



## **Clinical Protocol REN-002**

A Phase 1b dose-escalating study with Iron Sucrose (FeS), in  
healthy volunteers and subjects with chronic kidney disease stage  
3-4

**IND 138109**

### **SPONSOR**

Renibus Therapeutics, Inc.  
950 E State Highway 114, Suite 160  
Southlake, TX 76092

Original Protocol: 05 September 2018

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Protocol Number: REN-002  
Date: 05 September 2018

## 1 STUDY TITLE

A Phase 1b dose-escalating study with Iron Sucrose (FeS), in healthy volunteers and subjects with chronic kidney disease stage 3-4

## 2 SPONSOR INFORMATION

### 2.1 Sponsor:

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Southlake, TX 76092

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Bhupinder Singh, MD, FASN, FNKF  
Chief Scientific Officer and Medical Monitor  
Renibus Therapeutics, Inc.

*3 Oct 2018*

Date



### 3 LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
AE	Adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ARB	angiotensin-receptor blockers
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
Cr	creatinine
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FeS	Iron sucrose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
HO-1	Heme oxygenase
ICF	informed consent form
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
NOAEL	no-observed-adverse-effect level
POC	Proof of Concept
PP	Per Protocol
TEAE	treatment emergent adverse event

## 4 STUDY SYNOPSIS

<b>Renibus Therapeutics, Inc.</b>	<b>Protocol No. REN-002</b>
<b>Name of Drug:</b> Iron Sucrose	<b>Phase of Development:</b> 1b
<b>Name of Active Ingredient:</b> Iron sucrose (FeS)	<b>Date of Study Synopsis</b> 5 September 2018 D1
<b>Protocol Title:</b> A Phase 1b dose-escalating study with FeS, in healthy volunteers and subjects with chronic kidney disease stage 3-4.	
<b>Investigational Sites:</b> One contract research organization in the US.	
<b>Study Objectives:</b> The primary objectives of the study are to evaluate: <ol style="list-style-type: none"> <li>1. The effect of FeS on biomarkers which are potential surrogates for cytoprotective activity in healthy volunteers and in subjects with stage 3-4 CKD.</li> <li>2. To establish the biomarkers response to different doses of FeS.</li> <li>3. Evaluate safety of FeS in comparison to levels of cytoprotective biomarkers.</li> </ol>	
<b>No. Subjects to be Enrolled:</b> Up to a total of 18 subjects consisting of 9 healthy volunteers and 9 subjects with chronic kidney disease will receive single escalating doses of FeS. Six subjects consisting of 3 healthy volunteers and 3 subjects with stage 3-4 CKD will be enrolled in one of three dose levels, starting at the lowest dose of 120 mg FeS.	
<b>Study Design:</b> This is a Phase 1b single-center, dose-escalating study to evaluate the pharmacodynamic effect of FeS in healthy volunteers and in subjects with stage 3-4 CKD. The following biomarkers will be used as surrogate measures of protective activity: Haptoglobin, Ferritin, Hemopexin, IL-10, and Heme Oxygenase-1. Additionally, the P21 biomarker will be monitored at various points of the study.  Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria are eligible to be enrolled into the study.  The study is designed as follows: <ul style="list-style-type: none"> <li>• A screening period with baseline evaluations for study eligibility.</li> <li>• If subjects meet eligibility criteria, they will receive FeS by IV infusion on study day 1.</li> <li>• Subjects will stay in the clinic for the initial 24 hours after administration of FeS and will be discharged at the end of Day 2 if no safety issues appear.</li> <li>• The study will be dose-escalating in 3 groups of 6 subjects consisting of 3 healthy volunteers and 3 subjects with stage 3-4 CKD, evaluating doses of 120 mg FeS, 240 mg FeS and 360 mg FeS.</li> </ul>	



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- Subjects will be followed for 8 days after the dose of FeS. Response biomarkers will be assessed at baseline and 2,4, 8, 12, 18, 24, 48, 72, 96 and 168 hours after study drug administration.
- Total study duration will be 8 days for each subject, in addition to a screening period of up to 14 days.

**Endpoints:**

**Biomarker Monitoring**

Change from baseline in biomarkers from before to after dosing; biomarkers will be measured at baseline and 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours after administration of FeS. The following biomarkers will be evaluated: Haptoglobin (Hp), Ferritin, Hemopexin, IL-10, Heme Oxygenase 1 (HO-1) and P21. All biomarkers will be measured at the same time points.

**Healthy Volunteer Subjects**

**Inclusion Criteria:**

1. Male and female subjects age 18 to 80 years (inclusive, at time of ICF).
2. Body weight <125 kg.
3. Able and willing to comply with all study procedures.
4. Female subjects must be either post-menopausal for at least 1 year or surgically sterile (tubal ligation, hysterectomy or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity from Screening until 8 days after study drug administration.

Male subjects with female partners of childbearing potential must agree to use a highly effective method of contraception from screening until 8 days after study drug administration. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

**Exclusion Criteria:**

1. History of malignancy except carcinoma in situ in the cervix, early stage prostate cancer or non-melanoma skin cancers.
2. Use of investigational drugs or participation in another clinical trial within 30 days or 5 half-lives prior to screening, whichever is longer.
3. Serum ferritin > 500 ng/ml or who have received IV iron within 28 days of screening.
4. Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.
5. Any significant acute or chronic diseases.
6. Regular use of drugs of abuse and/or positive findings on urinary drug screening.
7. Current tobacco use and/or positive findings on urinary cotinine screening.
8. Subjects who are severely physically or mentally incapacitated and who, in the opinion of investigator, are unable to perform the subjects' tasks associated with the protocol.
9. Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated.
10. Known hypersensitivity or previous anaphylaxis to FeS.



### **CKD Subjects**

#### **Inclusion Criteria:**

1. Male and female subjects age 18 to 80 years (inclusive, at time of ICF).
2. Body weight <125 kg.
3. Able and willing to comply with all study procedures.
4. Female subjects must be either post-menopausal for at least 1 year or surgically sterile (tubal ligation, hysterectomy or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity from Screening until 8 days after study drug administration.

Male subjects with female partners of childbearing potential must agree to use a highly effective method of contraception from screening until 8 days after study drug administration. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

5. CKD as determined by estimated glomerular filtration rate (GFR) between 15-59 ml/min as estimated using the CKD-EPI equation (CKD class 3-4).

#### **Exclusion Criteria:**

1. History of malignancy except carcinoma in situ in the cervix, early stage prostate cancer or non-melanoma skin cancers.
2. Use of investigational drugs or participation in another clinical trial within 30 days or 5 half-lives prior to screening, whichever is longer.
3. Serum ferritin > 500 ng/ml or who have received IV iron within 28 days of screening, or currently being treated with oral iron.
4. Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.
5. Regular use of drugs of abuse and/or positive findings on urinary drug screening.
6. Current tobacco use and/or positive findings on urinary cotinine screening.
7. Subjects who are severely physically or mentally incapacitated and who, in the opinion of investigator, are unable to perform the subjects' tasks associated with the protocol.
8. Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated.
9. Known hypersensitivity or previous anaphylaxis to FeS or to components thereof.

**Drug, Dose and Mode of Administration:**

FeS is supplied as sterile liquid in glass vials for intravenous (IV) injection and intended for single use. Glass vials are plugged with Teflon-coated rubber stoppers and sealed with aluminum seals. Vials of 5 mL will be used for each cohort.

FeS at a dose of either 120 mg FeS, 240 mg FeS or 360 mg FeS will be administered on study Day 1. The infusions should be given over a 60-120 minute period.

**Rationale for the Dose and Schedule Selection:**

The proposed FeS doses and administration schedules are based on established doses and use for FeS products.

**Study Duration:**

Study duration is for 8 days per subject.

**Criteria for Evaluation:**

Biomarkers

- Key parameters: Haptoglobin, Ferritin and Bilirubin, Hemopexin, IL-10, Heme Oxygenase 1 (HO-1),
- Additional secondary parameters: P21

**Study Hypothesis:**

FeS has been used commercially for several decades, it is hypothesized that FeS will modulate biomarker levels in a dose-related fashion and these modulations will not be correlated with changes in safety measures.

**Statistical Considerations**

**Sample Size:** No formal sample size calculation has been performed for this phase 1b study. However, it is believed that 6 subjects per dose group will be adequate to establish POC based on biomarker response and identify an optimal dose for further testing, recognizing that a battery of different surrogate biomarkers will be evaluated.

**Analysis Populations and General Methodology:** Subjects who receive study medication and have a post-baseline efficacy assessment will be included in the Modified Intent-to-Treat (MITT) population for efficacy analysis. All subject data will be listed. When appropriate, summary statistics will be provided (number of non-missing values, mean, median, standard deviation, minimum, and maximum for continuous variables and number and percentage of subjects for categorical variables) by treatment group for all measures, including demographic and baseline assessments, safety, and efficacy endpoints. Baseline for all efficacy endpoints is defined as the last observations before administration of the first IV infusion of study drug. No imputation will be used for missing data.

**Safety Analysis:** Safety measures including AEs, infusion-related reactions, clinical laboratory tests, vital signs, physical exams, and concomitant medication usage will be summarized descriptively by treatment group and study visit, where appropriate.

**Biomarker Analysis:** Biomarker response will be summarized by treatment group and study visit, comparing change from baseline at 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours.



Percent change from baseline will be analyzed using the mixed model for repeated measures (MMRM). The between-group comparison will be performed using the simple contrast at 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours post-dosing.

In addition to absolute and percent changes from baseline, a responder analysis will also be considered. The responder definition and its appropriate analysis methodology will be detailed in the statistical analysis plan (SAP) for the study. Exploratory analysis using Cochran-Mantel-Haenszel test stratified by baseline or primary diagnosis will be carried out.

**Pharmacokinetic Analysis:** Pharmacokinetic parameters of each treatment group may be analyzed. The maximum serum concentration ( $C_{max}$ ) and time to maximum serum concentration ( $T_{max}$ ) will be obtained directly from the data. The elimination rate constant ( $\lambda_z$ ), elimination half-life ( $T_{1/2}$ ), area under the concentration-time curve from time 0 to time t ( $AUC_{[0-t]}$ ) and area under the concentration-time curve from time 0 to infinity ( $AUC_{[0-inf]}$ ), clearance (CL), and volume of distribution ( $V_z$ ) will be calculated for each subject and summarized by treatment group.

## 5 EVENT SCHEDULE

### 5.1 Event Schedule – All subjects

Study Day	Screening	1	2,3,4,5,8(EOS) <sup>1</sup>
Parameter	Within 14 days prior to first dose		
Written informed consent	X		
Eligibility criteria	X		
Demographics	X		
Medical history	X		
Physical examination and weight	X	X <sup>2</sup>	
Electrocardiogram	X	X <sup>1,2</sup>	
Vital signs	X	X <sup>2</sup>	X
Serum chemistry <sup>7,8</sup>	X	X <sup>2</sup>	X
Hematology <sup>7,8</sup>	X	X <sup>2</sup>	X
Response biomarkers <sup>7, 10</sup>		X <sup>2,3</sup>	X
Urinalysis including sediment <sup>8</sup>	X	X <sup>2</sup>	X
Urine pregnancy test <sup>9</sup>	X	X	X at Day 8 (EOS)
Urine drug/alcohol/cotinine screen	X		
Confinement in clinical testing unit <sup>4</sup>		X <sup>4</sup>	
FeS infusion		X <sup>5</sup>	
Discharge from clinical testing unit			X <sup>6</sup>
Prior/Concomitant medications	X	X	X
Adverse events		X	X
Investigational product reconciliation			X

<sup>1</sup> Day 8 (EOS) visit will occur ( $\pm 1$ ) days after administration of FeS.

<sup>2</sup> Baseline parameters performed prior to dosing on Study Day 1.

<sup>3</sup> Additional biomarker samples collected at 2, 4, 8, 12, 18 hours ( $\pm 15$  minutes) after completion of infusion

<sup>4</sup> Subjects will be confined in the clinical testing unit a minimum of 24 hours from the morning of Study Day 1 until after collection of the 24-hour post-dose sample on Study Day 2.

<sup>5</sup> FeS will be administered as an infusion over 60-120 minutes after Baseline ECG, vital signs and blood and urine samples are collected.

<sup>6</sup> Discharge from unit following evaluations and sample collection required on Study Day 2

<sup>7</sup> Measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to sample collection at the clinic).

<sup>8</sup> Parameters to be measured are detailed in [Appendix 1](#).

<sup>9</sup> For women of childbearing potential using kits supplied by the laboratory

<sup>10</sup> Haptoglobin, Ferritin, Hemopexin, IL-10, P21 and HO-1.



## 6 INTRODUCTION

### 6.1 Background Information

Acute kidney injury (AKI) is an abrupt loss of kidney function in which the body accumulates waste products and is unable to maintain electrolyte, acid-base, and water balance [Tögel 2014]. It is a major risk factor for morbidity, mortality, and the development of chronic kidney disease (CKD) [Goldberg 2009, Ishani 2009, Liangos 2006, Wald 2009, Xue 2006]. A meta-analysis of 154 studies conducted worldwide in over 3.5 million subjects reported pooled incidence and mortality rates of AKI in hospitalized adult subjects of 21.6% and 23.9%, respectively [Susantitaphong 2013]. In cardiac surgery subjects, the incidence of postoperative AKI is approximately 30% and significantly increases the risk of death after cardiac surgery [Rosner 2006]. Progression to advanced-stage CKD within 24 months occurs in approximately 15 to 20% of subjects who survive AKI [Chawla 2012].

Many different types of exposure may cause AKI; however, the chance of developing AKI after exposure depends on a number of susceptibility factors that vary widely among individual subjects [Kellum 2013]. Sepsis, critical illness, circulatory shock, burns, trauma, cardiac surgery (particularly with cardiopulmonary bypass), major non-cardiac surgery, nephrotoxic drugs, radiocontrast agents, and poisonous plants and animals are all recognized as causes of AKI. Susceptibility factors that increase a subject's risk of developing AKI include dehydration or volume depletion, advanced age, female gender, Black race, chronic kidney disease, chronic disease (heart, lung, liver), diabetes mellitus, cancer, and anemia. AKI can lead to a number of complications, including metabolic acidosis, hyperkalemia, uremia, changes in body fluid balance, and effects on other organ systems, including need for dialysis and possibly death. People who have experienced AKI have an increased risk of developing chronic kidney disease possibly requiring dialysis in the future. The annual cost to the US health care system is estimated at approximately \$15B [Silver 2017].

The diagnosis of AKI is based on the following criteria introduced by the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group in 2012 [KDIGO 2012]: increase in serum creatinine  $\geq 0.3$  mg/dL within 48 hours; or increase in serum creatinine  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume  $< 0.5$  mL/kg/hour for 6 hours. The management of AKI is purely symptomatic, with the aim of limiting damage and preventing further loss of function. No pharmacologic therapy is approved for the treatment or prevention of AKI.

It has long been recognized that after an initial ischemic or toxic injury, the kidney develops marked resistance to subsequent damage [Honda 1987, Zager 1984, Zager 1995a, Zager 1995b, Zager 1995c]. This phenomenon, which is mediated in part by an upregulation of renal cytoprotective and anti-inflammatory stress proteins (e.g., heme oxygenase 1 [HO-1], ferritin, haptoglobin, hemopexin, alpha 1 antitrypsin, interleukin 10 [IL-10]), has been referred to as "ischemic preconditioning" or "acquired cytoresistance." This phenomenon could be used in a clinical setting to preemptively protect organs, especially when a known insult is approaching.



## 6.2 Study Drug

A pharmacological intervention with the ability to stimulate the kidney's natural protective pathways to prevent AKI would represent a significant medical advance. FeS is under study as one prophylactic agent to induce cytoresistance in organs when a known insult is imminent. The initial target for development is the kidneys and prevention of AKI. However, the phenomenon of acquired cytoresistance is also relevant to other bodily organs such as the heart and liver, and will be the focus of extended development of FeS in combination with other agents.

Iron sucrose (Venofer®) is an intravenous iron replacement product that has been in use for more than 65 years and is currently registered in more than 90 countries worldwide. In the United States, iron sucrose is approved for the treatment of iron deficiency anemia in pediatric and adult CKD subjects [Venofer 2015], with expanded indications (i.e., need for rapid iron supply, subjects unable to tolerate or comply with oral iron therapy, subjects with inflammatory bowel disease in whom oral iron therapy is ineffective) approved for use outside the United States [Venofer 2016]. Preclinical Experience

FeS has been shown to induce renal preconditioning and the emergence of a cytoprotective state in animal models that resulted in marked protection against diverse forms of AKI [Zager 2016]. In contrast to ischemic preconditioning, which induces local or remote ischemia, the acquired cytoresistance induced by FeS was achieved without resultant damage to the kidney, liver, or heart. Thus, these data suggest that FeS alone and in combination with other agents may provide a clinical prophylactic strategy for protecting against both renal and extrarenal injuries prior to an insult, such as exposure to surgery, balloon angioplasty, or administration of a radiocontrast agent.

## 6.3 Clinical Experience

Safety data in humans are available for FeS. The most common adverse reactions ( $\geq 2\%$ ) following the administration of iron sucrose are diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain, and peripheral edema [Venofer 2015].

# 7 STUDY OBJECTIVES

## 7.1 Primary Objectives

The primary objectives of the study are to evaluate:

1. The effect of FeS on biomarkers which are potential surrogates for cytoprotective activity in healthy volunteers and in subjects with stage 3-4 CKD.
2. To establish the biomarkers response to different doses of FeS.
3. Evaluate safety of FeS in comparison to levels of cytoprotective biomarkers.



## 8 INFORMED CONSENT

The investigator or designee will be responsible for obtaining a signed, written informed consent form (ICF) and providing a copy to each subject, legally authorized guardian, or a person with legal responsibility for the subject's health care decisions prior to the performance of any clinical activities or procedures pursuant to this protocol. Subjects who are vision impaired may have the ICF read to them and their witnessed consent documented. Only the consent form approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be used. If English is NOT the subject's primary language, the subject will be consented using an IRB-approved ICF in the requisite language. This consent will be conducted by a member of the research team who is fluent in the language and thus able to answer any scientific or procedural questions raised by a non-English speaking subject.

## 9 STUDY POPULATION

### 9.1 Healthy Volunteers

#### 9.1.1 HV Inclusion Criteria

1. Male and female subjects age 18 to 80 years (inclusive, at time of ICF).
2. Body weight <125 kg.
3. Able and willing to comply with all study procedures.
4. Female subjects must be either post-menopausal for at least 1 year or surgically sterile (tubal ligation, hysterectomy or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity from Screening until 8 days after study drug administration.

Male subjects with female partners of childbearing potential must agree to use a highly effective method of contraception from screening until 8 days after study drug administration. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

#### 9.1.2 HV Exclusion Criteria

1. History of malignancy except carcinoma in situ in the cervix, early stage prostate cancer or non-melanoma skin cancers.
2. Use of investigational drugs or participation in another clinical trial within 30 days or 5 half-lives prior to screening, whichever is longer.
3. Serum ferritin > 500 ng/ml or who have received IV iron within 28 days of screening.
4. Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.
5. Any significant acute or chronic diseases.

6. Regular use of drugs of abuse and/or positive findings on urinary drug screening.
7. Current tobacco use and/or positive findings on urinary cotinine screening.
8. Subjects who are severely physically or mentally incapacitated and who, in the opinion of investigator, are unable to perform the subjects' tasks associated with the protocol.
9. Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated.
10. Known hypersensitivity or previous anaphylaxis to FeS or to components thereof.

## **9.2 CKD Subjects**

### **9.2.1 CKD Inclusion Criteria**

1. Male and female subjects age 18 to 80 years (inclusive, at time of ICF).
2. Body weight <125 kg.
3. Able and willing to comply with all study procedures.
4. Female subjects must be either post-menopausal for at least 1 year or surgically sterile (tubal ligation, hysterectomy or bilateral oophorectomy) for at least 3 months, or if of childbearing potential, have a negative pregnancy test and agree to use dual methods of contraception, or abstain from sexual activity from Screening until 8 days after study drug administration.

Male subjects with female partners of childbearing potential must agree to use a highly effective method of contraception from screening until 8 days after study drug administration. All fertile men with female partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

5. CKD as determined by a GFR between 15-59 ml/min as estimated using the CKD-EPI equation (CKD class 3-4).

### **9.2.2 CKD Exclusion Criteria**

1. History of malignancy except carcinoma in situ in the cervix, early stage prostate cancer or non-melanoma skin cancers.
2. Use of investigational drugs or participation in another clinical trial within 30 days or 5 half-lives prior to screening, whichever is longer.
3. Serum ferritin > 500 ng/ml or who have received IV iron within 28 days of screening.
4. Women who are pregnant, breastfeeding, or planning to become pregnant while participating in the study.
5. Regular use of drugs of abuse and/or positive findings on urinary drug screening.
6. Current tobacco use and/or positive findings on urinary cotinine screening.



7. Subjects who are severely physically or mentally incapacitated and who, in the opinion of investigator, are unable to perform the subjects' tasks associated with the protocol.
8. Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated.
9. Known hypersensitivity or previous anaphylaxis to FeS or to components thereof.

### 9.3 Study Design

This is a Phase 1b, single-center, dose-escalating study to evaluate the pharmacodynamic effect of FeS in healthy volunteers and in subjects with stage 3-4 CKD. The following biomarkers will be used as surrogate measures of protective activity: Haptoglobin, Ferritin, Hemopexin, IL-10, P21 and HO-1.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria are eligible to be enrolled into the study.

The study is designed as follows:

- A screening period with baseline evaluations for study eligibility.
- If subjects meet eligibility criteria, they will receive FeS by infusion over 60-120 minute period on study day 1.
- Subjects will stay in the clinic for the initial 24 hours after administration of FeS and will be discharged on day 2 if no safety issues appear.
- The study will be dose-escalating in 3 groups of 6 subjects consisting of 3 healthy and 3 3-4 CKD subjects, evaluating doses of 120 mg FeS, 240 mg FeS or 360 mg FeS. The infusions should be given over a 60-120 minute period.
- Subjects will be followed for 8 days after the dose of FeS. Response biomarkers will be assessed at baseline and 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours after study drug administration.
- Total study duration will be up to 8 days per subject.

#### 9.3.1 Stopping Rules

There are no pre-established stopping rules for the study.

### 9.4 Recordkeeping and Monitoring

All subject data will be reported in the electronic data capture (EDC) system with the exception of the laboratory reports, which will be uploaded by electronic transfer by the laboratory. All original source documents should be available for periodic monitoring and/or retrieval by a Sponsor representative designee. The investigator is responsible for the accuracy of all data entered in the electronic case report forms (eCRFs) and for the timely completion of the eCRFs. The supporting documentation will be maintained at the site for a minimum of:

1. Two (2) years following notification by Renibus Therapeutics, Inc. to the FDA of the termination of the entire investigation.

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The Sponsor must be contacted and give written authorization prior to any study records being destroyed at investigative sites.

This study will be conducted in compliance with Good Clinical Practice (GCP), which includes the Sponsor and IRB-approved protocol and ICF and the FDA and International Conference on Harmonisation (ICH) regulatory guidelines and requirements. No changes will be made without prior approval unless it is imperative for subject safety. Any such departures from the protocol will be reported immediately to the Sponsor and relevant IRB.

All subjects' medical records and study-related documents will be made available to the Sponsor for regular monitoring and audits as well as to the IRB and FDA or other governmental agency with oversight or compliance responsibilities for assuring subject rights and welfare.

### **9.5 Investigational Supplies**

Subjects will be dosed with open-label FeS.

#### **9.5.1 Study Drug Description**

The investigational product is an iron sucrose solution buffered with sodium bicarbonate (FeS). The term investigational product refers to FeS.

#### **9.5.2 Packaging**

FeS will be packaged and labeled in filled vials of 5 ml at Patheon, Inc.. Iron sucrose will be packaged in a clear vial.

Following receipt of Form FDA 1572 and IRB approval for a given site, investigational product will be sent to the study site.

#### **9.5.3 Investigational Product Dispensing**

All investigational product will be dispensed by designated and trained site pharmacy staff.

#### **9.5.4 Dosage Preparation and Administration**

The infusion bag is commercially available 100 or 250 mL bags of 0.9% sodium chloride injection, USP. Dosing will be detailed in the Pharmacy Manual.

Total infusion time will be 60-120 minutes as detailed in the Pharmacy Manual.

Observe for signs and symptoms of hypersensitivity during and after administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.

#### **9.5.5 Storage Requirements**

The investigational product should be stored at controlled room temperature conditions (defined as 20 - 25°C/68 - 77°F with excursions of less than 24 consecutive hours permitted between 15 - 30°C/59 - 86°F).

The infusion bags should be stored in accordance with the manufacturer's instructions.



### **9.5.6 Investigational Product Accountability**

The investigator or designee is responsible for maintaining accurate records accounting for the receipt, dispensing, and final disposition of all investigational products using the appropriate investigational product logs provided by Renibus Therapeutics, Inc.

### **9.5.7 Retrieval and Destruction**

Periodically throughout the study, sites will perform investigational product reconciliation on a per-subject basis. The Renibus site monitor will review the log and once any discrepancies have been resolved, authorize destruction/disposition of the supplies associated with a given subject by signing the reconciliation log and will witness the destruction/disposition.

## **9.6 Study Visits**

### **9.6.1 General Information**

- All recorded clock times should utilize a 24-hour clock.
- In accordance with the clinical site's standard operating procedures, an intravenous catheter or a butterfly needle (of a sufficient gauge to avoid sample hemolysis) may be inserted for the purpose of collection of blood samples. Alternatively, the site preference may be to use direct venipuncture for the purpose of collection of blood samples. Either method is acceptable.
- There are no dietary restrictions in this study. Subjects should continue to eat their normal diet.
- Subjects will be encouraged to remain well hydrated during the study to promote sample collection.
- Blood samples for Chemistry, Hematology, biomarkers and pharmacokinetic analysis (if done) will be collected into the appropriate collection tubes and processed in accordance with the instructions specified in the laboratory manual.
- The informed consent must be signed before any of the Screening or Study procedures are performed.

### **9.6.2 Screening (Within 14 Days Prior to Study Day 1)**

1. Subjects will arrive at the clinical testing unit in the morning after fasting (defined as nothing by mouth except water) for at least 8 hours prior to the collection of any blood samples.
2. Eligibility will be confirmed.
3. Demographic characteristics and medical history will be obtained.
4. Physical examination (including height and weight), vital signs (after sitting  $\geq 5$  minutes), and 12-lead ECG (after sitting  $\geq 5$  minutes) will be performed.
5. Blood and urine will be collected for clinical laboratory tests ([Appendix 1](#)) and drug/alcohol/cotinine screen.
6. For women of childbearing potential, urine pregnancy test will be performed.

7. Eligible subjects will return to the clinical testing unit within 14 days for confinement and dosing.

### 9.6.3 Study Day 1

1. Subjects will arrive at the clinic at 8:00am ( $\pm$  60 minutes).

2. All eligibility criteria will be assessed.

For CKD subjects, subjects whose GFR value does not meet the inclusion criteria may be re-screened 2 more times during the trial. If the ICF has been signed within 30 days and there are no new revisions, a new ICF is not necessary. If a subject is re-screened, the subject will be given a new screening number in the eCRF system and source documents.

3. If all eligibility criteria are met, the following Baseline samples will be collected (Appendix 1):

- Blood samples for standard assessment of hematology and serum chemistry.
- Blood samples for measurement of response biomarkers (Haptoglobin, Ferritin, Hemopexin, IL-10, P21 and HO-1).
- Urine for standard assessment of urinalysis parameters.
- Urine samples for measurement of response biomarkers (Hemopexin, Ferritin, P 21 and HO-1).

- 4 A Baseline ECG will be performed (Section 9.8.1).

- 5 A full physical examination including height, weight, and vital signs will be performed (Sections 9.8.3 and 9.8.4).

- 6 Medical history and prior/concomitant medication information will be collected. (Section 9.8.2)

- 7 Subjects who meet all inclusion/exclusion criteria will be enrolled into the Study and the following procedures will take place:

- The dose of FeS will be administered in the clinic as an infusion over a 60-120 minute period. Food may be given before or after infusion.

**Observe for signs and symptoms of hypersensitivity during and after administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Should a subject experience nausea during or after infusion, the investigator may order Ondansetron (Zofran®) per its label instructions.**

- The clinic staff will solicit any adverse events.
- Response biomarker samples will be collected at 2, 4, 8, 12, and 18 hours ( $\pm$  15 minutes) after infusion.
- Lunch and dinner will be provided by the clinic.



#### 9.6.4 Study Day 2

The following procedures will be done at 24 hours ( $\pm$  15 minutes) after dosing:

1. Blood samples for standard assessment of clinical chemistry, hematology, and safety and response biomarkers will be collected ([Appendix 1](#)).
2. Urine samples for standard assessment of urinalysis parameters and response biomarkers will be collected ([Appendix 1](#)).
3. The clinic staff will solicit any adverse events and note any changes in concomitant medications.
4. The subject is discharged from the clinic per site discharge procedures.

#### 9.6.5 Study Days 3,4,5,8 (Day 8-EOS $\pm$ 1 day)

1. Subjects will arrive at the clinic at 8:00am ( $\pm$  60 minutes).
2. Blood samples for standard assessment of clinical chemistry, hematology, and response biomarkers will be collected ([Appendix 1](#)).
3. Urine samples for standard assessment of urinalysis parameters and response biomarkers will be collected ([Appendix 1](#)).
4. A urine pregnancy test will be performed if the subject is a woman of childbearing potential at Day 8.
5. The clinic staff will solicit any adverse events and note any changes in concomitant medications since the last visit.
6. A full physical examination including weight and vital signs will be performed ([Sections 9.8.3 and 9.8.4](#)).

### 9.7 Clinical Laboratory Evaluations

All samples for clinical laboratory evaluations will be collected under fasting conditions, defined as nothing by mouth except water, and essential medications only (for CKD patients) for a minimum of 8 hours prior to collection of the samples.

#### 9.7.1 Blood Chemistry, Hematology and Response biomarker Samples

The Chemistry, Hematology and response biomarker parameters to be evaluated during the study are presented in [Appendix 1](#). Detailed instructions regarding sample collection and processing are provided in the laboratory manual. Collection times are summarized in the Events Schedules ([Section 5](#) and [Section 9.6](#)).

#### 9.7.2 Urine Samples

The urine parameters and response biomarkers to be evaluated during the Study are presented in [Appendix 1](#). Detailed instructions regarding sample collection and processing are provided in the laboratory manual. Collection times are found in the Events Schedules ([Section 5](#) and [Section 9.6](#)). All urine samples will be analyzed by the laboratory, except for urine pregnancy tests for women of childbearing potential.



All women of childbearing potential (defined as not surgically sterile nor postmenopausal for at least 2 years) will have a urine pregnancy test performed at the clinic as part of the screening procedure prior to any investigational product administration and at an End of Study using the pregnancy kit supplied by the laboratory.

## **9.8 Clinical Procedures and Observations**

The research clinic will follow its own standard operating procedures for the daily ongoing monitoring of subjects while subjects are in the clinic (e.g. pulse, O<sub>2</sub> saturation, etc.). Subjects will be monitored for any adverse events occurring at any time throughout the study.

### **9.8.1 ECG**

ECGs will utilize a 12-lead recording. Collection times are summarized in the Events Schedules (Section 5 and Section 9.6). ECG results will be assessed by the investigator/sub-investigator.

### **9.8.2 Concomitant Medications**

All concomitant medications taken by the subject from 30 days prior to Study Day 1 through the end of study (28 [± 1] days after the dose of investigational product) will be recorded.

### **9.8.3 Physical Examination**

A full physical examination, including height (Study Day 1 only) and weight (weighed on the same scale in the same state of dress), will be conducted at Day 1 and at end of the study. Collection times are summarized in the Events Schedules (Section 5 and Section 9.6).

All physical examinations are to be performed by the investigator/sub-investigator or designee whose license permits the performing of physical examinations.

### **9.8.4 Vital Signs**

Blood pressure (systolic and diastolic), pulse, and body temperature will be measured before investigational product is administered and after the subject has been in a sitting position for ≥ 5 minutes. Collection times are summarized in the Events Schedules (Section 5 and Section 9.6).

### **9.8.5 Meals and Dose Administration**

There are no dietary restrictions in this study. Subjects should continue to eat their normal diet. Breakfast may be eaten before or after the infusion of FeS on Study Day 1.

### **9.8.6 Prohibited Medications**

None

Oral iron medication may be taken prior to screening but must be discontinued upon enrollment.

## **10. ADVERSE EVENT REPORTING**

All adverse events will be recorded on the designated study eCRF for each subject beginning with the first administration of investigational product and ending with the date of the end of study treatment follow-up. Any unresolved adverse events will be followed by the investigator until event resolution, the subject is lost to follow-up, the adverse event is otherwise explained or not considered clinically significant by the investigator.



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## 10.1 Investigator Reporting Requirements

The investigator must immediately report (within 24 hours by telephone and followed by a written report sent by fax or e-mail) all serious adverse events to Renibus Therapeutics, Inc. regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population independent of drug exposure (see Section 10.2).

These serious adverse events must be reported to:

Bhupinder Singh, MD, FASN, FNKF

Medical Monitor

Renibus Therapeutics, Inc  
950 E State Highway 114, Suite 160  
Southlake, TX 76092

Cell: (480) 220-7084

Fax (817) 549-1254

E-mail: [medicalmonitor@renibus.com](mailto:medicalmonitor@renibus.com)

Because the investigator is knowledgeable about the human subject (e.g., medical history, concomitant medications), administers the investigational drug, monitors the subject's response to the drug, is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to an underlying disease process versus events that may be drug-related, and may have observed the event, the investigator must include an assessment of causality (i.e., whether there is a reasonable possibility that the drug caused the event) in the report to Renibus Therapeutics, Inc. Copies of each report to Renibus Therapeutics, Inc. will be kept in the investigator's study file.

The investigator is responsible for complying with their IRB's requirements for reporting serious adverse events. Any expedited safety report (i.e., serious unexpected suspected adverse reaction) received from Renibus Therapeutics, Inc. should be submitted to the IRB. Copies of each report and documentation of IRB notification will be kept in the investigator's study file.

The investigator must record non-serious adverse events in the eCRF and report them to Sponsor according to the timetable for reporting (e.g., end of study). The investigator's assessment of causality is not required for non-serious adverse events.

## 10.2 Definitions

**Adverse Event:** Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

**Adverse Reaction:** Adverse reaction means any adverse event definitely caused by the drug.

**Suspected Adverse Reaction:** Suspected adverse reaction means any adverse event for which there is a "reasonable possibility" (i.e., evidence indefinite but suggests a causal relationship



between the drug and the adverse event) that the drug caused the adverse event. By definition, a suspected adverse reaction is identical to the definition of adverse drug reaction per ICH E2A.

Examples that would suggest a causal relationship:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (e.g., known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Unexpected Adverse Event or Unexpected Adverse Reaction: An adverse event or 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.

Adverse events or adverse reactions that are mentioned as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug will be considered “unexpected” if they are not specifically mentioned as occurring with the particular drug under investigation.

Until the investigator brochure is updated to include a new serious suspected adverse reaction, subsequent occurrences of similar serious suspected adverse reactions must be submitted expeditiously to FDA in IND Safety Reports and to other appropriate regulatory authorities in countries other than the US in an Individual Case Safety Report (ICSR) or using a Council for International Organizations of Medical Sciences (CIOMS) I form, as appropriate.

Serious Adverse Event or Serious Adverse Reaction: An adverse event or 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
- In subject hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If either the investigator or Sponsor believes that the event is serious, it must be evaluated by the Sponsor for expedited reporting to regulatory authorities.



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**Life-Threatening Adverse Event or Life-Threatening Adverse Reaction:** An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or Renibus, its occurrence places the subject at immediate risk of death.

**Serious Unexpected Suspected Adverse Reaction:** An adverse event for which there is a reasonable possibility that the drug caused the adverse event, and it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed, and it results in any of the serious outcomes listed above. This criterion is consistent with the concepts of FDA 21 Code of Federal Regulation (CFR) 312 and the ICH E2A Guideline for expedited safety reports.

The Sponsor must notify the appropriate regulatory authority(ies) and all participating investigators in an expedited safety report (e.g., IND Safety Report or ICRS) of potentially serious risks from clinical trials or any other source (i.e., a serious unexpected suspected adverse reaction), as soon as possible, but no later than 15 calendar days after Renibus Therapeutics, Inc. receives the safety information and determines that the information qualifies for reporting.

During the course of drug development, the Sponsor may become aware of new safety information from a variety of sources and will decide if an individual case of a serious and unexpected adverse event meets the criteria for reporting to regulatory authorities.

If the adverse event does not meet all criteria (i.e., reasonable possibility of causality, serious and unexpected), it should not be submitted as an expedited safety report.

Any unexpected fatal or life-threatening suspected adverse reaction must be reported to regulatory authorities no later than 7 calendar days after Renibus Therapeutics, Inc. receives the safety information.

### **10.3 Breaking the Blind**

Not applicable as this is an open label study.

## **11. STATISTICAL CONSIDERATIONS**

This section outlines the nature and rationale for the statistical methods to be used for the analysis of the data from the study. A separate Statistical Analysis Plan (SAP) will describe data handling and statistical techniques in full detail.

### **11.1 Study Populations**

All subjects who receive study medication will be included in the safety and PD analyses. All subjects who receive study medication and provided sufficient and valid serum FeS concentration data to allow the determination of PK parameters will be considered as potential PK evaluable subjects. No imputation will be used for missing data.

### **11.2 Demographic and Baseline Characteristics**

Demographic and baseline variables that will be summarized by dose group include:

- Demographics
- Medical history
- Complete PE



- Efficacy and Safety variables including vital signs and laboratory tests, including chemistry, hematology, and urinalysis obtained at Screening.

### 11.3 Analysis of Efficacy Endpoints

Descriptive statistics will be used to summarize Response biomarker results at baseline, each visit, and the change from baseline for each visit.

Percent change from baseline will be analyzed using the mixed model for repeated measures (MMRM). In this analysis, percent change from baseline at each post treatment time point will be the response variable; treatment, visit, and treatment-by-visit interaction as fixed factors, patient as repeated measure unit over visits, and baseline as covariate. The between-group comparison will be performed using the simple contrast at 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours post-dosing.

In addition to the percent changes from baseline, absolute change from baseline will also be analyzed using MMRM. Moreover, a responder analysis will also be considered. The responder definition and its appropriate analysis methodology will be detailed in the statistical analysis plan (SAP) for the study. Exploratory analysis using Cochran-Mantel-Haenszel test stratified by baseline or primary diagnosis will be carried out.

### 11.4 Analysis of Pharmacodynamic/Safety

The evaluation of safety will include adverse events, clinical laboratory parameters, vital signs, physical examinations, and ECGs.

The principle of treatment emergence will be employed for the analysis of adverse event data. A Treatment emergent adverse event (TEAE) is defined to be any event that occurs during the observation period of the study and was not present at baseline, or exacerbation of a condition present at baseline.

TEAEs will be classified by the Medical Dictionary for Regulatory Activities (MedDRA). The type, incidence, timing (onset, duration), relationship, and severity of adverse events will be reported for treatment-emergent and serious adverse events. Reasons for withdrawal due to adverse events will also be reported.

Descriptive statistics, including mean, mean change from baseline, standard deviation, minimum, maximum, and median, will be presented for laboratory parameters, vital signs, and ECG parameters. The numbers and percentages of subjects with treatment-emergent laboratory, vital sign, and ECG values that meet Sponsor-defined potentially clinically significant criteria will be summarized. Categorical (low, normal, and high relative to the normal range) shifts from baseline will be summarized with the number and percentage of subjects for laboratory parameters.

All safety data will be displayed in listings.

### 11.5 Analysis of Pharmacokinetic (PK) Data

Pharmacokinetic (PK) parameters may be calculated for each subject and summarized by treatment group. PK profiles in which the pre-dose concentration is and  $> 5\%$  of the corresponding  $C_{max}$  (and therefore greater than the lower limit of quantification (LLOQ)) will be excluded from all descriptive statistics and statistical analyses.



If PK analysis is performed, actual blood sampling times will be used in all PK analyses. Protocol-specified times will be used to calculate mean plasma or serum concentrations for tabular and graphical displays. All PK calculations and generation of individual subject plasma or serum concentration versus time graphs will be performed using SAS®.

If performed, PK parameters will be calculated using non-compartmental analysis. Only plasma or serum samples with concentrations  $\geq$  LLOQ will be used in the PK analysis. Plasma or serum concentrations  $<$  LLOQ will be taken as 0 for the calculation of the descriptive statistics at each sampling time. For the PK analysis, plasma or serum concentrations  $<$  LLOQ that occur from pre-dose to the first concentration  $\geq$  LLOQ will be taken as 0 and those that occur thereafter will be taken as missing.

### **11.6 Sample Size Calculations**

No formal sample size calculation has been performed for the study. However, it is believed that 6 subjects per dose group will be adequate to establish differences in biomarker response between groups.

### **11.7 Interim Analysis**

No interim analysis is planned.

## **12. WITHDRAWAL FROM STUDY**

Every reasonable effort should be made to maintain protocol compliance and participation in the study. Should a subject withdraw or be prematurely terminated from the study for any reason, the reason for early study withdrawal will be recorded. If withdrawal is the result of a serious adverse reaction, the subject will be followed until the condition has resolved, as determined by the investigator.

The investigator or Sponsor may withdraw any subject at any time for medical reasons or for administrative reasons (i.e., subjects unable or unwilling to comply with the protocol). If so, the subject will be censored at time of withdrawal and, if possible, a final evaluation (End of Study procedures) will be made. All treated subjects (those who have received at least 1 dose of investigational product) will be included in the ITT and safety analyses.

In the unlikely event the Sponsor or FDA should determine it is appropriate to terminate the study early, every effort will be made for transitioning subjects with minimal disruption to the subject and investigator. The IRB will be notified of termination, and reason(s) and procedures for follow-up of research subjects will be developed by the study physician in consultation with the Sponsor and IRB.

## **13 DATA MANAGEMENT**

The standard procedures for handling and processing records will be followed as per GCP and the data management standard operating procedures of the contract research organization (CRO). A comprehensive Data Management Plan will be developed and approved by a representative of the Data Management CRO and the Sponsor.

### **13.1 Database Lock**

The database will be locked in order to protect write access after the following preconditions are fulfilled:

- All data are entered in the database
- All data queries have been resolved to the satisfaction of the Lead Biostatistician
- All decisions have been made regarding all protocol violators and ITT population exclusions
- The eCRF will be signed off/approved by the Site Investigator
- Written authorizations to lock the database are obtained from Renibus Clinical Data Management and the Chief Scientific Officer.

## **14 ETHICAL CONSIDERATIONS**

### **14.1 Ethical Conduct of the Study**

The study will be conducted in accordance with United States Title 21 CFR and the ICH E6 (R1) Guidelines of Good Clinical Practice. The Declaration of Helsinki and its most recent updates (Seoul, 2008) will be observed.

The investigator will provide the Sponsor/designee with documentation of IRB approval of the protocol and the sample informed consent document before the study may begin at the investigative site. The IRB will review the protocol as required.

The investigator will supply the following to the IRB:

- The current Investigator's Brochure and updates
- Study protocol and amendments
- Informed consent and assent document and updates
- Relevant curricula vitae
- Safety alerts
- Serious adverse reaction reports

The investigator must provide the following documentation to the Sponsor or designee:

- The IRB original approval of the protocol and the informed consent, and re-approval of the study (annual or semi-annual, per IRB guidelines)
- The IRB approvals of any revisions to the informed consent document or amendments to the protocol
- All other documents that are required by local regulatory authorities



## **14.2 Regulatory Considerations**

After reading the protocol, each investigator/sub-investigator will sign a protocol signature page and return a copy of the signed page to the Sponsor/designee, while maintaining the original at the site.

## **14.3 Protocol Amendments and Study Termination**

The IRB must be informed and give approval for any amendments likely to affect the safety of the subjects or the conduct of the study.

The IRB must be advised in writing of the study's completion or early termination and a copy of the notification must be provided to the Sponsor.

## **14.4 Safety Monitoring**

The Sponsor's Medical Monitor and will monitor safety data throughout the course of the study. Renibus Drug Safety, or their designee, will expedite to the regulatory authorities only the suspected adverse reactions that are product-related and unexpected in accordance with FDA 21 CFR 312, FDA draft guidance (Sept 2010) on Safety Reporting Requirements for INDs, and the ICH E2A guideline.

## **14.5 Quality Control and Quality Assurance**

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCPs, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, IRB review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents. Investigators will be given notice before a quality assurance audit occurs.

The investigator shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations, and promptly submit to the Sponsor all forms and reports required by this protocol following completion or termination of the clinical study or as otherwise required due to any agreement with the Sponsor.

# **15 GENERAL CONSIDERATIONS**

## **15.1 Discontinuation of the Study**

The Sponsor reserves the right to discontinue this study or investigator's participation in this study for safety or administrative reasons at any time.

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## 16 AGREEMENT WITH PROTOCOL

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Renibus Therapeutics, Inc. and its appointed Contract Research Organizations (CROs) during the study. I will adhere to all Food and Drug Administration (FDA), International Conference on Harmonisation (ICH), revised Declaration of Helsinki (2008) and other applicable regulations and guidelines regarding clinical trials on a study drug during and after study completion.

### Principal Investigator:

Printed Name:

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Signature:

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Date:

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### Protocol REN-002

A Phase 1b dose-escalating study with FeS, in healthy volunteers and subjects with chronic kidney disease stage 3-4.

Original Protocol: 05 September 2018



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**Appendix 1 Safety Clinical Chemistry, Hematology, and Urinalysis Tests Performed by the Laboratory at Screening, During the Study, and at Follow-up (EOS)**

<p><b>Clinical Chemistry<sup>1</sup></b>                  Total protein                  Albumin                  Bicarbonate                  Blood urea nitrogen (BUN)<sup>5</sup>                  Creatinine<sup>5</sup>                  Total bilirubin                  Alkaline phosphatase                  Glucose                  Sodium                  Potassium                  Inorganic phosphate                    Magnesium                  Gamma-glutamyl transferase                    Alanine aminotransferase (ALT)                  Aspartate aminotransferase (AST)</p>	<p><b>Hematology<sup>2</sup></b>                  Hemoglobin                  Hematocrit                  Erythrocyte count (red blood cells)                  Differential leukocytes                  Total leukocytes (white blood cells)                  Platelets</p> <hr/> <p><b>Urinalysis<sup>3</sup></b>                  pH                  Specific gravity                  Glucose                  Ketones                  Bilirubin                  Urobilinogen                  Blood                  P21                  HO-1                  Hemopexin                  Ferritin                  Urine sediment                  Urine pregnancy test<sup>4</sup></p>
<p><b>Response Biomarkers</b>                  Haptoglobin                  Ferritin                  Hemopexin                  IL-10                  P21                  HO-1</p>	

<sup>1</sup> Collect into serum separator tubes.  
<sup>2</sup> Collect into K2 EDTA tubes.  
<sup>3</sup> Approximately 10 mL of urine required for urinalysis including sediment.  
<sup>4</sup> Urine dipstick: all women of childbearing potential prior to the first dose of FeS on Study Day 1 and End of Study. Perform in the clinic using the pregnancy kit supplied by the laboratory.