIAL DISCLOSURE BY CLINICAL INVESTIGATORS Revised as of April 1, 2015).

14.4 Study Files

Documentation verifying the Investigator's legal and regulatory authority and acceptable scientific background to conduct the trial will be available at both the site and the sponsor before shipments of IMP are sent to the investigative center.

Following study initiation, the Investigator will maintain adequate records to re-create and justify the complete conduct of the trial at a later date. Document inventory will adhere to ICH/GCP and CFR requirements and will include those pertaining to the Investigator's qualifications, inventory and handling details of investigational products, and detailed medical and study histories for all subjects.

[redacted]

[redacted]