Official Title:	Open Label Single Arm Pilot Study to Assess Feasibility and Safety of Iron Repletion With Feraheme in Iron Deficient Patients With Durable Ventricular Assist Device Support
NCT Number:	NCT04080908
Study Number:	19-00866
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• August 15, 2022

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Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
0.9	22 April 2019	Original version
1.0	15 July 2019	Minor edits pre IRB submission
1.1	12 August 2019	Initial IRB review
1.2	**03 August 2022**	**Removing Claudia Gidea, MD**

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STUDY TITLE: OPEN-LABEL SINGLE-ARM PILOT STUDY TO ASSESS FEASIBILITY AND SAFETY OF IRON REPLETION WITH FERAHEME IN IRON-DEFICIENT PATIENTS WITH DURABLE VENTRICULAR ASSIST DEVICE SUPPORT

Principal Investigator:	Stuart Katz, MD MS Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 stuart.katz@nyumc.org 212-263-3946
Additional Investigators:	Shaline Rao, MD Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 shaline.rao@nyumc.org 646-501-0119 Alex Reyentovich, MD Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 Alex.reyentovich@nyumc.org 646-501-0119 Tajinderpal Saraon, MD Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 Tajinderpal.saraon@nyumc.org 646-501-0119
NYULMC Study Number:	S19-00866
Funding Sponsor:	AMAG Pharmaceuticals, Inc. 1100 Winter Street Waltham, MA 02451 617-498-3300
IND/IDE Number:	Not applicable
Regulatory Sponsor:	Not applicable
Study Product:	Ferumoxytol injection (Ferumoxytol injection ®)
Study Product Provider:	AMAG Pharmaceuticals, Inc. 1100 Winter Street Waltham, MA 02451 617-498-3300
ClinicalTrials.gov Number	

Initial version: 12 august 2019
Amended: **03 August 2022**
Amended:

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSI	Clinical Translational Science Institute
DHHS	Department of Health and Human Services
FDA	Food and Drug Administration
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NYULH	New York University Langone Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
VAD	Ventricular Assist Device

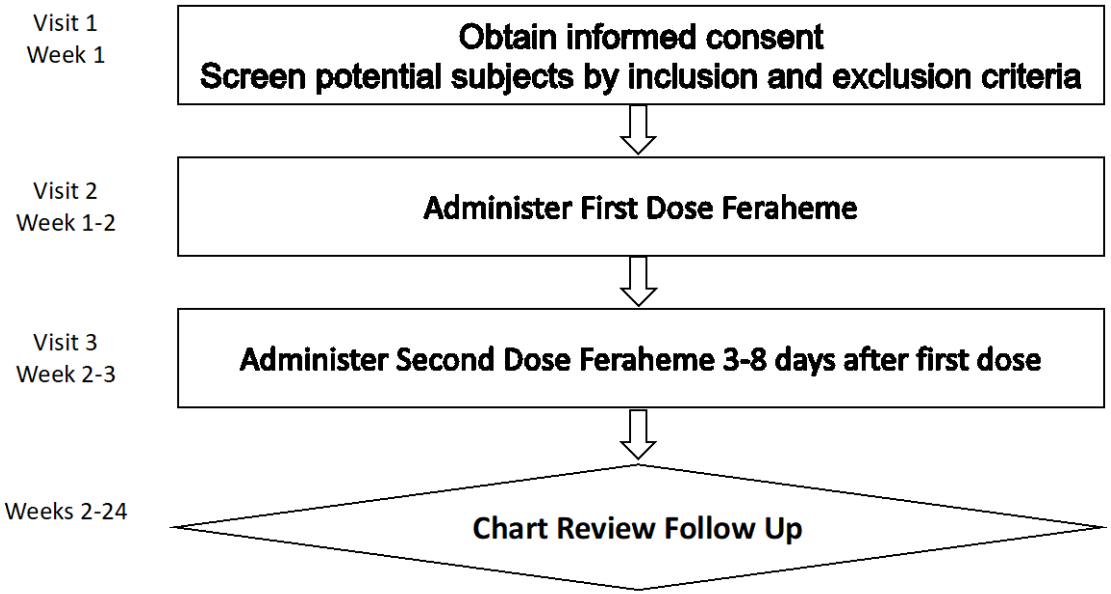
Protocol Summary

Title	Open-Label Single-Arm Pilot Study To Assess Feasibility and Safety of Iron Repletion with Feraheme® Injection in Iron-Deficient Patients with Durable Ventricular Assist Device Support
Short Title	Ferumoxytol injection in VAD patients
Brief Summary	Ferumoxytol injection (Feraheme®) is a parenteral form of iron supplementation that is FDA-approved for treatment of iron deficiency anemia. Ferumoxytol injection achieves iron repletion in fewer doses (2) when compared with other available injectable iron formulations (5-6) available at NYU Langone Health, and thus may be useful to reduce travel burden and expedite full iron repletion in patients with iron deficiency. Iron-deficiency anemia is common in patients after placement of a ventricular assist device (VAD) for treatment of end-stage heart disease. This is a pilot study to test the feasibility of iron repletion with ferumoxytol injection in 20 eligible subjects with laboratory evidence of iron deficiency after placement of a VAD.
Phase	Phase 4
Objectives	Primary Objective: To assess feasibility of iron-repletion with ferumoxytol injection administered according to FDA-approved prescribing instructions (initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later, each dose infused over at least 15 minutes while the patient is in a reclined or semi-reclined position) in iron-deficient patients with durable VAD support. Secondary Objective: To assess safety of ferumoxytol injection in iron-deficient patients with durable ventricular assist device support. Exploratory Objectives: To characterize the clinical response to ferumoxytol injection from chart review of the medical record (biomarkers of iron stores (serum ferritin and transferrin saturation), hemoglobin level, six-minute walk distance, bleeding episodes and hospitalizations).
Methodology	Open-label single-arm pilot study will assess feasibility and safety of iron repletion with ferumoxytol injection.

Endpoint	Primary Feasibility Outcome: Proportion of subjects who complete ferumoxytol injection therapy according to the study protocol. Primary Safety Outcome: Incidence of treatment related adverse events Other Exploratory Outcomes based on clinically available data obtained by review of the medical record: • Change from pre-treatment baseline in serum ferritin 1-24 weeks after ferumoxytol injection therapy • Change from pre-treatment baseline in transferrin saturation 1-24 weeks after ferumoxytol injection therapy • Change from pre-treatment baseline in hemoglobin level 1-24 weeks after ferumoxytol injection therapy • Change from pre-treatment baseline in 6-minute walk distance 1-24 weeks after ferumoxytol injection therapy
Study Duration	Total anticipated duration of study (subject accrual, completion of study therapy and assessments, data analysis, manuscript preparation) is 18 months.
Participant Duration	Six months including three study visits over about two weeks, and data extraction from medical record for up to six months after ferumoxytol injection.
Duration of IP administration	Two doses of ferumoxytol injection will be administered intravenously 3-8 days apart.
Population	Adult subjects with stable clinical status after clinically-indicated VAD placement and iron deficiency anemia will be enrolled
Study Sites	NYULH is the only clinical site for enrollment and study procedures
Number of participants	20 subjects from the NYULH VAD program will be enrolled
Description of Study Agent/Procedure	Ferumoxytol injection will be administered to eligible subjects according to FDA-approved prescribing information. Two doses of ferumoxytol injection will be administered: an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later, each dose given as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP while the subject is in a reclined or semi-reclined position.
Reference Therapy	There is no reference therapy for this study
Key Procedures	The only study procedures are the administration of IP. Other data will be collected from clinical information in the medical record.

Statistical Analysis	The null hypothesis for the primary feasibility objective is that 75% of the subjects will successfully complete ferumoxytol injection treatment as per study protocol. 20 subjects will provide >80% power (one-tailed alpha=0.05) to detect <40% successful completion of ferumoxytol injection treatment. Chi-Square analysis will be used to compare the observed proportion of successful completion of ferumoxytol injection treatment with the null hypothesis of 0.75. Statistical significance will be inferred for one-tailed p-value <0.05. Descriptive analysis techniques will be used to characterize clinical characteristics of the study participants, and incidence of adverse events and change in secondary exploratory outcomes. Center and variability of continuous variables will be presented as means (SD) when they follow a normal distribution and as medians and interquartile range otherwise. Log transformation will be applied on variables with skewed distribution

Schematic of Study Design



Schedule of Assessments

Visit Name	Screening	First Dose Ferumoxytol injection	Second Dose Ferumoxytol injection (3-8 days after first dose)
Visit Number	**1**	**2**	**3**
Study Week (±7days)*	**0**	**0-2**	**1-3**
Informed consent	X		
Screening Evaluation	X		
Medical History	X	X	X
Bleeding/Blood Transfusion History	X	X	X

Vital Signs	X	X	X
Cardiovascular exam	X	X	X
VAD settings	X	X	X
Ferumoxytol injection Administration*		X	X
Infusion Monitoring		X	X
AE monitoring		X	X
Concomitant Meds	X	X	X

*Ferumoxytol injection will be administered according to FDA-approved prescribing instructions 3-8 days apart

1 Key Roles

Principal Investigator:	Stuart Katz, MD MS Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 stuart.katz@nyumc.org 212-263-3946
Additional Investigators:	Shaline Rao, MD Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 shaline.rao@nyumc.org 646-501-0119 Alex Reyentovich, MD Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 Alex.reyentovich@nyumc.org 646-501-0119 Claudia Gidea, MD Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 Claudia.gidea@nyumc.org 646-501-0119 Tajinderpal Saraon, MD Department of Medicine, Leon H. Charney Division of Cardiology 530 First Avenue, Skirball 9R, New York, NY. 10016 Tajinderpal.saraon@nyumc.org 646-501-0119

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Ventricular assist devices (VADs) are surgically implantable pumps used to support circulation of blood in patients with advanced heart failure.[1] Approximately 2500-3000 VADs are implanted annually in the US.[2] Iron-deficiency anemia is common in patients with VADs due to high prevalence of pre-operative chronic anemia associated with advanced heart failure, surgical blood loss during implantation, mandatory chronic aspirin and warfarin therapy to reduce risk of device thrombosis, and increased risk of gastrointestinal bleeding after placement of the VAD.[3] Chronic iron-deficiency may contribute to reduced functional capacity in these patients.[4]

Erythropoiesis stimulating agents are contraindicated in patients with VADs due to increased risk of device thrombosis.[5] Oral iron therapy is poorly tolerated, and is not likely to be effective for repletion of iron stores due to poor gastrointestinal iron absorption in the heart failure population.[6] In the NYU VAD program, nine patients with iron-deficiency anemia have previously received clinical treatment with intravenous formulations of iron (iron sucrose or ferric gluconate) with no reported adverse effects.

Ferumoxytol injection (Feraheme®) is FDA-approved to treat iron deficiency anemia in adult patients, but there are no published data for ferumoxytol injection or any other FDA-approved intravenous iron preparations in VAD patients with iron deficiency anemia.[7] This pilot study is being proposed to assess feasibility and safety of iron repletion with ferumoxytol injection in VAD patients with iron deficiency.

2.2 Name and Description of the Investigational Agent

Ferumoxytol injection will be administered to eligible subjects according to FDA-approved prescribing information. Two doses of ferumoxytol injection will be administered: an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later, each dose given as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP while the subject is in a reclined or semi-reclined position.

2.2.1 Clinical Data to Date

Ferumoxytol injection has been demonstrated to be safe and effective in the treatment of iron deficiency anemia and is FDA-approved for treatment of iron deficiency in adult patients with chronic kidney disease.

The pharmacokinetic (PK) behavior of ferumoxytol injection has been examined in healthy subjects and in patients with CKD stage 5D on hemodialysis. Ferumoxytol injection exhibited dose-dependent, capacity-limited elimination from plasma with a half-life of approximately 15 hours in humans. The clearance (CL) was decreased by increasing the dose of ferumoxytol injection. Volume of distribution (Vd) was consistent with plasma volume, and the mean maximum observed plasma concentration (Cmax) and terminal half-life (t1/2) values increased with dose. The estimated values of CL and Vd following two 510 mg doses of ferumoxytol injection administered intravenously within 24 hours were 69.1 mL/hr and 3.16 L, respectively. The Cmax and time of maximum concentration (tmax) were 206 mcg/mL and 0.32 hr, respectively. Rate of infusion had no influence on ferumoxytol injection PK parameters. No gender differences in Ferumoxytol injection PK parameters were observed. Ferumoxytol injection is not removed by hemodialysis.

2.2.2 Dose Rationale (if applicable)

The dosing regimen will be identical to the FDA-approved prescribing information.

2.3 Rationale

Ferumoxytol injection has been demonstrated to be safe and effective in the treatment of iron deficiency anemia and is FDA-approved for treatment of iron deficiency in adult patients with chronic kidney disease with or without requirement for chronic dialysis. Chronic kidney disease is common in the VAD population, but there are no previous data to demonstrate the safety and feasibility of the regimen described in the FDA-approved prescribing information.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Ferumoxytol injection has been demonstrated to be safe and effective in the treatment of iron deficiency anemia and is FDA-approved for treatment of iron deficiency in adult patients with chronic kidney disease. The most common adverse reactions (≥ 2%) following the administration of Ferumoxytol injection are diarrhea, nausea, dizziness, hypotension, constipation, and peripheral edema. Fatal and serious hypersensitivity reactions including anaphylaxis have occurred in patients receiving ferumoxytol injection. In clinical studies predominantly in patients with CKD, serious hypersensitivity reactions were reported in 0.2% (3/1,726) of subjects receiving Ferumoxytol injection. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1,726) of these subjects. In other trials excluding patients with Stages 4 and 5 CKD, moderate to severe hypersensitivity reactions were reported in 2.6% (26/1,014) of patients treated with ferumoxytol injection. Severe adverse reactions of clinically significant hypotension have been reported in the post-marketing experience. In clinical studies, hypotension was reported in 1.9% (33/1,726) of subjects, including three patients with serious hypotensive reactions. The following additional serious adverse reactions have been reported from the post-marketing experience with ferumoxytol injection : tachycardia/rhythm abnormalities, angioedema, ischemic myocardial events, congestive heart failure, pulse absent, and cyanosis. This safety information is derived from studies in patients with chronic kidney disease with or without dialysis requirement. The dosing and route of administration used in this study are consistent with the FDA-approved prescribing information for this drug. There is no reason to suspect that VAD patients with iron deficiency are at greater risk for adverse effects of ferumoxytol injection when compared with completed clinical trials and post-marketing experience in chronic kidney disease patients.

Protections Against Risk:

To minimize risk, all procedures will be performed in clinically stable participants who meet eligibility criteria under the direct supervision of the principal investigators and other research personnel with appropriate training and licensure. All study procedures are performed at the NYU Clinical Translational Science Institute Clinical Research Center located within Bellevue Hospital with immediate access to emergency support equipment and personnel in the event of deterioration in clinical status.

Participant risks are also minimized by the following protections described in the study protocol:

- Study entry criteria to exclude potential participants at greater risk of adverse events
- Administration of ferumoxytol injection according to the FDA-approved prescribing information
- Active monitoring for potential treatment related adverse effects and other adverse events
- Pre-specified criteria for participant withdrawal to protect participant safety
- Pre-specified criteria for study termination or suspension to protect participant safety

It is important to note that VAD patients with iron deficiency not enrolled in this study will be referred for standard of care treatment with other FDA-approved intravenous iron formulations that have comparable safety profiles to ferumoxytol injection. Accordingly, the risks related to drug infusion during participation in this study are no different than risk related to standard of care, and may actually be lower since ferumoxytol requires only two infusions, whereas other commonly used preparations require 5-6 infusions.

2.4.2 Known Potential Benefits

Ferumoxytol injection has been demonstrated to be safe and effective in the treatment of iron deficiency anemia and is FDA-approved for treatment of iron deficiency in adult patients with chronic kidney disease with or without dialysis requirement. A summary of the findings of the three major efficacy trials is presented in the table below.[7]

TABLE I. Primary Efficacy Endpoint

		Ferumoxytol 2 × 510 mg		Oral iron 200 mg/day	
Nondialysis CKD	**Primary efficacy endpoint**	***n***	**Mean ± SD**	***n***	**Mean ± SD**
	Hgb (g/dL): ITT population		***N* = 228**		***N* = 76**
	Baseline	228	9.96 ± 0.69	76	9.95 ± 0.78
	Day 35	206	10.88 ± 1.27	63	10.15 ± 1.07
	Mean change from baseline at Day 35	228	0.82 ± 1.24	76	0.16 ± 1.02
	P-value for treatment difference <0.001				
Nondialysis CKD	**Hgb (g/dL): ITT population**		***N* = 226**		***N* = 77**
	Baseline	225	9.85 ± 0.77	77	9.94 ± 0.73
	Day 35	214	11.15 ± 1.33	68	10.55 ± 1.14
	Mean change from baseline at Day 35	226	1.22 ± 1.25	77	0.52 ± 0.98
	P-value for treatment difference		<0.001		
Dialysis CKD	**Hgb (g/dL): ITT population**		***N* = 114**		***N* = 116**
	Baseline	114	10.59 ± 0.67	115	10.69 ± 0.57
	Day 35	102	11.72 ± 1.20	101	11.22 ± 1.22
	Mean change from baseline at Day 35	114	1.02 ± 1.13	116	0.46 ± 1.06
	P-value for treatment difference		<0.001		

3 Objectives and Purpose

The proposed pilot study will provide preliminary feasibility and safety data to guide design of future clinical trials of ferumoxytol injection therapy in the VAD population.

3.1 Primary Objective

To assess feasibility of iron-repletion with ferumoxytol injection (initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later, each dose infused over at least 15 minutes while the patient is in a reclined or semi-reclined position) in iron-deficient patients with durable ventricular assist device support.

3.2 Secondary Objectives

To assess safety of ferumoxytol injection administration in iron-deficient patients with durable ventricular assist device support.

To determine the effects of ferumoxytol injection on biomarkers of iron stores (serum ferritin and transferrin saturation), hemoglobin level, and six minute walk distance when compared with pre-treatment baseline.

4 Study Design and Endpoints

4.1 Description of Study Design

Open-label single-arm pilot study will assess feasibility and safety of iron repletion of ferumoxytol injection. Total anticipated duration of study (subject accrual, completion of study therapy and assessments, data analysis, manuscript preparation) is 18 months.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The null hypothesis for the primary feasibility objective is that 75% of the subjects will successfully complete ferumoxytol injection treatment as per study protocol.

4.2.2 Secondary Study Endpoints

Primary Safety Endpoint: The incidence of treatment-related adverse events

4.2.3 Exploratory Endpoints

- Change from pre-treatment baseline in serum ferritin 2-24 weeks after ferumoxytol injection therapy
- Change from pre-treatment baseline in transferrin saturation 2-24 weeks after ferumoxytol injection therapy
- Change from pre-treatment baseline in hemoglobin level 2-24 weeks after ferumoxytol injection therapy
- Change from pre-treatment baseline in 6-minute walk distance 2-24 weeks after ferumoxytol injection therapy

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Age >18 years
- Status post placement of durable ventricular assist device with stable clinical status for >30days
- Hemoglobin >6 g/dL AND <13 g/dL (men) or <12 g/dL (women) within last 90 days
- Serum ferritin <100 ng/mL OR Serum ferritin 100-299 ng/mL with transferrin saturation <20% within last 90 days
- Able and willing to provide written informed consent

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Known hypersensitivity to Ferumoxytol injection or other intravenous iron preparation

- History of anaphylaxis
- Treatment with erythropoiesis stimulating agent or intravenous iron in last 3 months
- Renal failure on hemodialysis
- Respiratory failure on mechanical ventilation
- Disabling Stroke
- Ventricular assist device thrombosis
- Evidence of active gastrointestinal bleeding or other active blood loss
- Hospitalization <30 days
- Pregnant or breastfeeding women

5.3 Vulnerable Subjects

There will be no vulnerable subjects enrolled in this study.

5.4 Strategies for Recruitment and Retention

Study participants will be recruited from the population of 40-50 VAD patients followed at NYULH. These patients are followed by a dedicated multidisciplinary VAD team at regular intervals as outpatients. Assessment of iron deficiency anemia and 6-minute walk testing are standard of care during follow-up in these patients, and iron-deficient patients are routinely referred for intravenous iron infusions as part of standard clinical care. Participation in the study differs from clinical care only in the formulation of intravenous iron and the location of the iron infusion. Clinical staff in the outpatient VAD clinic will assess patient interest in participation in the study and will inform study personnel. Trained study personnel will obtain consent in a private quiet setting at the NYU CTSI at a time of clinical stability.

5.5 Duration of Study Participation

The study will require active participation at three visits conducted over 1-3 weeks. The screening visit and first injection of study drug may occur on the same day. Clinical data from the medical record will be reviewed and entered in the research database for 6 months. There are no study procedures other than data collection from medical record after completion of the two visits for study drug infusion.

5.6 Total Number of Participants and Sites

Recruitment will end when 20 participants are enrolled. It is expected that 20 participants will be enrolled in order to produce 20 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant is not able to return for the second dose of ferumoxytol within 15 days of the first dose.

5.7.2 Handling of Participant Withdrawals or Termination

Withdrawn or terminated participants will be followed for extraction of clinical data from the medical record for 6 months with participant permission. Since the primary outcome is feasibility, there will be no replacement of withdrawn subjects.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the principal investigator. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent Description

Ferumoxytol injection, an iron replacement product, is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether. The overall colloidal particle size is 17-31 nm in diameter. The chemical formula of ferumoxytol injection is $Fe_{5874}O_{8752}$- $C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa.

Ferumoxytol injection is an aqueous colloidal product that is formulated with mannitol. It is a black to reddish brown liquid, and is provided in single use vials containing 510 mg of elemental iron. Each mL of the sterile colloidal solution of ferumoxytol injection contains 30 mg of elemental iron and 44 mg of mannitol, and has low bleomycin-detectable iron. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives, and has a pH of 6 to 8.

Ferumoxytol injection consists of a superparamagnetic iron oxide that is coated with a carbohydrate shell, which helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

Ferumoxytol injection Injection is available in single use vials. Each vial contains 510 mg of elemental iron in 17 mL (30 mg per mL).

Use of ferumoxytol injection in this study meets criteria for IND exemption, since all of the following conditions apply:

(i) the investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) Ferumoxytol injection is lawfully marketed as a prescription drug product; the investigation is not intended to support a significant change in the advertising for the product;

(iii) the investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) the investigation is conducted in compliance with the requirements for review by an IRB (21CFR56) and the requirements for informed consent (21CFR 50); and

(v) the investigation is conducted in compliance with the requirements of 21CFR312.7 (Promotion and sale of investigational drugs).

6.1.1 Acquisition

Investigational product will be obtained from the US manufacturer of ferumoxytol injection (AMAG pharmaceuticals).

6.1.2 Formulation, Appearance, Packaging, and Labeling

Ferumoxytol injection is available in single use vials in the following package sizes:

Table 3: Feraheme Packaging Description

NDC Code	Dose / Total volume per vial	Vials / Carton
NDC 59338-775-01	510 mg/ 17 mL	1
NDC 59338-775-10	510 mg/ 17 mL	10

6.1.3 Product Storage and Stability

Investigational product will be stored according to FDA-approved prescribing information (Store at 20° to 25°C (68° to 77°F). Excursions permitted to 15° – 30°C (59° – 86°F)).

6.1.4 Preparation

In accord with FDA-approved prescribing information, ferumoxytol injection will be administered as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes.

6.1.5 Dosing and Administration

In accord with FDA-approved prescribing information, ferumoxytol injection will be administered as an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later. Once added to intravenous infusion bags containing either 0.9% Sodium Chloride Injection, USP (normal saline), or 5% Dextrose Injection, USP, at concentrations of 2-8 mg elemental iron per mL, the investigational product will be used immediately but may be stored at controlled room temperature (25°C ± 2°C) for up to 4 hours.

6.1.6 Route of Administration

The investigational product will be administered by intravenous infusion.

6.1.7 Dose Adjustments/Modifications/Delays

Dosing may be discontinued due to intolerance, patient request, or protocol non-adherence. Modifications/Delay of dose outside of the FDA-approved prescribing information is not permitted.

6.1.8 Duration of Therapy

Participants will receive the FDA-approved regimen of two doses of ferumoxytol injection (an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later).

6.1.9 Tracking of Dose

Study drug will be administered under supervision of research personnel at the NYU CTSI. The investigational product will be ordered in the EPIC medical record by the principal investigator and will be dispensed according to the protocol by the NYU Research Pharmacy.

6.2 Study Agent Accountability Procedures

The investigational product will be sent by AMAG pharmaceuticals to the NYU Research Pharmacy and stored according to instructions in the FDA-approved prescribing information. Drug accountability logs will be maintained by the NYU Research Pharmacy. Unused investigational product will be returned to AMAG pharmaceuticals or disposed according to NYU Research Pharmacy protocol.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

Study visits (See Attached Study Schematic Figure and Schedule of Assessments Table): The study will require 3 visits over approximately 2 weeks for each subject.

- Visit 1: Informed consent and screening*
- Visit 2: First dose of ferumoxytol injection Study Drug*
- Visit 3: Second dose of ferumoxytol injection Study Drug

*Visits 1 and 2 may occur on the same day.

Screening procedures. After the informed consent form is signed, chart review and patient interview will be performed to determine eligibility. Screening will include subject interview and chart review to determine eligibility. Clinical information on co-morbid conditions, VAD settings, and concomitant medications will be collected. Vital signs in the seated position and a brief cardiovascular exam will be recorded. Women of childbearing potential will undergo urine or blood pregnancy testing.

Study Drug Administration: Ferumoxytol injection will be administered to eligible subjects according to FDA-approved prescribing information. Prior to administration, interim history, concomitant medications, VAD settings, vital signs and a cardiovascular exam will be recorded. Two doses of ferumoxytol injection will be administered: an initial 510 mg dose followed by a second 510 mg dose 3 to 8 days later, each dose given as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP while the subject is in a reclined or semi-reclined position. Subjects will be observed for signs or symptoms of hypersensitivity reactions (including monitoring of blood pressure and pulse rate) during and for at least 30 minutes after ferumoxytol injection administration. The dose, date and time of infusion, duration of infusion, and treatment-related adverse effects (diarrhea, nausea, dizziness, hypotension, hypersensitivity) will be recorded.

Clinical Data Collection for Research

Laboratory data. Clinical blood test results (serum ferritin, transferrin saturation, and hemoglobin) before administration of ferumoxytol injection and from 2-24 weeks after administration of ferumoxytol injection will be recorded by medical chart review.

Bleeding/Transfusion data. Information on bleeding events (source of bleeding, need for hospitalization, intervention(s)) and number of blood transfusion for 2-24 weeks after treatment will be collected from medical chart review.

Six-minute walk test. The six-minute walk test is routinely performed in VAD patients for clinical assessment of functional capacity. Results will be obtained by medical chart review.

7.1.2 Standard of Care Study Procedures

The only research procedure that differs from standard of care procedures is the administration of ferumoxytol injection, since this intravenous iron preparation is not available on the NYULH formulary. Iron-deficient VAD patients not participating in this study would be referred to outpatient infusion centers to receive other formulations of intravenous iron that require a greater number of visits for iron repletion. The risks associated with ferumoxytol injection are comparable to the known risks of other FDA-approved intravenous iron preparations on the formulary at NYULH.

VAD patients routinely undergo laboratory testing for iron-deficiency anemia and serial assessment of submaximal exercise capacity with 6-minute walk testing as part of standard of care.

7.2 Laboratory Procedures/Evaluations

There are no research laboratory procedures or evaluations.

7.3 Study Schedule

Study visits will occur within a time window ±7 days of the times listed in this section.

7.3.1 Screening

Screening Visit (Visit 1, Day -14 to 0)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Record concomitant medications
- Record VAD settings, seated vital signs (mean blood pressure, heart rate, oxygen saturation) and cardiovascular examination.
- Schedule study visits for participants who are eligible and available for the duration of the study. If the participant is eligible to receive Ferumoxytol injection , the first administration of study drug may be completed on the same day as the screening visit.
- Obtain urine or blood pregnancy test in women of child-bearing potential.
- Provide participants with instructions for the return for the infusion of Ferumoxytol injection .

7.3.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 2, Day 0)

- Verify informed consent documentation.
- Verify inclusion/exclusion criteria.

- Assess for interim changes in clinical status or concomitant medications.
- Record VAD settings, seated vital signs (mean blood pressure, heart rate, oxygen saturation) and cardiovascular examination.
- Obtain urine or blood pregnancy test in women of childbearing potential (if visit is occurring >1 day after screening visit).
- Record vital signs and assess clinical stability of subject.
- Administer the study treatment as described with monitoring for hypersensitivity.
- Provide participants with instructions for the return for the infusion of Ferumoxytol injection .

7.3.3 Final Study Visit

Enrollment/Baseline Visit (Visit 3, Day 3-8)

- Verify informed consent documentation.
- Verify inclusion/exclusion criteria.
- Assess for interim changes in clinical status or concomitant medications.
- Record VAD settings, seated vital signs (mean blood pressure, heart rate, oxygen saturation) and cardiovascular examination.
- Obtain urine or blood pregnancy test in women of childbearing potential.
- Record vital signs and assess clinical stability of subject.
- Administer the study treatment as described with monitoring for hypersensitivity reactions.
- Report status of iron repletion to clinical care team.

7.3.4 Withdrawal/Early Termination Visit

There will be no visit required for early termination. Participants will be asked to provide permission for continued access to their medical record for 6 months.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

8 Assessment of Safety

8.1 Specification of Safety Parameters

Ferumoxytol injection is lawfully marketed in the US and is being administered according to FDA-approved prescribing information. The PI will serve as the medical monitor for the study. Subjects will be observed for known treatment-related adverse events as described in the prescribing information including evidence of hypersensitivity for 30 minutes after infusion of ferumoxytol injection.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

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***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition,

other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related,” as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The principal investigator or an appropriately licensed Co-investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the 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 investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject’s personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may

reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Adverse events that do not meet criteria as Serious Adverse Events or Unanticipated Problems will be reported to the IRB at the time of annual continuation review.

8.4.2 Serious Adverse Event Reporting

Serious adverse events will be reported to the IRB within 72 hours.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 72 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 7 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within<insert timeline in accordance with policy> of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

Pregnancy will be reported to the IRB within 72 hours. If pregnancy is discovered before administration of the two doses of ferumoxytol injection, participation in the study will be terminated. If pregnancy is determined during the 6-month follow-up period, the subject will be requested to allow continued follow-up to determine the pregnancy outcome.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 72 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Study Halting Rules

Administration of study agent will be halted when three grade 3 AEs determined to be “probably related” are observed.

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. The data and safety monitoring plan will include systematic review of accrual, protocol deviations, data integrity and adverse event monitoring by the PI on an ongoing basis. The PI will report a summary of the data and safety monitoring record to the IRB at the time of annual continuation application, or earlier in accord with IRB regulation in the event of Reportable New Information.

9 Statistical Considerations

9.1 Statistical and Analytical Plans (SAP)

The statistical analysis plan is summarized in the following sections.

9.2 Statistical Hypotheses

Primary Feasibility Objective: The null hypothesis for the primary feasibility objective is that 75% of the subjects will successfully complete ferumoxytol injection treatment as per study protocol.

There are no hypotheses to be tested for the primary safety objective and exploratory secondary objectives. Descriptive statistics will be used to analyze these data. The purpose of the analyses is to obtain estimates of the study treatment risk in the study population, and the magnitude and variance of change in the exploratory endpoints in the study population. These pilot data will be useful for planning of future clinical trials.

9.3 Analysis Datasets

Feasibility analysis dataset. Intention to treat (ITT) will be defined as all patients who provide consent and are eligible to receive study treatment. The ITT data set will be used for the primary feasibility endpoint.

Safety objective and exploratory objectives analysis dataset. All eligible subjects who received any study drug, and for whom post-dose data are available, will be included in the safety and exploratory objectives analysis set.

9.4 Description of Statistical Methods

9.4.1 General Approach

This is a single-arm open label study with a primary feasibility outcome. Descriptive statistics will be used to summarize pertinent characteristics of the study population.

Study Endpoints:
Primary Feasibility Endpoint: The proportion of eligible subjects who complete ferumoxytol injection therapy per study protocol.

Primary Safety Endpoint: The incidence of treatment-related adverse events

Other Exploratory Endpoints:

- Change from pre-treatment baseline in serum ferritin 2-24 weeks after ferumoxytol injection therapy
- Change from pre-treatment baseline in transferrin saturation 2-24 weeks after ferumoxytol injection therapy
- Change from pre-treatment baseline in hemoglobin level 2-24 weeks after ferumoxytol injection therapy
- Change from pre-treatment baseline in 6-minute walk distance 2-24 weeks after ferumoxytol injection therapy

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Chi-Square analysis will be used to compare the observed proportion of successful completion of ferumoxytol injection treatment with the null hypothesis of 0.75. Statistical significance will be inferred for one-tailed p-value <0.05.

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9.4.3 Analysis of the Secondary Endpoint(s)

Descriptive analysis techniques will be used to characterize clinical characteristics of the study participants, and incidence of adverse events and change in secondary exploratory outcomes. Center and variability of continuous variables will be presented as means (SD) when they follow a normal distribution and as medians and interquartile range otherwise. Log transformation will be applied on variables with skewed distribution

9.4.4 Safety Analyses

Descriptive analysis techniques will be used to characterize clinical characteristics of the study participants, and incidence of adverse events and change in secondary exploratory outcomes. Center and variability of continuous variables will be presented as means (SD) when they follow a normal distribution and as medians and interquartile range otherwise. Log transformation will be applied on variables with skewed distribution

9.5 Sample Size

The null hypothesis for the primary feasibility objective is that 75% of the subjects will successfully complete ferumoxytol injection treatment as per study protocol. 20 subjects will provide >80% power (one-tailed alpha=0.05) to detect <40% successful completion of ferumoxytol injection treatment.

10 Source Documents and Access to Source Data/Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study findings. 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. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be recorded. If the item is not applicable to the individual case, "N/A" will be recorded. All entries will be printed legibly in black ink. If any entry error has been made, a single straight line will be drawn through the incorrect entry and enter the correct data above it. All such changes will be initialed and dated. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups 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.).

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

11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

The investigators will comply with applicable regulatory requirements and should adhere to 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or ICH GCP. Prior to the beginning of the trial, the investigator will have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

12.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

12.3.2 Consent Procedures and Documentation

The consent process will be conducted by trained IRB-appproved personnel during a time of clinical stability in a quiet private room located in the NYULH Clinical Research Center. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

12.4 Participant and Data Confidentiality

All patient data will be kept strictly confidential, except when published for purposes of reporting data. In that case, the patients are never identified. All electronic data will be de-identified and transmitted and stored with secure systems that meet or exceed Federal guidelines (REDCap). The Principal Investigator will maintain files with identifying information in a locked cabinet in a locked room or in password-protected files on a password-protected computer. No vulnerable subject populations will be enrolled in this study.

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 (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The representatives of the IRB or other governmental regulatory office may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

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). A random Study ID code will be assigned to each participant. This code will be used on all written and electronic research records. The Principal Investigator and study coordinator will be able to link the Study ID code back to the personal information during the interval of active participation in the study, but this link will be destroyed after the subject has completed the study procedures. Consent forms, links between Study ID and personal information, paper case report forms, laboratory reports, and other study data will be kept in a project notebook in a locked cabinet in a locked office. Research data without identifiers will be maintained on the NYU School of Medicine REDCap system. The REDCap system provides secure password protected storage of research information behind the NYU firewall and provides quality control and audit trail functions to validate the integrity and quality of the research data. Study data records will be maintained for a minimum of 3 years, or longer if requested by Sponsor.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, the original entry will be crossed out with a single line, and initialed and dated.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations that change subject risk within 3 working days of identification of the protocol deviation.

All protocol deviations must be addressed in study source documents, reported to IRB on an annual basis at time of continuing review.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

13.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's

responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

14 Study Finances

14.1 Funding Source

This study is funded by an unrestricted grant from AMAG pharmaceuticals. The study design was determined by the Principal Investigator.

14.2 Costs to the Participant

There will be no costs to the participant for research procedures (infusions of ferumoxytol injection). Standard of care procedures will continue to be billed to the patient and their insurer.

14.3 Participant Reimbursements or Payments

Subjects will receive $50 via check for each completed study visit, even if the visits occur on the same day. The total for completion of the study is $150.

15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

16 References

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