An Open-Label, Cohort Dose Escalation Study to Assess the Safety and Efficacy Signals of F-652 in Patients with Alcoholic Hepatitis

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CLINICAL TRIAL PROTOCOL

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Disclosure

This study is conducted by the TREAT (Translational Research and Evolving Alcoholic Hepatitis Treatment) Consortium which is funded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to pursue translational investigations in alcoholic hepatitis. The TREAT Consortium is made up of investigators from Indiana University School of Medicine (Indianapolis, IN), Mayo Clinic (Rochester, MN) and Virginia Commonwealth University (Richmond, VA). Study drug will be provided by Generon (Shanghai) Corporation, Ltd.

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List of Abbreviations

Ab	Antibody
AH	Alcoholic hepatitis
ALB	Albumin
ALD	Alcoholic liver disease
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body Mass Index
cGMP	Current good manufacturing practice
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
ConA	Concanavalin A
CRF	Case Report Form
CRP	C-Reactive Protein
CV	Coefficient of variation
DP	Drug product
DS	Drug substance
ECG	Electrocardiogram
FAS	Fatty acid synthase
FDA	Food and Drug Administration of United States
FIB	Fibrinogen
GI	Gastrointestinal
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GvHD	Graft vs host disease
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCT	Hematocrit
HCV	Hepatitis C virus
HFD	High fat diet
HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
IL-22	Interleukin 22
IND	Investigational New Drug
IP	Intraperitoneal
IRB	Institutional review board
IV	Intravenous
MCH	Mean corpuscular hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MELD	Model for End Stage Liver Disease
MHV	Mouse hepatitis virus

NIAAA	National Institute on Alcohol Abuse and Alcoholism
PK	Pharmacokinetics
PLT	Platelets
PTSD	Post-Traumatic Stress Disorder
RBC	Red blood cells
SAA	Serum amyloid A
SAMe	S-adenosylmethionine
SC	Subcutaneous
SD	Standard deviation
STAT	Signal transducer and activator of transcription
TBil	Total bilirubin
USP	The United States Pharmacopeia
WBC	White blood cell

Investigator's Affirmation

I have received and read the current version of the Investigator's Brochure (IB) for F-652 and this protocol (TREAT-008). Having fully considered all the information available, I agree that it is ethically justifiable to give F-652 to selected subjects/patients according to this protocol.

I understand that all information concerning F-652 supplied to me by the TREAT Consortium and from Generon Corporation Ltd. and not previously published is confidential. This includes the IB, Clinical Trial Protocol, Case Report Forms (CRF) and any other preclinical and clinical data.

I understand that no data are to be made public or published without prior knowledge and written approval by the TREAT Steering Committee.

By my signature below, I hereby attest that I have read, understood and agreed to abide by all the conditions, instructions and restrictions contained in Protocol TREAT-008 and in accordance with Good Clinical Practice and all applicable regulatory requirements.

I acknowledge that the Steering Committee of the TREAT Consortium has the right to discontinue this trial at any time.

_____

Investigator's Name (Printed)

_____ _____

Investigator's Signature Date

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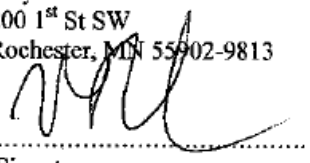


Signature

12-21-2015

Date

Study Summary

Title	An Open-Label, Cohort Dose Escalation Study to Assess the Safety and Efficacy Signals of F-652 in Patients with Alcoholic Hepatitis
Protocol Number	TREAT- 008
Phase	Clinical Study Phase 1b-2a
Methodology	Cohort dose escalation study
Overall Study Duration	Approximately three years
Subject Participation Duration	Estimated duration of participation is up to 56 days.
Single or Multi-Site	A multi-center clinical trial by the TREAT consortium.
Objectives	a. Assess the safety and tolerability of F-652 in patients with alcoholic hepatitis as determined by absence of unexpected serious adverse events up to Day 42 or Day 56 following administration of first dose of study drug. b. Determine the pharmacokinetics (PK) and pharmacodynamics (PD) of F-652 in patients with alcoholic hepatitis. c. Assess the efficacy signals of F-652 in patients with alcoholic hepatitis (compared to historical patient data) as determined by : A. Clinical: improvement in clinical status B. Biochemical: Improvement in liver biochemistry, MELD and Lille scores at days 7, 28, 42 and 56. C. Biomarkers of Il 22 activity (CRP, SAA, triglycerides),
Number of Subjects	Up to 18 participants at approximately six sites.

Diagnosis and Main Inclusion Criteria	Alcoholic hepatitis is a syndrome of progressive inflammatory liver injury associated with long-term heavy intake of ethanol. The pathogenesis is not completely understood[7]. Patients who are severely affected present with subacute onset of fever, hepatomegaly, leukocytosis, marked impairment of liver function (e.g., jaundice, coagulopathy), and manifestations of portal hypertension (e.g., ascites, hepatic encephalopathy, variceal hemorrhage). However, milder forms of alcoholic hepatitis often do not cause any symptoms. To participate in this study, patients must meet all of the following criteria: 1. Able to provide written informed consent (either from patient or patient's legally acceptable representative) 2. Male or female patients 21 years of age or older 3. Patients with alcoholic hepatitis defined as: a. History of heavy alcohol abuse use: >40 g/day in females and >60 g/day in males for a minimum period of 6 months AND b. Consumed alcohol within 6 weeks of entry into the study AND c. Serum bilirubin > 3mg/dL AND AST >ALT, but less than 500 U/L d. MELD score between 11-28 e. Liver biopsy will be carried out to confirm diagnosis in all patients except those who meet criteria a-c and in whom other causes of liver disease have been excluded (viral, drug, autoimmune etc). 4. Women of child-bearing potential must utilize appropriate birth control. *Patients on steroids and/or pentoxifylline will not be excluded from the study.
Study Product, Dose, Route, Regimen	F-652 with a dose escalation regimen using 10 μg/kg, 30 μg/kg and 45 μg/kg.
Duration of Administration	Participants will be given a dose of F-652 on Day 1 and Day 7 of the study. Following demonstration of safety with the Day 1 and Day 7 dose in the patient group with MELD score 21-28, a 3rd dose of the maximum tolerated dose will be administered on Day 14
Reference therapy	There is not a standard reference therapy or placebo against which the study product is being compared.
Statistical Methodology	Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan, which will be implemented by the Indiana University Data Coordinating Center. This document will expand upon and may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. In this cohort dose escalation study all statistical tests will be two-sided with no adjustment for multiplicity. Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be summarized. For categorical variables, the number and percent of each variable will be summarized. All collected data will be presented in listings.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures. The described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations, and all applicable institutional research requirements.

1.1 **Background**

Alcohol-related liver disease is a major cause of morbidity and mortality in the US, and is the third leading preventable cause of death in the US. In general, the risk of alcoholic liver disease increases with the quantity and duration of alcohol intake. Alcoholic liver disease encompasses a clinical/histologic spectrum of disease including fatty liver, alcoholic hepatitis, and cirrhosis. While fatty liver is a benign and generally reversible condition with abstinence or moderation, further progression to alcoholic hepatitis is more ominous. One in five heavy drinkers develops alcoholic hepatitis, and among these patients, one in four develops cirrhosis.

Alcoholic hepatitis is a syndrome of progressive inflammatory liver injury associated with long-term heavy intake of ethanol. The pathogenesis is not completely understood. Patients who are severely affected present with subacute onset of fever, hepatomegaly, leukocytosis, marked impairment of liver function (e.g., jaundice, coagulopathy), and manifestations of portal hypertension (e.g., ascites, hepatic encephalopathy, variceal hemorrhage). However, milder forms of alcoholic hepatitis often do not cause any symptoms.

The characteristic clinical manifestation of AH is new onset jaundice, often accompanied by malaise, tender hepatomegaly, and hepatic decompensation (ascites, encephalopathy and variceal bleeding). Patients are diagnosed to have alcoholic hepatitis in the presence of:

a. History of heavy alcohol abuse use: >40 g/day in females and >60 g/day in males for a minimum period of 6 months
b. Consumed alcohol within 6 weeks of entry into the study
c. Serum bilirubin > 3mg/dL AND AST >ALT, but less than 500 U/L

Serum bilirubin is > 3 mg/dL (and, in most patients, is >5 mg/dL). AST is elevated (>40 IU/mL), and AST>ALT ratio is typically more than 1.5. When the AST exceeds 500 IU/mL other liver diseases such as drug induced liver injury (DILI) and ischemic hepatitis need to be excluded. Imaging may be required to exclude biliary obstruction. Viral hepatitis, autoimmune liver disease, and Wilson disease also need to be excluded. If these conditions (biliary obstruction and viral, drug, or autoimmune disease) are excluded in a patient with alcohol abuse and liver test abnormalities outlined earlier, fewer than 10% of patients will have a diagnosis other than alcoholic hepatitis.

A liver biopsy is required for confirmation of ASH for all patients with clinically-diagnosed AH who have one or more of the following possible confounding factors:

1. Possible ischemic hepatitis (e.g., severe upper gastrointestinal bleed, hypotension, or cocaine use within the prior 7 days)
2. Possible drug-induced liver injury/jaundice
3. Recent sepsis (i.e., infection requiring antibiotics within the prior 7 days)
4. Uncertain alcohol assessment (e.g., patient denies recent/excessive alcohol use)
5. Atypical laboratory tests (e.g., AST < 40 IU/mL or >500 IU/mL, AST/ALT ratio <1.5.

Alcoholic hepatitis usually persists and progresses to cirrhosis if heavy alcohol use continues. If alcohol use ceases, alcoholic hepatitis resolves slowly over weeks to months, sometimes without permanent sequelae but often with residual cirrhosis.

Corticosteroids have been utilized as a standard of care in various treatment guidelines for patients with severe alcoholic hepatitis, as manifested by hepatic encephalopathy or a Maddrey Discriminant Function > 32. However, their applicability in clinical practice is limited in "special populations" of patients who have contraindications to corticosteroids and/or fall into subcategories of patients who were not included in the corticosteroid treatment trials that formed the basis of these treatment guidelines. These special populations are substantial and include patients with renal failure, infection, GI bleed, pancreatitis, and viral hepatitis. Pentoxifylline has also been used because of its safety, but several well-conducted studies have not supported the efficacy of pentoxifylline for the treatment of severe AH. A recent study has questioned the efficacy of both prednisone and pentoxifylline inn the treatment of alcoholic hepatitis. Mortality at 6 months was similar in patients on either prednisone, pentoxifylline, or both as compared with placebo. Therefore, there is a need for investigational therapies.

Translational investigations are needed on new mechanisms and suitable pharmacological agents relevant to alcoholic hepatitis (AH). This study is one of five studies of a consortium that includes Indiana University, Virginia Commonwealth University, and Mayo Clinic (Translational Research and Evolving Alcoholic Hepatitis Treatment; TREAT Consortium). This study is being funded by a grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), one of the institutes that comprise the National Institutes of Health (NIH).

Generon (Shanghai) Corporation, Ltd. is the sponsor of the Investigational New Drug application (IND 121673) for F-652 in graft versus host disease (GvHD). Generon is providing the investigational medicinal product, F-652, for this study.

1.2 **Investigational Agent**

F-652 is a recombinant fusion protein consisting of human interleukin 22 (IL-22) and human IgG2 Fc fragments. F-652 is glycosylated with an apparent molecular weight of approximately 101.97 kDa and is produced in CHO cells with serum-free medium. F-652 has an immunoglobulin-like structure with an IL-22 dimer at the N-terminal. Therefore,

F-652 is expected to have the same mechanism of action as the native or recombinant IL-22 described in literatures, but with extended and/or improved pharmacokinetics and pharmacodynamics properties due to the addition of human Fc fragments at the C-terminal.

1.3 **Preclinical Data**

F-652 under development is intended to treat patients with graft vs host disease (GvHD) after bone marrow transplantation, and acute alcoholic hepatitis (AAH), a severe form of alcoholic liver disease (ALD). Both GvHD and AAH are diseases with unmet medical need. The current investigational new drug application is to conduct a phase 1b-2a clinical study in alcoholic hepatitis patients to evaluate the safety and pharmacokinetic profile, and measures biomarkers associated with treatment with F-652 which is administered by intravenous infusion (IV).

IL-22 is a member of the IL-10 family of cytokines which control bacterial infection, homeostasis, and tissue repair. IL-22 may be used to treat patients with ALD because of its antioxidant, anti-apoptotic, anti-steatotic, anti-microbial, and proliferative effect that have been demonstrated in various experimental systems (Gao 89-93; Gao and Bataller 1572-85).

Alcoholic hepatitis (AH) is a severe form of ALD and includes a spectrum that ranges from mild injury to severe, life threatening injury. The prevalence of AH has not been accurately determined; it is believed to occur in 10% to 35% of heavy drinkers. On histology, AH is characterized by infiltration of the liver by inflammatory cells and hepatocellular injury. AH is usually associated with progressive fibrosis in the presence of continued alcohol abuse. No new drugs for ALD have been successfully developed since the introduction of corticosteroids as a treatment in the early 1970s. Therefore, development of novel therapeutics to treat ALD, especially for AH remains a tremendous challenge. Based on the current accumulated knowledge of IL-22 biology, the sponsor believes that IL-22 could be used for the treatment of ALD.

Several publications have described the protective role of IL-22 in hepatitis in various animal models. *In the ConA and carbon tetrachloride (CCl_4)-induced liver injury mouse model, injection of rmIL22 ameliorated the elevated serum levels of ALT and AST*. Delivery of IL-22-expressing plasmid in the liver significantly reduced the elevated serum levels of ALT, AST and apoptotic damage in these models. In an alcoholic hepatitis mouse model, mice fed with ethanol exhibited elevated serum levels of ALT, AST and TG. *Administration of IL-22 adenovirus ameliorated the elevation of serum AST, ALT as well as the TG level in the liver*. In the HFD-induced liver steatosis mouse model, administration of rmIL-22 not only reduced liver steatosis, but also down-regulated SREBP1-c and HMGCR, key enzymes for the synthesis of triglyceride and cholesterol, and the mRNA level of FAS, a critical modulator for *de novo* lipogenesis. The efficacy of IL-22 in mitigating liver injury induced by alcohol, CCl_4 and high fat diet was clearly demonstrated.

In developing recombinant IL-22 for human therapeutic use, it is anticipated that the restriction of IL-22 receptors (IL-22 R1) to epithelial cells, such as hepatocytes, would also limit the potential side effects. Corticosteroids, which are widely used to treat AH, have well-documented side effects that include increased risk of infection. Therefore, Corticosteroids and IL-22 could be a good combination treatment for AH because IL-22 might overcome the corticosteroid-mediated promotion of infection. For this study, concomitant steroid use is therefore not an exclusion criterion. IL-22could potentially also be used as monotherapy for AH due to its unique biology acting specifically on epithelial cell types.

The sponsor has developed F-652, a recombinant human IL-22 IgG_2 Fc fusion protein produced in serum-free culture of Chinese Hamster Ovary (CHO) cells. F-652 is able to protect tissue from damage and enhance tissue repair during the inflammation process and infection by activation of STAT3 mediated by the IL-22R1 expressed on epithelial cells such as hepatocytes.

The efficacy of F-652 was demonstrated in the acute liver injury models including ConA and MHV-A59-induced murine hepatitis. In monkey models of alcohol-induced liver steatosis with and without CCl_4 treatment, F-652 was able to reduce hepatic steatosis and serum levels of ALT and AST. F-652 demonstrated a favorable safety profile in acute and long-term (3-month) toxicity studies in rats and monkeys with a large safety window.

Administration of pharmacological doses of F-652 could benefit patients with alcoholic hepatitis, and is unlikely to induce immunological complications since the specific IL-22 R1 is not expressed on immune or hematopoietic cells.

1.4 **Clinical Data to Date**

A Phase I randomized double-blind, placebo-controlled, single dose escalating study of F-652 was conducted in healthy male volunteers for the evaluation of the safety, tolerability and pharmacokinetics (PK) of this drug. A total of 40 subjects were enrolled in the study. F-652 was administered subcutaneously (2 μg/kg) or placebo, and intravenously (IV; 2, 10, 30, 45 μg/kg) or placebo. Safety evaluations were conducted during the study including adverse events (AEs), physical examination, clinical safety laboratory (hematology, biochemistry, coagulation panel, immunological test, urinalysis), vital signs and 12-lead electrocardiogram (ECG). PK endpoints were derived from the serum concentration-time profile of F-652: total exposure (area under the curve), maximum serum concentration, time at maximum concentration, last measurable serum concentration, time at last measurable concentration, clearance, volume of distribution, elimination half-life, accumulation ratio and dose proportionality.

A total of 41 treatment-emergent adverse events (TEAEs) were reported in 23 subjects (58%). All TEAEs reported were mild or moderate in severity. There were no severe or life threatening AEs, or any SAEs reported. Twenty-six TEAEs were considered related to F-652. Fewer TEAEs were reported following F-652 dosing via IV compared to subcutaneous at the 2 μg/kg dose level. TEAEs reported following 2.0 μg/kg IV dosing

were all mild in severity, while three moderate events were reported following 2.0 µg/kg subcutaneous dosing. This indicated that the study subjects better tolerated IV dosing. The number of TEAEs reported did increase with IV dose, increasing above what was observed for placebo at the 30 and 45 µg/kg dose groups. Further, the number of moderate TEAEs reported increased with dose, and compared to IV placebo. The most frequently reported related TEAEs were dry skin (12 events reported by 12 subjects occurring locally after subcutaneous administration and more widely after IV dosing) and eye pruritus (3 events reported by 3 subjects following IV dosing). These showed improvement with the use of moisturizer cream and saline containing ocular drops, respectively.

When AEs were assessed according to dosing, subcutaneous route at a dose of 2 µg/kg had a delayed injection site reaction (2 mild, 4 moderate) consistent of dry skin, erythema and rash whereas IV route at a dose of 30 µg/kg was associated with dry skin (1 moderate, 2 mild), skin allergic reaction (1 moderate), eye pruritus (1 moderate), and at a dose of 45 µg/kg with dry skin (2 mild, 5 moderate), erythema (1 moderate), eye pruritus (1 mild, 3 moderate). Review of laboratory test results, vital signs, or ECG parameters revealed no trends or changes over time following dosing with F-652 at any dose level as either subcutaneous or IV dosing.

To characterize the PK profile, single IV infusion of F-652 or placebo was administered to four cohorts of 32 healthy male volunteers at doses of 2, 10, 30 and 45 µg/kg. Both Cmax and exposure (area under the maximum plasma concentration-time curve [AUC]0-24h) of F-652 increased proportionally with increasing doses in the dose range of 2 µg/kg to 45 µg/kg. Tmax observed was 0.7 hr for 2 µg/kg and 0.2 hr for 10, 30, and 45 µg/kg. The t1/2 values ranged from 39.4–206 hours and also increased with increasing dose levels. No F-652 was detected in the samples collected from control subjects.

Summary of Related TEAEs for IV Infusion Adverse Event	**IV (N=40) S (%) E**
Dry skin	10 (25.0%)
Eye pruritus	3 (7.5%)
Rash erythematous	2 (5.0%)
Chills	1 (2.5%)
Infusion related reaction	1 (2.5%)
Headache	1 (2.5%)
Somnolence	1 (2.5%)
Dermatitis allergic	1 (2.5%)

1.5 **Risks/Benefits**

1. Beneficial Findings:

Animal studies have demonstrated that treatment with F-652 reduces ALT/AST levels in serum and TG in liver. Treatment with IL-22 adenovirus also reduces serum ALT and liver/serum TG levels. Activation of pSTAT3 was seen at 1 hr and was undetectable at 3 hrs. IL-22 induced ALT/AST/TG decreases, however, are not seen in STAT3 (hep-/-) mice. IL-22R1 expression was up-regulated in hepatocytes of alcoholic patients and ethanol-fed mice.

2. Potential Risks:

a. **Overdose risk**

There has been limited human experience with F-652, either at potential clinical doses or with overdose. Treatment of overdose with F-652 should consist of general supportive measures. If the symptom or sign is judged as a severe disease or disorder, treatment will be administered as per standard of care.
There is no known specific antidote for overdose with F-652.

b. Warnings, precautions

There are dose-dependent increases in C reactive protein (CRP) and fibrinogen (FIB) following IV dosing with higher doses of F-652 (30 and 45 μg/kg), commencing at 12-24 hours post-dose. FIB reaches a peak at 96-120 hours post-dose; CRP may reach a peak at 48-72 hours post-dose, returning to normal 2 weeks later.

c. Hypersensitivity

The risk of hypersensitivity reactions to F-652 is unknown. If a significant hypersensitivity reaction occurs, no further doses of F-652 will be administered to that patient and appropriate treatment initiated.

d. Laboratory abnormalities

Increased serum CRP and FIB levels may be observed; these increases will be documented.

e. Local reactions at the injection site

Local injection site reactions such as erythema, dry skin and nummular eczema have occurred after the investigational product was administrated by subcutaneous injection. These changes were seen following intravenous administration at the highest dose (45 ug/kg). Local reactions generally occurred 10 to 17 days after administration of F-652, are usually were mild to moderate. Some subjects required treatment with Elocon (mometasone furoate) 0.1% cream, a moderate to strong topical corticosteroid for their skin reactions.

f. Drug interaction
The potential for drug-drug interactions with F-652 is not known.

g. Pregnancy
Adequate contraceptive methods should be used during treatment with F-652.

h. Geriatric use
There has been no geriatric experience to date.

Since no clinical data is available for F-652; any related SAE will be considered as unexpected.

1.6 **Dose Rationale:**

Phase I: Patients with AH and MELD score 11-20

Cohort	N	F-652
1 (MELD 11-20)	3	10 ug/kg
2 (MELD 11-20)	3	30 ug/kg
3 (MELD 11-20)	3	45 ug/kg

Patients will initially be enrolled on dose level 1. At any dose level, three (3) patients will be treated. If no dose-limiting toxicity (DLT) is observed, the next cohort of three (3) patients will be treated at the next higher dose level. If 1 of the 3 patients demonstrates DLT in a given dose level, an additional 3 patients will be treated at that dose level. If only 1 of the 6 patients demonstrates DLT, the next cohort of three patients is entered at the next dose level. If 2 or more of the 6 demonstrate DLT at that dose level, we will deescalate to one dose level lower. At subsequent dose levels, the maximum tolerated dose (MTD) is defined as the dose level where no more than 1 of 6 patients experiences DLT.

Dose escalation will occur only when all patients in the given cohort have completed the 42 or 56 days follow up and PK/PD data are available. The MTD will be based on DLT in the first cycle, and the ability to receive at least 70% of the target dose in cycle 2.

Phase II: Patients with AH and MELD score 21-28

Cohort	N	F-652
1 (MELD 21-28)	3	10 ug/kg
2 (MELD 21-28)	3	30 ug/kg
3 (MELD 21-28)	3	45 ug/kg

In the second phase, once safety of the drug in patients with MELD scores 11-20 has been demonstrated, patients with AH as defined by criteria listed earlier and MELD scores 21-28 will be studied. Dose escalation in these patients will follow the identical format to the Phase 1 of the study as described earlier. That is, in patients with MELD scores 21-28, the initial dose will be 10mcg/kg in 3 patients followed by 30mcg/kg, and ultimately 45 mcg/kg. Finally, we will test a 3rd dose of the maximum tolerated dose at Day 14 (10mcg/kg, 30 mcg/kg, or 45mcg/kg dose) – dose expansion cohort (see below).

Dose Expansion cohort:

We define response to the study drug as a decrease in the AST/ALT or serum triglycerides by 30% or more from baseline to Day 42 or Day 56. We will evaluate the patients' response rate for each cohort in phase I. If at the MTD level, the response rate is seen in only 1 of the 3 patients, an additional group of 6 patients will be recruited and treated at the MTD dose level. If efficacy signals can yet not be demonstrated in 2 or more of the 6 patients, the drug will be deemed ineffective. If efficacy signals are demonstrated at the highest safe dose, patients in the final cohort will be administered a third dose (10mcg/kg, 30 mcg/kg, or 45mcg/kg) of the MTD on Day 7 ($\pm$3 days) following the second dose to determine if efficacy can be increased with additional dosing.

1.7 **Trial Conduct**

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

1.8 **Population**

Patients with alcoholic hepatitis that will be recruited for this study should meet the following criteria:

a. History of heavy alcohol abuse use: >40 g/day in females and >60 g/day in males for a minimum period of 6 months
b. Consumed alcohol within 6 weeks of entry into the study
c. Serum bilirubin > 3mg/dL AND AST >ALT, but less than 500 U/L
d. MELD score range between 11-28. Patients with MELD scores 11-20 will be included in the first phase and patients with MELD scores 21-28 will be recruited for the second phase and escalation phase.

Patients with alcoholic hepatitis will be enrolled at approximately six clinical sites in the US. Additional sites may be added later to help accrual. The target number of participants to complete the study is 18 (see below).

STUDY NUMBERS:	
Phase I (MELD scores 11-20):	3+3+3 = 9
Phase II (MELD scores 21-28):	3+3+3 = 9
TOTAL participants:	**18**

Expected duration of patient participation is as follows:

Time expected for all patients to be enrolled:

- Approximately 3 years

Duration of individual patient participation:

- Up to 56 days (3 days Screening, 7-17 days of treatment, Follow up for 42 days following first dose)
- In the Dose Expansion Cohort, subjects receive 3 doses at approximately 7 day intervals. The duration of follow up will be for 56 days following first dose, or 42 days following third dose.

1.9 **Power Calculation**

As the primary outcome is observational, we have powered this study based upon the efficacy outcome, which is defined as a biochemical signal for success if AST/ALT is reduced by at least 30% on treatment. With no treatment, approximately 15-20% of patients reach this outcome following study drug treatment. We anticipate that a minimum of 50% will achieve this outcome. Using a conservative 2-sided assessment of superiority (50% with outcome vs. 20%), we will require 22 subjects to reach 80% statistical power.

For our efficacy outcome of AST/ALT, our primary analysis will assess a binary outcome of at least 30% reduction when on treatment. We will evaluate this with a 95% confidence interval of the percentage of subjects who have at least 30% reduction in AST/ALT on treatment, using an exact binary confidence interval. As a secondary analysis, we will use

robust linear regression with the change in AST/ALT at follow-up as compared to baseline as the outcome variable and baseline AST/ALT as the predictor. We will pair this analysis with a Bland-Altman plot. The goal of the secondary analysis is to assess the degree to which the reduction in AST/ALT attributable to treatment changes according to the subject's baseline AST/ALT. We will use 2-sides 5% type I error rate throughout.

2 Study Objectives

Primary:

- Assess the safety and tolerability and find the MTD of F-652 in patients with alcoholic hepatitis as determined by:
    a. Absence of unexpected serious adverse events and,
    b. Absence of worsening of alcoholic hepatitis (as determined by increase in MELD score > 5) up to Day 56 following administration of first dose of study drug.

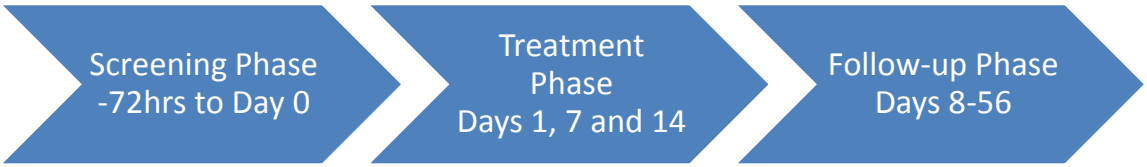
Secondary:

- Determine the pharmacokinetics (PK) and pharmacodynamics (PD) of F-652 in patients with alcoholic hepatitis.

Additional:

- Assess the efficacy signal of F-652 in patients with alcoholic hepatitis as determined by:
    a. Clinical: improvement in clinical status
    b. Biochemical: Improvement in liver biochemistry, MELD and Lille scores at days 7, 28, 42 and 56
    c. Biomarkers of Il 22 activity (CRP, SAA, triglycerides)

2.1 Trial Design:



The following study evaluations will be performed during the course of the Screening period (Day -3 to Day 0):

- 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 and/or mineral supplements
- Patient demographics
- Completion of questionnaires: Alcohol Use Disorder Identification Test (AUDIT), Alcohol Use- NIAAA Six Question Set
- Alcohol consumption for the last 30 days assessed using the Timeline Follow Back Questionnaire

- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Complete physical examination, including height, weight, and BMI
- 12-lead ECG
- Liver biopsy (if performed)
- Chest X-ray
- Assessment of MELD Score
- Calculate Maddrey Score
- Clinical chemistry, hematology, coagulation, lipid profile, CRP, SAA1 Nutritional Assessment and correction as necessary
- Evaluation by Addiction Services and Social Services to outline rehabilitation plan for alcohol abuse. This may include pharmacotherapy.
- Nutritional Assessment
- Immunogenicity Testing
- Urinalysis
- Serum pregnancy test (for women of childbearing potential)
- Collection of specimens (blood and urine) for bio-specimen banking (optional)

The following study evaluations will be performed during the course of Dosing Day 1 (±1):

- Review of inclusion and exclusion criteria
- Update medical and surgical histories
- Assess for Adverse Events
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Vital signs (blood pressure, pulse, respiratory rate, and temperature) pre-dose then 3 hours post-infusion with blood pressure and heart rate monitoring every 30 minutes.Weight and BMI
- Assessment of MELD Score and recording of Lille score parameters
- Clinical chemistry, hematology, and coagulation prior to study drug dosing
- Urine pregnancy test (for women of childbearing potential)
- Receive first dose of study drug
- Pharmacokinetic testing
- Confirmation that patient is abstinent from alcohol

The following study evaluations will be performed during Day 3 (± 1 day):

- Update medical and surgical histories
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Update Adverse Events
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Weight and BMI
- Calculation of MELD Score
- Clinical chemistry, hematology, and coagulation
- Pharmacokinetic testing
- Confirmation that patient is abstinent from alcohol

The following study evaluations will be performed during the course of Dosing Day 7 (±3 days):

- Update medical and surgical histories
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Confirmation that patient is abstinent from alcohol
- Update Adverse Events
- Vital signs (blood pressure, pulse, respiratory rate, and temperature) pre-dose then 3 hours post-infusion with blood pressure and heart rate monitoring every 30 minutes.
- 12-Lead ECG
- Complete physical examination, including weight and BMI
- Calculation of MELD Score
- Calculation of Lille Score
- Clinical chemistry, hematology, coagulation, lipid profile, CRP, SAA1, total protein and albumin prior to study drug dosing
- Urine pregnancy test prior to study drug dosing
- Receive second dose of study drug
- Pharmacokinetic testing
- Collection of specimens (blood and urine) for bio-specimen banking
- Nutritional Assessment

The following study evaluations will be performed during the *Follow-up* Day 14 (± 3 days):

- Update medical and surgical histories
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Confirmation that patient is abstinent from alcohol
- Update Adverse Events
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Weight and BMI

- Calculation of MELD Score
- Clinical chemistry, hematology and coagulation
- Pharmacokinetic testing
- Immunogenicity Testing
- Collection of specimens (blood and urine) for bio-specimen banking

The following study evaluations will be performed during the course of *Dosing* Day 14 (±3 days):

- Update medical and surgical histories
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Confirmation that patient is abstinent from alcohol
- Update Adverse Events
- Vital signs (blood pressure, pulse, respiratory rate, and temperature) pre-dose then 3 hours post-infusion with blood pressure and heart rate monitoring every 30 minutes.
- 12-Lead ECG
- Complete physical examination, including weight and BMI
- Calculation of MELD Score
- Clinical chemistry, hematology, coagulation, lipid profile, CRP, SAA1, total protein and albumin prior to study drug dosing
- Urine pregnancy test prior to study drug dosing
- Receive third dose of study drug
- Pharmacokinetic testing
- Collection of specimens (blood and urine) for bio-specimen banking
- Nutritional Assessment

The following study evaluations will be performed during the follow-up Day 28 (± 4 days):

- Update medical and surgical histories
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Confirmation that patient is abstinent from alcohol
- Update Adverse Events
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Complete physical examination, including weight and BMI
- 12-Lead ECG
- Alcohol consumption for the last 30 days assessed using the Timeline Follow Back Questionnaire
- Calculation of MELD Score
- Clinical chemistry, hematology, coagulation, lipid profile, CRP, SAA1, total protein and albumin
- Pharmacokinetic Testing
- Immunogenicity Testing

- Collection of specimens (blood and urine) for bio-specimen banking.

The following study evaluations will be performed during Day 42 (±2 days):

- Update medical and surgical histories
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Confirmation that patient is abstinent from alcohol
- Update Adverse Events
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Weight and BMI
- Physical Examination
- Calculation of MELD Score
- Clinical chemistry, hematology, and coagulation
- Complete Timeline Follow-back Questionnaire
- Collection of specimens (blood and urine) for bio-specimen banking.
- Pharmacokinetic Testing
- Immunogenicity Testing
- Nutritional Assessment

The following study evaluations will be performed during Day 56 (±2 days) (Only completed if patient received three doses of study drug):

- Update medical and surgical histories
- Update record of concomitant medication usage, including use of prescription and over-the-counter medications, and vitamin and/or mineral supplements
- Confirmation that patient is abstinent from alcohol
- Update Adverse Events
- Vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Weight and BMI
- Physical Examination
- Calculation of MELD Score
- Clinical chemistry, hematology, and coagulation
- Complete Timeline Follow-back Questionnaire
- Collection of specimens (blood and urine) for bio-specimen banking.
- Nutritional Assessment

2.2 **Study Design/Type**

Schedule of Procedures

Safety Assessments	Screening (-72 hrs)	Day 1 (± 1 day)	Day 3 (± 1 day)	Day 7 (±3 days)	Day 14 (±3 days)	Day 28 (±4 days)	Day 42 (±2 days)	Day 56[6] (±2 days)
Inclusion/Exclusion Criteria	X	X						
Physical Examination	X			X	X[5]	X	X	X
Medical/Surgical History	X		X	X	X	X	X	X
Nutritional Assessment	X				X[5]		X	X
AUDIT and NIAAA Questionnaires	X							
Timeline Followback Questionnaire	X					X	X	X
Vital Signs	X		X		X	X	X	X
Serial Vital Signs		X		X	X[5]			
Serum Chemistry[A]	X	X	X	X	X	X	X	X
Coagulation[A]	X	X	X	X	X	X	X	X
Hematology[A]	X	X	X	X	X	X	X	X
Serum pregnancy test	X							
Urine pregnancy test		X		X	X[5]			
Lipid profile, CRP, SAA1, total protein, albumin[A]	X			X	X[5]	X		
Calculate MELD Score	X	X	X	X	X	X	X	X
Calculate Lille Score				X				
Calculate Maddrey Score	X							
Urinalysis[1]	X							
ECG[2]	X			X	X[5]	X		
Chest X-ray[3]	X							
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Study Drug Dosing		X		X	X[5]			
Pharmacokinetic Sample Collection[7]		X	X	X	X	X	X	
Immunogenicity Testing[8]	X				X	X	X	
Biomarkers(blood and urine)	X[7]			X	X	X	X	X
Confirmation that patient is abstinent from alcohol		X	X	X	X	X	X	X

1. Urinalysis results can be used for Screening if tested within 7 days.
2. ECG results can be used for Screening if tested within 7 days.
3. Chest X-ray results can be used for Screening if tested within 30 days.
4. Day 1, Day 7 and Day 14 labs and testing must be completed prior to dosing.
5. These tests/procedures will occur only on Day 14 if the patient is receiving a 3rd dose at that visit.
6. Day 56 will only occur if the patient received a 3rd dose on Day 14.
7. Biomarkers are optional at Screening.

[A]Clinical Laboratory Tests

Hematology	Coagulation	Serum Chemistry		Urinalysis	Other
		Liver Function Tests	Other Chemistry		
Complete Blood Count with differential, Platelet count, MCV	PT, INR	AST, ALT, Total Bilirubin, Direct Bilirubin	Sodium, Potassium, Chloride, Bicarbonate, Calcium, Magnesium, Phosphate, Creatinine, BUN, Glucose, Total protein, Albumin, Lipid profile, CRP, SAA1	Specific gravity, pH, Blood, Protein, Glucose, Ketones	β-HCG serum pregnancy test Urine pregnancy test

Blood will be collected for PK sampling per the schedule below:

[8]Pharmacokinetic Sampling Schedule

Study Visit Day					Study Visit Day +0*	Study Visit Day +2*	Study Visit Day +3*	Study Visit Day +4*
					24 hrs	48 hrs	72 hrs	96 hrs
	Pre-dose	30 mins (±5 mins)	1 hr (±10 mins)	8 hr (±30 mins)				
Day 1	X	X	X	X			X	
Day 7	X	X	X	X	X	X	X	X
Follow-Up Visit Day								
Day 14	X							
Day 28	X							
Day 42	X							

* +/- 2 hour window for PK points > 8 hours after dosing

[9]Immunogenicity Sampling Schedule

Dosing Day			
Baseline	**Day 14**	**Day 28**	**Day 42**
X	**X**	**X**	**X**

2.3 Primary Study Endpoints/Secondary Endpoints

Primary:

- Absence of unexpected serious adverse events.

Secondary:

- Pharmacokinetics (PK) and pharmacodynamics (PD) of F-652 in patients with alcoholic hepatitis.

Efficacy Signal endpoints:

- Decrease in MELD score, Lille score, triglyceride, CRP, AST, ALT and SAA1

2.4 Trial Treatment

Participants will receive 10 μg/kg, 30 μg/kg or 45 μg/kg of F-652 on Day 1 and Day 7 via slow intravenous infusion. Three patients will receive 10 μg/kg of F-652. Pharmacokinetic testing will be completed on these subjects. If evaluations demonstrate safety and efficacy signals, the next 3 patients will receive 30 μg/kg. If pharmacokinetic testing demonstrates safety and efficacy signals, the next 3 patients will receive 45 μg/kg. If evaluations demonstrate safety and efficacy signals, patients with a MELD score of 21-28 will receive a third dose of the study drug at the maximum tolerated dose on Day 14.

2.5 Remuneration

Each site will compensate participants for their time, travel and parking. The amount will be determined by the site study team and reflected in the consent form.

2.6 Duration

The screening process will occur in the 72 hrs leading up to Day 1. The dosing phase will occur from Day 1 to Day 14. Follow-up will occur between Day 14 to Day 56. Visit activities are described in the previously mentioned Schedule of Procedures.

2.7 Discontinuation

Discontinuation of the F-652 will occur if a participant experiences a Serious Adverse Event or UPIRTSO **AND**, in the opinion of the investigator and study ajudicator, is related to the study drug. Patients will be discontinued if grade 3 or higher CTCAE develop that are determined to be possibly or likely attributable to study drug.

2.8 Product Accountability

The study drug product will be manufactured, labeled, and supplied by AAI Pharma Services Corporation on behalf of Generon (Shanghai) Corporation, Ltd. The drug will be managed and accounted for by each site's Research or Clinical Pharmacy.

2.9 Data Identification

During the Screening phase, patients will be identified by a unique screening number and by their initials (first and last). On Day 1, patients will be identified by a unique five-digit patient number and initials. Only qualified patients will be assigned a patient number.

3 Subject Selection Enrollment and Withdrawal

3.1 Inclusion Criteria

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

1. Able to provide written informed consent (either from patient or patient's legally acceptable representative)
2. Male or female patients 21 years of age or older
3. Patients with alcoholic hepatitis defined as:
    a. History of heavy alcohol abuse use: >40 g/day in females and >60 g/day in males for a minimum period of 6 months
    b. Consumed alcohol within 6 weeks of entry into the study
    c. Serum bilirubin > 3mg/dL AND AST >ALT, but less than 500 U/L
    d. MELD score between 11-28
    e. Liver biopsy will be carried out to confirm diagnosis in all patients except those who meet criteria a-c and in whom other causes of liver disease have been excluded (viral, drug, autoimmune etc).
4. Women of child-bearing potential must utilize appropriate birth control.

***Patients on steroids and/or pentoxifylline will not be excluded from the study.**

3.2 Exclusion Criteria

1. Other or concomitant cause of liver disease as a result of:
    a. Autoimmune liver disease

   b. Wilson disease
   c. Vascular liver disease
   d. Drug induced liver disease
      Note: Concurrent viral hepatitis is not excluded.
2. Co-infection with human immunodeficiency virus (HIV)
3. Any active malignancies other than curatively treated skin cancer (basal cell or squamous cell carcinomas) or any other malignancy diagnosed within the last five years.
4. Active tuberculosis on chest x-ray at study entry
5. 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 patient from participating in and completing the study
6. Patients requiring the use of vasopressors or inotropic support
7. Liver biopsy, if carried out, showing findings not compatible with alcoholic hepatitis
8. Any patient that 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
   Note: Investigational drug includes any drug that is used off-label.
9. If female, known pregnancy, or has a positive urine or serum pregnancy test, or lactating/breastfeeding
10. Serum creatinine >2.5 mg/dL

3.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited, enrolled and screened using the following resources:

- From the Principal Investigator or Co-Investigator clinical practices
- Referring physicians, advertisement, etc.
- Information that is to be given to potential subjects (handouts, brochures, etc.)
- Advertisements
- Screening requirements or qualifying lab values
- Evaluation and documentation of inclusion/exclusion criteria

3.4 Subject Withdrawal

A subject may be withdrawn from the study prior to that subject completing all of the study-related procedures. Some reasons include:

Criteria for Subject Withdrawal

The following are criteria for subject discontinuation from the study:

1. Subject withdraws study consent.

2. Subject is found to be ineligible for the protocol as per the Inclusion/Exclusion criteria.
3. Subject experiences disease progression.
4. Lille scores at any time are >0.45 (treatment failure). Patient will be taken off study drug, however, we will request that they complete follow-up.
5. Failure of the subject to comply with protocol requirements.
6. Exhibition of unacceptable toxicity which would make it difficult or dangerous to comply with further protocol requirements such as study visits, blood draws, etc.
7. There are changes in medical status of the subject such that the Investigator believes that subject safety will be compromised or that it would be in the best interest of the subject to stop participation in the study.
8. Death of the subject.
9. Subjects with a test consistent with pregnancy such as a positive beta-hCG.
10. Subject is lost to follow-up.
11. Any complication that requires prolongation of the hospitalization or change in treatment and in the opinion of the investigator is related to the study drug.

Procedures for Subject Withdrawal

At the time of study withdrawal, subjects, if capable, will be asked to complete all of the procedures that would normally be performed at the Day 42 assessment. Withdrawn subjects will have a 30-day follow up phone call after their last clinical assessment.

3.5 Data Collection and Follow-up for Withdrawn Subjects

Even though a subject has withdrawn from the study, these patients will be followed up in the hospital and to 42 days following the last administration of the study drug. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, for subject safety reasons, attempts should be made to obtain permission to collect follow up information whenever possible.

4 Study Drug

4.1 Description

F-652 (Recombinant human IL-22)

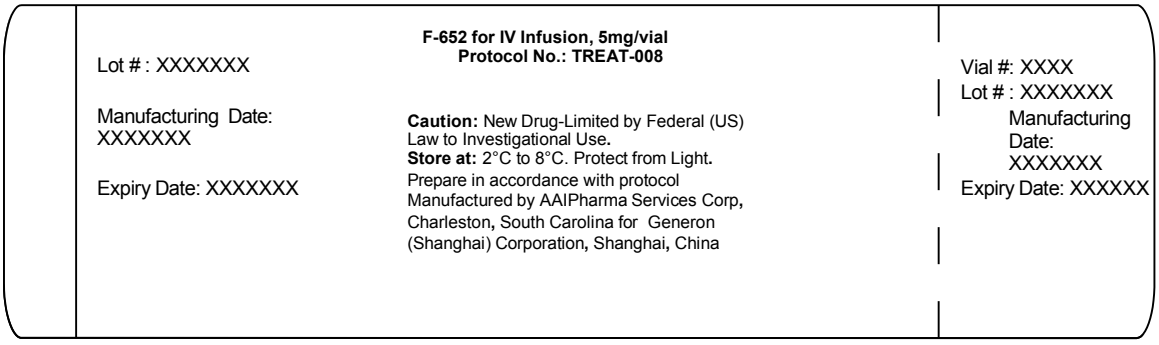
The drug product (DP) was manufactured by AAIPharma Services Corp, Charleston, South Carolina under Good Manufacturing Practice for pharmaceutical products (GMP).
F-652 drug substance (DS) used to manufacture the DP was produced using standard monoclonal antibody manufacturing process. The drug substance is sent from China at -77 degrees F to South Carolina. In South Carolina, it is defrosted and lyophilized into a cake. This will be then be shipped at -2 degrees F to the sites and reconstituted.

The F-652 DP in lyophilized formulation is stored at 2–8°C prior to reconstitution. F-652 is supplied lyophilized white cake in 2 mL glass vials. Each vial contains 5 mg/mL when reconstituted with 1 mL of sterile water.

4.2 Packaging, Labeling and Storage

The Generon Corporation, Ltd. or its Agent will provide labeled study medication for the clinical trial. The investigational drug is supplied as 5 mg/vial lyophilized product in 2-mL clear glass vials. A unique number is associated with each vial and is the means of drug assignment and inventory. A sample label is provided in the figure below. Please note that the label is subject to change format but the information contained therein will not change. The label has a tear off section that should be used to identify which drug was distributed to which subject and remain with the source documentation.

Sample F-652 Product Label



Study drug should be stored and maintained between 2°–8°C prior to dispensing. The product should not be frozen at any time.

4.3 Treatment Regimen

F-652 will be administered by slow intravenous infusion over approximately 100 minutes. The study medication is reconstituted as per the protocol in 100 ml of 5% dextrose in water. To monitor, as well as prevent hypersensitivity reactions, the infusion rate will be as follows:

1. 10 ml/hr for 15 minutes
2. 20 ml/hr for 15 minutes
3. 40 ml/hr for 15 minutes
4. 80 ml/hr for 15 minutes
5. 100 ml/hr until infusion complete

That is, the total infusion will be over approximately 100 minutes. Patients will be monitored for 3 hours post-infusion with blood pressure and heart rate monitoring every 30 minutes.

Patients will receive two separate IV infusions separated by 6-10 days (i.e. one infusion on Day 1 and a repeat infusion approximately one week later depending on outpatient scheduling). After information is received regarding the primary end point (safety) at the first dose (10ug/kg), and the 10ug/kg dose determined to be safe, the 2nd cohort of patient will be administered the 30ug/kg dose. Further escalation will follow this scheme. If evaluations demonstrate safety and efficacy signals, patients in the final dose escalation cohort will receive a third dose of the study drug at the maximum tolerated dose on Day 14.

Medications allowed: Corticosteroids, pentoxifylline, antibiotics, acamprosate, and Baclofen, as well as any other medication deemed to be essential for the treatment of the patient will be allowed.

Prohibited medications: Biological agents and any other concomitant investigational agents.

4.4 Preparation and Administration of Study Drug

Reconstitution of F-652:

Remove the F-652 vial from the refrigerator. Using an appropriately sized syringe and needle, withdraw 1.0 mL of water for injection. Reconstitute the vial by slowly adding the 1.0 mL of water for injection into the interior of the vial's neck. Gently dissolve the drug powder with a slow swirling motion. This results in a solution of F-652 at a concentration of 5 mg/mL. Allow up to 2 minutes for the F-652 to dissolve. The solution should not be used if discolored or cloudy, or if particulate matter remains.

IV Preparation:

The research or clinical pharmacist will withdraw a volume of Baxter 5% Glucose IV solution and insert into the Baxter Empty Viaflex bag (PVC) 150mL. Based on the weight dose provided by the study team, withdraw the required volume of F-652 from the vial containing 5 mg/mL F-652 drug solution. Slowly add the appropriate volume of F-652 into the Baxter Empty Viaflex bag 150 mL containing 5% dextrose in water (D5W) to make the volume up to 100 mL, then gently invert the IV bag up to 5 times to ensure that the investigational product and Baxter 5% Glucose IV solution are well mixed.

Investigational Product at Study Site:

Study medication will be shipped to each institution site upon site initiation. The Investigator is responsible for monitoring the inventory of medication supplies, in order to ensure sufficient supply for the site. The study monitors will also verify the drug accountability during each site-monitoring visit. At the end of the study, all study drug supplies will be returned to the Sponsor/designee by the study monitor for each site.

Test Article Accountability:

The Investigator will maintain accurate records of the receipt of all study medication. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each subject in the study. Drug accountability and distribution of drug will be done at each visit as needed during the course of the study. Reasons for deviation from the expected dispensing regimen must also be recorded. A storage temperature log is to be maintained to document proper storage conditions. Malfunctions must be reported to the sponsor immediately. The clinical supplies for this study must be maintained under adequate security and stored under conditions specified on the label.

Investigational Product at Study Site at Study Conclusion:

At completion of the study, all study medication will be reconciled by the designee and then returned, retained, or destroyed according to applicable country regulations. Prior to any action being taken with study medication after the study is completed; the investigator will contact the Generon Corporation, Ltd. or the contracted CRO for approval of such action.

4.5 Immunogenicity Testing

Immunogenicity testing will occur at Baseline, on Day 14, Day 28 and Day 42. Three assays will be used to evaluate the anti-F-652 antibodies in serum samples collected in this trial. The first assay is a Bridging ELISA binding assay which screens antibody binding activities in the serum samples. Positive samples identified in the binding assay will be analyzed in the confirmatory assay, in which a serum sample is first incubated with F-652 in vitro, and the sample is then analyzed by the binding assay. Positive samples identified in the confirmatory assay will be further analyzed in the cell-based neutralizing assay, in which the neutralizing bioactivity to F-652 (IL-22) in the serum samples is analyzed. The binding and confirmatory assay have been developed and validated in minimal required dilution (MRD), cut point and cut point correction factor, sensitivity, specificity, selectivity, inter and intra precision, and drug tolerance followed “Guidance for Industry, Assay Development for Immunogenicity Testing of Therapeutic Proteins” (FDA, CMC, 2009). The neutralizing assay has been developed and under validating. The validation reports have been sent to FDA in the IND 121673 Serial Number 0004.

5 Assessment of Efficacy Signals

5.1 Efficacy Parameters

- Change in MELD score, Lille score, triglycerides, CRP, AST, ALT and SAA1.

5.2 Method and Timing

1. MELD score will be calculated at each visit.
2. Lille score will be calculated on Day 7.

3. Triglycerides, CRP and SAA1 will be collected at Screening, Day 7, Day 14 (if dosed) and Day 28.
4. AST and ALT will be collected at Screening, Day 3, Day 7, Day 14, Day 28, Day 35, Day 42 and Day 56 (if applicable).
5. Adverse events will be evaluated at each study visit per the Schedule of Procedures by the study coordinator and reviewed by the investigator

6 Assessment of Safety

6.1 Safety Variables

During study drug infusion: Patients will be monitored as per our standard protocol followed for a biological agent such as infliximab. The protocol is as follows:

a. Intravenous access. Peripheral intravenous access is started for those who do not have an intravenous access. Central lines may be used for administration of intravenous fluids, medications and blood draws unless otherwise specified.
b. Pre-medication. Acetaminophen 500 mg and diphenhydramine 25 mg will be given by mouth prior to the infusion.
c. Infusion- related reaction medication. The following would be the medications used:
    i. Diphenhydramine 25 mg intravenously for skin rashes
    ii. Demerol 25 mg intravenously single dose and repeated every 15 minutes if ineffective for rigors.
    iii. Methylprednisone (Solu-Medrol) 1 mg/kg intravenously as a bolus for more severe infusion-related reactions like hypotension or severe bronchospasm.

Monitoring for hypersensitivity reactions: The infusions are all carried out at the clinical research center under the direction of trained personnel who have expertise in recognizing hypersensitivity reasons, as well as in treating these reactions. Hypersensitivity reactions may also occur when the patient is at home. Preliminary studies in normal volunteers have indicated that the only possible hypersensitivity reactions noted in these patients are skin rashes. The care giver will be instructed on skin rashes and will be shown flash cards to facilitate recognition of reactions.

<u>*During follow-up:*</u> Safety will be determined based on clinical and laboratory monitoring.

<u>*Clinical:*</u> At each study follow-up visit, patients will have a physical examination with specific attention to skin changes, hypersensitivity reactions, pulmonary abnormalities, worsening in liver function as noted by increasing jaundice, ascites, or hepatic encephalopathy and presence of infection.

Laboratory: Biochemical parameters that are monitored include CRP, liver biochemistry, creatinine, and electrolytes. The study will be **stopped** if two or more patients have **either** A. AST or ALT > 500 U/L **or** B. Lille score > 0.85. The study will also be stopped if more than one patient (that is, two or more) has an adverse event grade 3 or above on the CTCAE scale that is determined to be possibly or likely attributable to study drug as per the study adjudicator. A patient will be **WITHDRAWN** from the dosing phase if Lille scores at any time are > 0.45 (treatment failure).

We recognize that determination of whether worsening of liver biochemical tests is due to the alcoholic hepatitis or study drug induced liver injury (DILI) is very difficult. An AST or ALT increase >500 IU/L would be considered an indication that the patient might have DILI since AST and ALT are typically < 250 U/L in AH. Such an increase of > 500 IU/L would trigger prompt evaluation and consideration of discontinuation of the study drug. A Lille score > 0.85 and an increase in MELD score >10 would also warrant discontinuation of the study drug. Considering how difficult it is to distinguish potential DILI from worsening of the underlying liver disease, we have incorporated an external adjudication of all suspected DILI events. This external adjudication is in addition to the data safety monitoring board (DSMB) which will monitor the entire study. A renowned hepatologist, Dr. Willis Maddrey, who is an internationally renowned expert both in the field of alcoholic hepatitis and DILI, has kindly agreed to serve as the external adjudicator for this IL 22 study. He will be contacted on an as needed basis when there is question of symptom causality.

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
- Chest X-Ray

6.2 Method and Timing

1. Adverse events, vital signs, chemistry, hematology and coagulation will be assessed at each study visit.
2. Urinalysis will be assessed at Screening.
3. ECG will be assessed at Screening, Day 7, Day 14 (if dosing) and Day 28.

6.3 Adverse Event Reporting

Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include:

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

Other important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 42 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event after the screening visit. For this study, clinically significant laboratory abnormalities will be defined as abnormal laboratory values that in the opinion of the site investigator are not explained by alcoholic hepatitis, underlying liver disease or other underlying health conditions.

All patients with laboratory tests containing clinically significant abnormal values should be followed regularly until the values return to normal ranges, until a valid reason for the AE (other than study medication related AE) is identified, or until further follow up is deemed medically unnecessary.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed

otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

6.4 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the Adverse Event Case Report Form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

6.5 Reporting of Serious Adverse Events and Unanticipated Problems

The sponsor-investigator is responsible to evaluate all adverse events to determine reporting requirements to the IRB and FDA. When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required. The reporting will need to occur within two working days.

6.6 Sponsor-Investigator Reporting: Notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than five working days after the investigator first learns of the problem/event.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's Name
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

6.7 Sponsor-Investigator Reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be

reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

For this multi-center clinical trial, in addition to reporting certain unanticipated problems and adverse events noted above to the FDA, it is the responsibility of the study sponsor to report those same adverse events or findings to participating investigators.

FDA Definitions (21 CFR 312.32(a))

A. **Adverse Event:** any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

B. **Suspected Adverse Reaction:** any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND 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.

C. **Adverse Reaction:** any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

D. **Unexpected:** 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; or, if an investigator 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, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis.

E. **Serious**: 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, or 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 patient or 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.

F. **Life-Threatening:** 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 patient or 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.

6.8 Stopping Rules

The study will stop if any of the following occur:

1. The participant decides to withdraw from the study.
2. The participant experiences a Serious Adverse Event (SAE) that, in the opinion of the investigator, is possibly, probably or definitely related to the study drug utilizing the National Cancer Institute's CTCAE system as a guide.
3. The participant experiences a medical condition that, in the opinion of the investigator, continuation on the study drug would be detrimental.
4. At least two patient have either:
    a. AST or ALT >500 U/L or
    b. Lille score >0.85.

In the event of a SAE, the site will report this to the Mayo Clinic study team. If the SAE is attributable to study drug, the Mayo Clinic study team will report the event to the Institutional Review Board and the FDA.

6.9 Individual Stopping Rules

The following are criteria for subject discontinuation from the study:

1. Subject withdraws study consent.
2. Subject is found to be ineligible for the protocol as per the Inclusion/Exclusion criteria.
3. Subject experiences disease progression.
4. Lille scores at any time are >0.45 (treatment failure). Patient will be taken off study drug, however, we will request that they complete follow-up.
5. A subject that requires more than 2 investigation drug (F-652) dose reductions.
6. Failure of the subject to comply with protocol requirements.
7. Exhibition of unacceptable toxicity which would make it difficult or dangerous to comply with further protocol requirements such as study visits, blood draws, etc.
8. There are changes in medical status of the subject such that the Investigator believes that subject safety will be compromised or that it would be in the best interest of the subject to stop participation in the study.
9. Death of the subject.
10. Subjects with a test consistent with pregnancy such as a positive beta-hCG.
11. Subject is lost to follow-up.
12. Any complication that requires prolongation of the hospitalization or change in treatment and in the opinion of the investigator is related to the study drug.

The investigator will utilize the National Cancer Institute's CTCAE system as a guide when determining the need for an individual participant to stop the study.

7 Statistical Plan

7.1 Statistical Methods

Primary endpoint (safety): The number and percentage of patients with SAE and increase in MELD score > 5 up to Day 56 following administration of first dose of study drug will be summarized by each dose level. Ninety-five percent confidence interval of the percentage will be calculated too.

Summary of adverse event will also be provided by each dose level.

Secondary endpoint: Pharmacokinetics (PK) and pharmacodynamics (PD) of F-652 in patients with alcoholic hepatitis at the first dose level (10ug/kg) and subsequent dose levels will be determined by the study sponsor using standard pharmacological tools**.** The total exposure (area under the curve), maximum serum concentration, time at maximum concentration, last measurable serum concentration, time at last measurable concentration, clearance, volume of distribution, elimination half-life, accumulation ratio and dose proportionality will be calculated.

Efficacy signal endpoint: The main efficacy end point is the reduction of AST/ALT or serum triglycerides. If patients show a reduction of AST/ALT or serum triglyceride by 30% at day 42, the drug shows efficacy in this patient. We will calculate the percentage of patients with efficacy (rate) and its 95% confidence interval for each dose level.

We will also use the proportion of patients with 30% change of AST, ALT from baseline to Day 3, Day7, Day14, Day 28, Day 42 and Day 56 as the dependent variable, dose level and baseline AST, ALT and other patients' characteristic at baseline as the covariates to evaluate the change (efficacy) or drug by dose level. A random intercept will be included for accommodating the correlation among the repeated measurement.

Other efficacy endpoints: Paired t-test or signed-rank test will be used to compare the level Lille score. Linear mixed-effect models will be used to analyze the MELD score, triglycerides, CRP, and SAA1 in a similar way to the AST/ALT.

7.2 Termination Criteria

The study will be terminated when accrual is completed. Patients may be terminated from this study according to the criteria discussed in Section 4.4 Subject Withdrawal whether voluntarily or by the recommendation of the site investigator.

7.3 Deviation Reporting

Any change from the study design will be reported to the IRB according to institutional policy.

8 Direct Access to Source Data/Documentation

Direct access to source data and documentation will be readily available to the study teams at each site through use of the OnCore electronic data capture system.

9 Quality Control and Quality Assurance

One of the investigators and a study coordinator will maintain quality control. All data entered will be reviewed by the investigator and the study statistician. Quality assurance of data accuracy will occur routinely through monthly checks for completeness and edits and form audits. Quality assurance of data analysis is achieved by independent replication of key analyses within the DCC and review reports by multiple individuals before distribution.

9.1 Monthly check for completeness and edits

On a monthly basis, the DCC will generate a database report of:

- Subject Accrual: Number of patients enrolled, number of subjects on/off study
- Data Entry timeliness (% of data entered within 2 weeks from subject visit)
- Quality of data/Edits (see below)
- Protocol Deviations: Number of deviations in each category, by site.
- Missed visits
- Incomplete visits
- Missed specimen collection or shipment
- Serious Adverse Events
- Site responsiveness to resolving edits (data queries and/or errors)

Edits are run on the database of the keyed forms monthly. Checks for missing, out of range, unusual and inconsistent values, cross-form checks and arithmetic errors are some of the type of checks performed. The Data Manager will record the edits to be resolved in the OnCore system. The site must respond within 2 weeks to each edit by making appropriate changes to the forms and database, provide documentation on each change, and file the documentation with the edited data collection form.

9.3 Form Audits

On a periodic basis the DCC selects and requests copies of forms for specific participants be sent by each clinical center to the DCC for auditing.

- Audited forms are compared with the database

- Discrepancies are noted and queried

9.4 Performance Monitoring

The DCC will generate recruitment and retention reports that will provide a count of participants enrolled at each site.

On approximately a bimonthly basis, the DCC will generate reports summarizing the performance of all sites. These reports will be reviewed by each site Principal Investigator, Consortium Coordinator and by the NIAAA program official.

9.5 Site Visits

Prior to commencement of the study, representatives of Generon and/or the Mayo Clinic 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.

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 Generon and/or the Mayo Clinic. 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 Generon and/or the Mayo Clinic 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 Generon and/or the Mayo Clinic will arrange for a final review of the study files, after which the study files should be secured for the appropriate time period. 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.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

Study monitoring will occur both on-site and remotely. The Investigator will ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Clinical trial monitoring will include review of the study documents and data generated throughout the duration of the study to help ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 **Data and Safety Monitoring Board (DSMB) for the TREAT Consortium**

The Data and Safety Monitoring Board (DSMB) for the TREAT Consortium will be reviewing the data for this study every six months. The charter will be reported to the Mayo Clinic IRB and shared with each site.

10.3 **Auditing and Inspecting**

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11 Ethical Considerations

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and institutional research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Data Handling and Record Keeping

12.1 **Confidentiality**

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

12.2 **Source Documents**

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. 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, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or 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.

12.3 **Case Report Forms**

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

12.4 **Data Management and Processing**

Source documents will be kept that include, but are not limited to, medical records, charts, appointment books, patient questionnaires, original laboratory records, equipment print-outs. All source documents must be made available to the CRA. The following data must be included in the source data:

- Consent to participate in Trial
- Letter to Primary Care Physician, if applicable
- Patient visit dates
- Screening Numbers
- Demographic Information
- Medical history
- Disease history
- Physical examination
- Vital signs
- Laboratory assessments (copy of laboratory reports)
- AEs and concomitant medications
- Dates of administering study medication
- ECGs
- Liver biopsy reports (if applicable)
- Patient questionnaires
- Issues with protocol compliance
- Completion of, or withdrawal from, trial

12.5 **Data Security and Confidentiality**

All information obtained during the conduct of the trial with respect to the patient will be regarded as confidential and confidentiality of all patients will be maintained. Clinical monitors (e.g. CRAs), auditors and inspectors will require access to a patient's medical notes for the purpose of source document verification source document verification but the patient'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 trial data shall not be disclosed to a third party (with the exception of auditors and/or regulatory authorities) without the written consent of the TREAT consortium. All data shall be secured against unauthorized access.

Apart from the site investigators, no one will have access to participant's identity. Each site will securely maintain the code that links participants' identity to their study numbers to prevent access to unauthorized third parties. Participants will be identified according to their study numbers in the data management system (OnCore) and by the investigators during any communications.

The written ICF will explain that, for data verification purposes, authorized representatives of the funding agency, IRB or Generon which is supplying the study medicine, may require direct access to parts of the hospital or practice records relevant to the trial, including patient's medical history.

12.6 **Data Quality Assurance**

Logic and consistency checks will be performed on all data entered into the CRF to ensure accuracy and completeness.

Training sessions, regular monitoring of the trial at the trial sites, instruction manuals, data verification, cross-checking and data audits will be performed to ensure quality of all trial data. Investigators' meetings and/or on-site trial initiations will be performed to prepare investigators and other trial site personnel for appropriate collection of trial data.

12.7 **Data Clarification Process**

The data manager for the TREAT consortium will conduct periodic data queries. Each site will be responsible for reconciling these queries.

12.8 **Records Retention**

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. The investigator should retain all correspondence relating to this trial in the Investigator Site File (ISF).

All documents relating to the trial including the ISF itself, source documents and patient medical files (retained per country specific regulations), completed trial patient log and confidential patient identification list will be retained by the investigator for a minimum period of 15 years, in accordance with regulations. In the event that storage of records becomes a problem at any time during this period, the Sponsor should be consulted for assistance. At the end of the minimum period, the investigator should obtain written authorization form the Sponsor prior to the destruction of any records. The investigator will notify the Sponsor if ownership documents or responsibility for the trial site is transferred. The sponsor will inform investigators should it become aware of any changes in storage requirements.

13 Finance and Insurance

This study is being funded by a grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), one of the institutes that comprise the National Institutes of Health (NIH).

Care for research-related injuries will be billed in the ordinary manner, to the participant or the participant's insurance. The participant will be responsible for all treatment costs not covered by their insurance, including deductibles, co-payments and coinsurance. No compensation will be provided for losses related to the subject's participation in this study (such as time off from work, disability, discomfort due to any research-related injury, etc.).

14 Publication Plan

No data is to be made public or published without prior knowledge and written approval by the TREAT Consortium Steering Committee.

The TREAT consortium publication policies will be applied. Generon will have the opportunity to review each paper prior to its submission for publication.

The study will be registered to ClinicalTrials.gov prior to subject recruitment and enrollment, as well as posting of results to ClinicalTrials.gov within 12 months of final data collection for the primary outcome.

15 List of Planned Laboratory Analytes

Serum Chemistry

1. Sodium
2. Potassium
3. Calcium
4. Chloride
5. Bicarbonate
6. Albumin
7. BUN
8. Creatinine
9. Total bilirubin
10. Direct bilirubin
11. Aspartate aminotransferase (AST)
12. Alanine transaminase (ALT)
13. Alkaline phosphatase
14. Glucose
15. Total Protein

Hematology

1. Hemoglobin
2. Hematocrit
3. White Blood Cell Count
4. Platelets
5. MCV
6. Prothrombin Time (PT and INR)

Urine and Serum Pregnancy Test

Special Investigations

1. Lipid profile
2. CRP
3. SAA1

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