Clinical Research Protocol

Triferic (Ferric Pyrophosphate Citrate) Administered Orally with Shohl's Solution for the Treatment of Iron-Refractory Iron-Deficiency Anemia

IND Number:	125570
Protocol Number:	RMFPC-15
Version:	1.3
Clinical Phase:	2
Investigational Drug:	Triferic (Ferric Pyrophosphate Citrate)
Indication:	Iron-Refractory Iron-Deficiency Anemia
Sponsor Signatory:	Raymond D Pratt, MD FACP Chief Medical Officer Rockwell Medical Inc.
Principal Investigator:	

Original Protocol Date:	19 November 2015
Amendment 1 Date:	17 December 2015
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PROTOCOL APPROVAL PAGE

Study Title:	Triferic (Ferric Pyrophosphate Citrate) Administered Orally with Shohl's Solution for the Treatment of Iron-Refractory Iron-Deficiency Anemia
Protocol Number:	RMFPC-15
Version:	1.3
Date of Issue:	08 March 2017
Sponsor Name and Address:	Rockwell Medical Inc. 30142 S. Wixom Rd Wixom, MI 48393

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

Sponsor Signatory:

Raymond D Pratt, MD FACP
Chief Medical Officer

(Date)

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title: Triferic (Ferric Pyrophosphate Citrate) Administered Orally with Shohl's Solution for the Treatment of Iron-Refractory Iron-Deficiency Anemia

Protocol Number: RMFPC-15 Version: 1.3

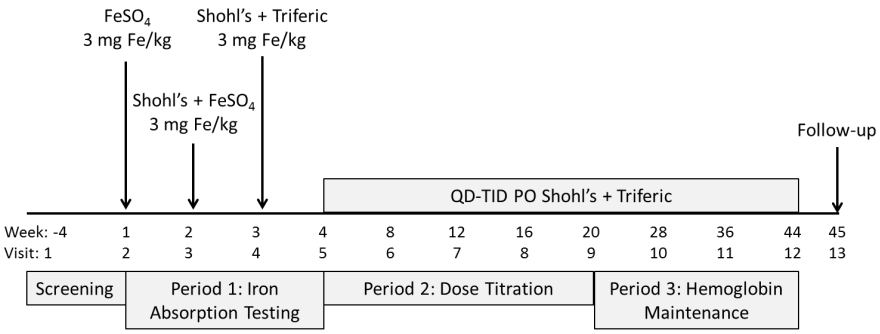
By my signature, I

- Confirm that my staff and I have carefully read and understand this protocol or protocol amendment and are thoroughly familiar with the appropriate use of the investigational drug described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by the Sponsor, Rockwell Medical.
- Agree to assume responsibility for the proper conduct of the study at this site, including complying with FDA regulations, the International Conference on Harmonisation (ICH) GCP guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human Patients.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Ethics Committee (EC), except when necessary to eliminate an immediate hazard to the Patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of the case report forms (CRFs) and source documents by Rockwell Medical or designee and to onsite inspection of CRFs and source documents by appropriate regulatory authorities, including but not limited to the US Food and Drug Administration (FDA), local governing regulatory bodies, and IRB/EC inspectors.

Investigator's Signature Date

Print Name

SYNOPSIS	
PROTOCOL TITLE	Triferic (Ferric Pyrophosphate Citrate) Administered Orally with Shohl's Solution for the Treatment of Iron-Refractory Iron-Deficiency Anemia
PROTOCOL NUMBER	RMFPC-15
SPONSOR	Rockwell Medical Inc.
INVESTIGATIONAL PRODUCT	Triferic® (ferric pyrophosphate citrate)
STUDY OBJECTIVE	**Primary Objective** The primary objective is to determine whether Triferic, administered orally with Shohl's solution, is safe and effective for the treatment of iron-refractory iron-deficiency anemia (IRIDA). **Secondary Objective** The secondary objectives are: • To compare the results of 4-hour iron-absorption tests conducted after administration of (i) ferrous sulfate, 3 mg Fe/kg; (ii) Shohl's solution, 0.67 mmol/kg, followed by ferrous sulfate, 3 mg Fe/kg; and (iii) Shohl's solution, 0.67 mmol/kg, followed by Triferic, 3 mg Fe/kg • To determine the effect on hemoglobin concentration of a 4-month trial of QD-TID oral iron therapy, given as Shohl's solution, 0.67 mmol/kg, followed by Triferic, 1 to 3 mg Fe/kg, titrated as needed based on laboratory results and patient tolerance • To determine the sustainability of response to Shohl's solution and Triferic by an additional 6-month trial of QD-TID oral iron therapy, given as Shohl's solution, 0.67 mmol/kg, followed by Triferic, 1 to 3 mg Fe/kg, titrated as needed based on laboratory results and patient tolerance
STUDY DESIGN & DURATION	Open-label, three-period study. Following screening, eligible patients will undergo oral iron absorption testing during 3 visits during Period 1. Visit 4 responders will then take Shohl's solution and Triferic orally QD-TID for 4 months, with the dose and frequency titrated as needed based on laboratory results and patient tolerance. Visit 9 responders will continue treatment for 6 additional months during Period 3. A follow-up visit will occur approximately 1 week afterwards. The

	duration from screening to the last study visit will be approximately 12 months. Study Design Schematic: 
NUMBER OF PLANNED PATIENTS	A total of 28 patients with IRIDA will be enrolled in this study. Patients will be stratified into 4 age groups as follows: • <6 years • 6 years to <12 years • 12 to <18 years • ≥18 years
INVESTIGATIONAL SITES	TBD
PARTICIPATING COUNTRIES	US
PATIENT POPULATION	Adult and pediatric patients with iron-refractory iron-deficiency anemia (IRIDA)
INCLUSION AND EXCLUSION CRITERIA	**Inclusion Criteria** 1. Adult patients have provided informed consent and have signed the informed consent form. For pediatric patients, parents/legal guardians of the patient have the ability to understand the requirements of the study and have demonstrated a willingness to have their child comply with all study procedures by signing the informed consent form. Where applicable, assent of the pediatric patient has also been obtained for all study procedures prior to any study-related activities. 2. Patient has a history of congenital hypochromic microcytic anemia. 3. Patient has a mean corpuscular volume (MCV) below the lower limit of normal for the clinical laboratory value at screening. 4. Patient has a serum transferrin saturation ≤15% at screening.

	5. Patient has a history of no or incomplete response to oral iron therapy. 6. Patient has a history of no or incomplete response to intravenous iron administration. 7. Patient has a history of hepcidin values that are elevated relative to the mean value for patients with iron deficiency anemia. 8. Patient is documented to have homozygous or compound heterozygous pathogenic mutations in *TMPRSS6*. 9. Patient has appropriate laboratory values for their disease state at screening (per investigator judgment). 10. Patient has no significant abnormal findings on physical examination at screening that would preclude participation in the study (per investigator judgment). 11. If the patient is female, she must be pre-pubertal, have had documented surgical sterilization ≥2 years prior to screening, or be practicing adequate birth control. All female patients 9 years of age and older, and also any who have reached menarche before age 9 years, must have a negative serum pregnancy test during screening. It is the investigator's responsibility to determine whether the patient has adequate birth control for study participation. **Exclusion Criteria** A patient will <u>not</u> be eligible for inclusion in the study if <u>any</u> of the following criteria apply: 1. Patient has had IV or oral iron supplements within 2 weeks prior to Visit 2. 2. Patient has had a blood transfusion within 3 months prior to Visit 2. 3. Patient is receiving intravenous or oral antibiotics or antifungals for any infectious process. Prophylactic antibiotics administered on a regular basis are allowed. Otherwise-eligible patients may be rescreened when they have recovered from any acute illnesses. 4. Patient has a body weight of <11 lbs (5 kg) at screening. 5. Patient has participated in an investigational drug study within the 30 days prior to Visit 2.

	6. Patient has any condition that, in the opinion of the investigator, is likely to prevent the patient from complying with or successfully completing the protocol.
EFFICACY ENDPOINTS	**Primary Endpoint** • The change from baseline in hemoglobin concentration (Hgb) at 4 months **Key Secondary Endpoint** • The change from baseline in serum iron and TSAT at 4 months **Additional Secondary Endpoints** • The change from baseline in Hgb, RBC, MCV, reticulocyte count, reticulocyte Hgb (CHr), serum iron, TIBC, ferritin, UIBC, TSAT, and soluble transferrin receptor (sTfR) and hepcidin concentrations every 4 weeks and at end-of-treatment (EoT) • The incidence of hemoglobin responders (patients with an increase from baseline in Hgb concentration ≥1.0 g/dL) every 4 weeks and at EoT • The serum iron C_{max} following oral Shohl's solution 0.67 mmol/kg and Triferic 3 mg Fe/kg body weight • The incidence of Triferic responders (patients with a maximal increase from baseline in serum iron concentration >15 µg/dL following oral Shohl's solution 0.67 mmol/kg and Triferic 3 mg Fe/kg body weight)
SAFETY ENDPOINTS	• Incidence of treatment-emergent adverse events and serious adverse events • Changes in clinical laboratory tests, vital signs, and weight
STATISTICAL METHODS	Where appropriate, the normality of data will assessed before analysis by using the Shapiro-Wilk test and graphically by evaluating histograms and Q-Q plots. Data not normally distributed will be log transformed for analysis. Log-transformed data will be back transformed for reporting. Normally distributed data will be presented as means (±SDs, ±95% confidence intervals (CI), or both), data normally distributed after log transformation will be presented as geometric means (±95% CI), and non-normally distributed data will be presented as medians and ranges. The baseline demographic and clinical characteristics of the study population will be presented in tabular form. For the primary and key secondary endpoints, a summary of results with the estimated effect size and its precision will be reported. Differences in changes between baseline and 4-month and subsequent 6-month measurements will be compared.

	A study-specific statistical analysis plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will give a detailed description of the summaries and analyses (primary and secondary) that will be performed.

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ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
ATC	anatomical therapeutic chemical
CBC	complete blood count
CFR	Code of Federal Regulations
CHr	reticulocyte hemoglobin concentration
CI	confidence interval
CKD-5HD	chronic kidney disease, stage 5, on hemodialysis
CL/F	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	peak serum concentration, observed
CMRC	Children's Memorial Research Center
CNS	central nervous system
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CUB	complement factor CIs/CIr, urchin embryonic growth factor, bone morphogenic protein 1
CV	cardiovascular
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
ENT	ear, nose, and throat
EoT	end-of-treatment
EU	European Union
FDA	Food and Drug Administration
Fe	iron
$FeSO_4$	iron sulfate
FPC	Triferic (ferric pyrophosphate citrate)
GCP	Good Clinical Practice
GI	gastrointestinal
HD	hemodialysis
Hgb	hemoglobin concentration
HIPAA	Health Insurance Portability and Accountability Act (of 1996)
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug
IRB	institutional review board
IRIDA	iron-refractory iron-deficiency anemia

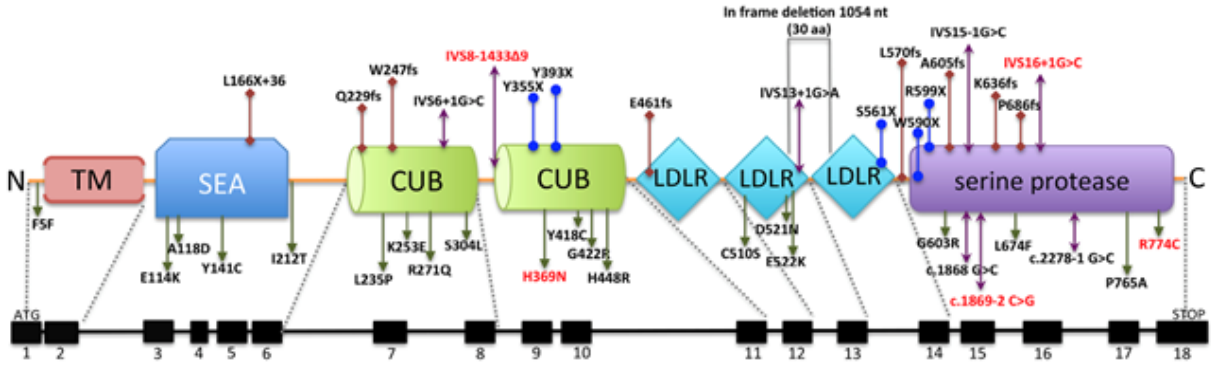
IV	Intravenous
LDLRA	low density lipoprotein receptor class A
LPI	labile plasma iron
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
Mr	relative molecular mass
MT-2	matriptase-2
NA	North America
NPO	nothing by mouth
NTBI	non-transferrin-bound iron
OMIM	Online Mendelian Inheritance in Man
PHI	protected health information
PK	pharmacokinetic
QD	once daily
RBC	red blood cell count
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEA	sea urchin sperm protein, enteropeptidase, agrin
sTfR	soluble transferrin receptor
TBD	to be determined
TBI	transferrin-bound iron
TBV	total blood volume
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIBC	total iron-binding capacity
TID	three times daily
TMPRSS6	gene encoding matriptase-2
TSAT	transferrin saturation
UIBC	unsaturated iron-binding capacity
US	United States
USP	United States pharmacopeia
WBC	white blood cell
WCX-TOF MS	weak cation exchange chromatography in combination with time-of-flight mass spectrometry
WHO	World Health Organization

1. INTRODUCTION

1.1. Current Therapies/Treatments

Iron-refractory iron-deficiency anemia (IRIDA; OMIM 206200) is a rare autosomal-recessive disorder characterized by iron-deficiency anemia unresponsive to oral iron therapy and a delayed, incomplete response to parenteral iron treatment.[1-3] Patients have a congenital microcytic, hypochromic anemia, low plasma iron and transferrin saturation, and a normal or decreased serum ferritin concentration. The mutations responsible are in the gene *TMPRSS6*, which encodes matriptase-2 (MT-2), a type II plasma membrane serine protease that cleaves hemojuvelin[4] to negatively regulate hepcidin, the systemic iron-regulatory protein.[2,5,6] Hepcidin acts by binding to and inactivating the iron-export protein, ferroportin, preventing the efflux of iron from enterocytes, macrophages, and hepatocytes into plasma for transport by transferrin to the erythroid marrow and other tissues.[7] The *TMPRSS6* gene mutations result in inappropriately high plasma hepcidin concentrations, leading to obstruction both of iron absorption by enterocytes and of iron release from macrophages and hepatocytes.[1,3] At present, 51 unrelated families with 74 patients with 58 *TMPRSS6* mutations resulting in iron-refractory iron-deficiency anemia have been described.[8] The responsible mutations seem to be sporadic and to lack any specific geographical or ethnic distribution. The diversity of the mutations is illustrated graphically in Figure 1.[6]

Figure 1: *TMPRSS6* Gene Structure and Mutations



The genomic organization and the corresponding structural domains of matriptase-2 with currently identified mutations reported in patients with IRIDA are shown. The missense, nonsense, frame shift and splice junction mutations are shown in green, blue, red and purple arrows, respectively. One in-frame deletion is boxed in gray. The mutations highlighted in red represent those that appear to have haploinsufficiency.[6] Shown are 42 mutations known at the time of the preparation of this figure; an additional 16 mutations have since been reported.[8]

Functional studies of the mutations have found considerable variability. The SEA (sea urchin sperm protein, enteropeptidase, agrin) and LDLRA (low density lipoprotein receptor class A) domains of matriptase-2 are important for trafficking to the cell surface while the CUB (complement factor Cls/Clr, urchin embryonic growth

factor, bone morphogenic protein 1), LDLRA and serine protease domains are required for cleavage of hemojuvelin.[4,23-25]

The phenotypic expression of iron-refractory iron-deficiency anemia reflects the underlying heterogeneity of the responsible mutations, apparently depending on whether hepcidin inhibition is completely or partially abolished.[1,2,6,8,22,25] With mutations with less hepcidin inhibition, oral iron, with or without ascorbic acid, may provide partial correction of the anemia.[26-28] While patients heterozygous for pathogenic mutations in *TMPRSS6* may be more susceptible to the development of iron deficiency, expression of the phenotype of iron-refractory iron-deficiency anemia requires homozygous or compound heterozygous pathogenic mutations. Furthermore, a variety of *TMPRSS6* polymorphisms that are *not* associated with iron-refractory iron-deficiency anemia have been reported[29], other conditions may mimic some features of the disorder[30,31], and the diagnosis of congenital microcytic anemia is complex.[32,33]

In the most severely affected, oral iron therapy is entirely ineffective and the response to parenteral iron is delayed and incomplete. The available parenteral iron preparations are iron-carbohydrate complexes that must first be taken up and processed by reticuloendothelial macrophages to free the iron from the carbohydrate for subsequent export via ferroportin. Consequently, parenteral iron treatment is unable to circumvent the hepcidin-induced block in iron export and produces only a sluggish, partial correction of the microcytic anemia.[1,3]

1.2. Rationale for Development

Ferric pyrophosphate citrate (Triferic®) can donate iron directly to transferrin without first requiring macrophage processing. Consequently, it may provide a means to bypass the hepcidin-induced obstruction of ferroportin iron export underlying IRIDA.

Citrate (given as Shohl's solution), a tricarboxylic anion, can complex with calcium in the proximal gastrointestinal tract, opening intracellular tight junctions and permitting paracellular uptake of soluble complexes.[12-17] Citrate-induced paracellular absorption of aluminum was responsible for increased absorption of aluminum and aluminum toxicity in patients with renal failure treated with aluminum citrate for control of hyperphosphatemia.[13-17] Ferric citrate, recently approved in Japan for control of hyperphosphatemia in patients with chronic kidney disease,[18] increases transferrin saturation and serum ferritin over 12 weeks of administration.[19]

In patients with iron-refractory iron-deficiency anemia, we hypothesize that oral co-administration of Triferic with Shohl's solution will bypass the hepcidin-mediated block of enterocyte iron uptake by permitting paracellular absorption (i) of intact Triferic that reaches the proximal duodenum and jejunum, with subsequent direct donation of iron to transferrin, and (ii) of iron derived from Triferic. We also will

examine the effects of oral co-administration of conventional ferrous sulfate ($FeSO_4$) with Shohl's solution.

1.3. Description of Study Drugs

Ferric pyrophosphate citrate (Triferic®; Rockwell Medical, Wixom, MI) $[Fe_4(C_6H_5O_7)_3(P_2O_7)_3]$ is a low-molecular-weight iron salt (Mr 1313). It is currently approved as an iron-replacement therapy that is added to the dialysate and administered during hemodialysis in adult patients with hemodialysis-dependent chronic kidney disease. Food-grade soluble ferric pyrophosphate[11] is widely used to fortify milk drinks and infant formula. Triferic has a neutral to slightly salty taste when administered orally. Triferic administered orally may be diluted with water or simple sugar syrup (in a maximum dilution ratio of up to 1:2 Triferic:sugar), but dilution is not necessary. If needed, Triferic may be administered orally using an oral medication syringe. After several patients have been enrolled in the study, we plan to develop an appropriate dose form for oral use and storage.

Citrate (as Shohl's solution, e.g., Oracit®; CMP Pharma, Farmville, NC) is a buffer of sodium citrate and citric acid that is used for prolonged treatment of children with cystinuria and some forms of renal tubular acidosis.[20,21] Citrate administered orally may be diluted with water or simple sugar syrup (in a maximum dilution ratio of up to 1:2 Citrate:sugar), but dilution is not necessary. The dosing of citrate for all US sites will be as Oracit. However, if Oracit is not available (e.g., in the European Union (EU), if the protocol is amended to include EU sites), any brand of Shohl's solution that contains sodium citrate may be used based on local availability.

Ferrous sulfate (Fer-In-Sol®, Mead Johnson, Glenview, IL) is available over-the-counter as an iron supplement.

1.4. Previous Clinical Experience with Triferic

Table 1: Summary of Clinical Studies Conducted with Triferic in Adults

Protocol Number	Country (# sites)	Study Design and Phase	Treatment Groups	Patient N Treatment Duration
SFP-8	US 1 site	Phase ½, single-dose, PK in CKD-5HD patients	Triferic 2 µM Placebo	12 6 individual HD sessions
SFP-9	US 1 site	Phase 1, single dose in healthy volunteers	Triferic mg IV: 2.5 mg/4 hr 5.0 mg/4 hr	48 Single Ascending Dose

Protocol Number	Country (# sites)	Study Design and Phase	Treatment Groups	Patient N Treatment Duration
			7.5 mg/4 hr 10 mg/4 hr 15 mg/12 hr 20 mg/12 hr Placebo	
FPC-12	US 1 site	Phase 1, two single sequential doses in healthy volunteers	Triferic: 6 mg IV/3 hr 35 µg/kg IV push	12 Two single sequential doses
SFP-1	US 1 site	Phase 2, randomized, open-label parallel group Placebo-controlled Dose escalation	Triferic iron µg/L dialysate: 0, 20, 40, 80 and 120	24 27 weeks Monthly dose escalation
SFP-2	US 29 sites	Phase 2, randomized, double-blind, parallel group Placebo-controlled Dose escalation	Triferic iron µg/L dialysate: 0, 50, 100, 120 and 150	136 26 weeks
SFP-3	US 2 sites	Phase 2, double-blind Crossover	Triferic 130 µg/L (food grade) Triferic 130 µg/L (GMP)	33 2X2 weeks
NIH-FP-01	US 23 sites	Phase 2, randomized, double-blind, parallel group Placebo-controlled	Triferic 2 µM (110 µg/L) Placebo	108 36 weeks
NIH-FP-01 Addendum	US	Phase 2, randomized, double-blind, parallel group	Triferic 2 µM (110 µg/L)	11

Protocol Number	Country (# sites)	Study Design and Phase	Treatment Groups	Patient N Treatment Duration
	1 site	Placebo-controlled	Placebo	36 weeks
SFP-4-RC	NA 44 sites	Phase 3, randomized, double-blind, parallel group Placebo-controlled	Triferic 2 µM (110 µg/L) Placebo	305 Up to 48 weeks
SFP-4-OL	NA 38 sites	Phase 3, open-label extension	Triferic 2 µM (110 µg/L)	207 24 weeks or a total of 72 weeks
SFP-5-RC	NA 41 sites	Phase 3, randomized, double-blind, parallel group Placebo-controlled	Triferic 2 µM (110 µg/L) Placebo	294 Up to 48 weeks
SFP-5-OL	NA 37 sites	Phase 3, open-label extension	Triferic 2 µM (110 µg/L)	214 24 weeks or a total of 72 weeks
SFP-6-RC	NA 51 sites	Phase 3, double-blind Crossover Placebo-controlled	Triferic 2 µM (110 µg/L) Placebo	718 2X2 weeks
SFP-6-OL	NA 34 sites	Phase 3, open-label extension	Triferic 2 µM (110 µg/L)	310 48 weeks

NA=North America

1.5. Rationale for the Current Study

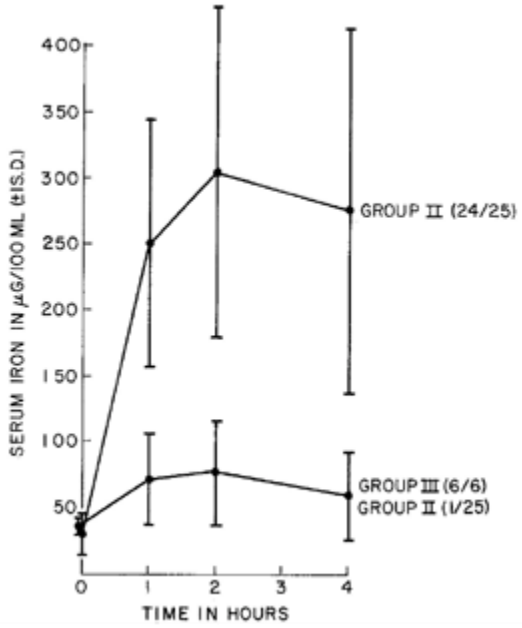
The current study is designed to determine whether Triferic, given with Shohl's solution, is safe and effective for the treatment of IRIDA.

First, the results of 4-hour oral iron-absorption tests (see Figure 2) conducted after administration of (i) $FeSO_4$, 3 mg Fe/kg; (ii) Shohl's solution, 0.67 mmol/kg, followed by $FeSO_4$, 3 mg Fe/kg; and (iii) Shohl's solution, 0.67 mmol/kg, followed by Triferic, 3 mg Fe/kg will be compared.

Then, "Triferic responders" (patients with increases of >15 µg/dL in serum iron following oral administration of Shohl's solution 0.67 mmol/kg and Triferic 3 mg

Fe/kg) will undergo up to 10 months of treatment with Triferic, given with Shohl's solution, to determine whether this treatment can increase the Hgb concentration by at least 1 g/dL after 4 months (termed "hemoglobin responders") and whether any increase can be sustained for an additional 6 months. The 4-month initial duration of the trial, corresponding to a period during which the entire population of circulating red blood cells normally would be replaced, should provide sufficient time for increased iron absorption from Triferic to improve the circulating hemoglobin concentration.

Figure 2: Four-hour Oral Iron-absorption Test



Oral iron absorption curves in *de novo* iron-deficient children (Group II) and in iron-deficient nonresponders (Group III: iron-deficient children who received prolonged course of therapeutic iron without correction of anemia). An elevated iron absorption curve was present in 24 of 25 Group II patients. A flat iron absorption curve was present in 1 of 25 Group II and 6 of 6 Group III patients. Gross *et al.*[34]

1.6. Justification for Dose

The oral doses of $FeSO_4$ and Triferic in this study are based on the 1-3 mg Fe/kg usual recommended range for treatment of iron deficiency anemia in both children and adults.[36]

The oral dose of Shohl's solution, 0.67 mmol, has been chosen based on the dose of Shohl's solution used for treatment of pediatric patients with cystinuria over a period of two years, i.e., 0.67 mmol given three times daily for a total daily dose of 2 mmol per day.[20, 21] Administration of Shohl's solution has been reported to raise

gastric pH to 3.80–3.94 over a period of 7 hours.[35] An elevated gastric pH would be expected to decrease transcellular iron absorption from $FeSO_4$ but the extent, if any, to which this decrease might be offset by increased paracellular uptake will be determined in these studies.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to determine whether Triferic, administered orally with Shohl's solution, is safe and effective for the treatment of iron-refractory iron-deficiency anemia (IRIDA).

2.2. Secondary Objectives

The secondary objectives are:

- To compare the results of 4-hour iron-absorption tests conducted after administration of (i) ferrous sulfate, 3 mg Fe/kg; (ii) Shohl's solution, 0.67 mmol/kg, followed by ferrous sulfate, 3 mg Fe/kg; and (iii) Shohl's solution, 0.67 mmol/kg, followed by Triferic, 3 mg Fe/kg
- To determine the effect on hemoglobin concentration of a 4-month trial of QD-TID oral iron therapy, given as Shohl's solution, 0.67 mmol/kg, followed by Triferic, 1 to 3 mg Fe/kg, titrated as needed based on laboratory results and patient tolerance
- To determine the sustainability of response to Shohl's solution and Triferic by an additional 6-month trial of QD-TID oral iron therapy, given as Shohl's solution, 0.67 mmol/kg, followed by Triferic, 1 to 3 mg Fe/kg, titrated as needed based on laboratory results and patient tolerance

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2, open-label, 3-period study assessing the safety, efficacy, and pharmacokinetics of Triferic and Shohl's solution administered orally to patients with IRIDA. A total of 28 patients stratified by 4 age groups (age 0 to <6 years, age 6 to <12 years, age 12 to <18 years, and age >=18 years) will be studied.

All patients who meet inclusion and exclusion criteria regardless of age at presentation will be considered for study participation. There are only a limited number of patients with IRIDA in the US (estimated to be less than 30 total patients), and they have no other options available to improve their anemia. Given the rarity of the diagnosis and the presentation of patients at an early age (typically <2 years), this study represents a minimal risk for tolerability and a positive benefit to risk

assessment for patients of all ages. The dose regimen of Shohl's solution has demonstrated long term safety in pediatric patients with renal tubular acidosis and cystinuria, and the iron form in Triferic has been used as a food additive and supplement to provide nutritional iron.

The study design schematic is shown in Figure 3 below.

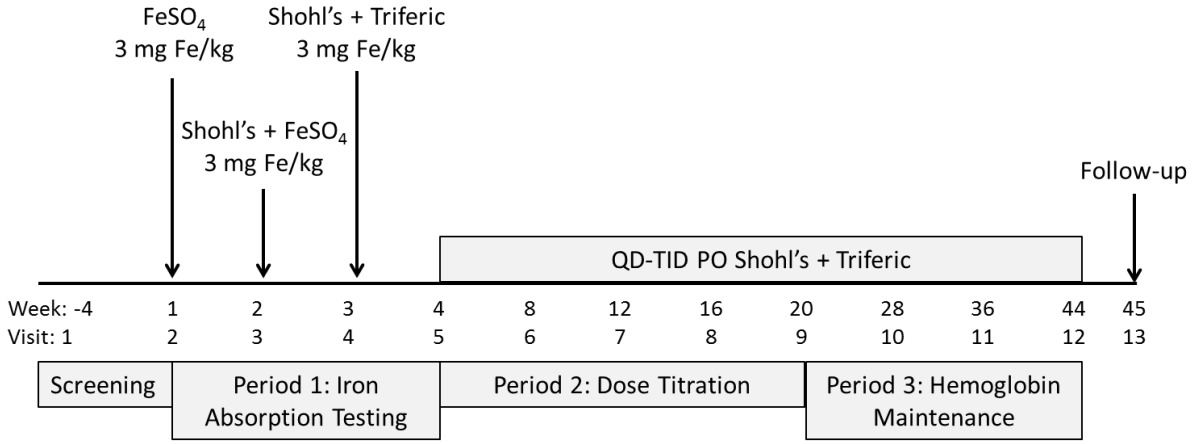
Following screening, in Period 1, patients will undergo oral iron absorption testing during 3 visits to confirm that they adequately absorb iron from Triferic when it is administered with Shohl's solution. The order in which the different treatment visits are scheduled during Period 1 will be determined by the site.

In Period 2 (dose titration), Period 1 "Triferic responders" (patients with a maximal increase from baseline in serum iron concentration >15 µg/dL following an oral Shohl's solution and Triferic dose) will receive Shohl's solution and Triferic orally up to 3 times per day for 4 months, titrated as needed based on laboratory results and patient tolerance, to determine whether their hemoglobin levels respond to this treatment.

In Period 3 (hemoglobin maintenance), Period 2 "hemoglobin responders" (patients with an increase from baseline in Hgb concentration ≥1.0 g/dL at Visit 9) will receive Shohl's solution and Triferic orally up to 3 times per day for an additional 6 months to determine whether the hemoglobin response observed in Period 2 is sustainable. During Period 3, Shohl's solution and Triferic dose and frequency may continue to be titrated as needed based on laboratory results and patient tolerance.

A follow-up visit will occur approximately 1 week afterwards. The duration from screening to the last study visit will be approximately 12 months.

Figure 3. Study Design Schematic



Blood samples will be obtained at various times specified in Appendices 1 and 2 to analyze for changes in CBC, reticulocyte count, the reticulocyte hemoglobin concentration (CHr), the serum iron profile (serum iron, ferritin, transferrin TSAT,

TIBC, and UIBC), other serum iron parameters (TBI [optional], NTBI, and LPI), and soluble transferrin receptor (sTfR) and hepcidin concentrations.

Patients will be also monitored for safety parameters, including AEs, clinical laboratory parameters, and vital signs during the study.

If any of Visits 2-4 are interrupted and the patient and parent/guardian (if applicable) agree, a repeat visit can be performed provided that the total blood volume drawn does not exceed the maximum allowable (refer to Appendix 2; if the patient is between body weight categories, use the lower weight category). The repeat visit should be performed at least 48 hours after the interrupted visit but no later than 1 month. If an enrolled patient cannot attend a study visit, the study visit can be rescheduled to take place no later than 1 month after the missed visit.

3.2. Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Primary

The primary efficacy endpoint is:

- The change from baseline in hemoglobin concentration at 4 months

3.2.1.2. Secondary

The key secondary efficacy endpoint is:

- The change from baseline in serum iron and TSAT at 4 months

Additional secondary efficacy endpoints are:

- The change from baseline in Hgb, RBC, MCV, reticulocyte count, CHr, serum iron, TIBC, ferritin, UIBC, TSAT, and sTfR and hepcidin concentrations every 4 weeks and at end-of-treatment (EoT)
- The incidence of hemoglobin responders (patients with an increase from baseline in Hgb concentration ≥1.0 g/dL) every 4 weeks and at EoT
- The serum iron C_{max} following oral Shohl's solution 0.67 mmol/kg and Triferic 3 mg Fe/kg body weight
- The incidence of Triferic responders (patients with a maximal increase from baseline in serum iron concentration >15 µg/dL following oral Shohl's solution 0.67 mmol/kg and Triferic 3 mg Fe/kg body weight)

3.2.2. Safety Endpoints

The safety endpoints are:

- Incidence of treatment-emergent adverse events and serious adverse events
- Changes in clinical laboratory tests, vital signs, and weight.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

A patient will be eligible for inclusion in the study only if all of the following criteria are met:

1. Adult patients have provided informed consent and have signed the informed consent form. For pediatric patients, parents/legal guardians of the patient have the ability to understand the requirements of the study and have demonstrated a willingness to have their child comply with all study procedures by signing the informed consent form. Where applicable, assent of the pediatric patient has also been obtained for all study procedures prior to any study-related activities.
2. Patient has a history of congenital hypochromic microcytic anemia.
3. Patient has a mean corpuscular volume (MCV) below the lower limit of normal for the clinical laboratory value at screening.
4. Patient has a serum transferrin saturation ≤15% at screening.
5. Patient has a history of no or incomplete response to oral iron therapy.
6. Patient has a history of no or incomplete response to intravenous iron administration.
7. Patient has a history of hepcidin values that are elevated relative to the mean value for patients with iron deficiency anemia.
8. Patient is documented to have homozygous or compound heterozygous pathogenic mutations in *TMPRSS6*.
9. Patient has appropriate laboratory values for their disease state at screening (per investigator judgment).
10. Patient has no significant abnormal findings on physical examination at screening that would preclude participation in the study (per investigator judgment).
11. If the patient is female, she must be pre-pubertal, have had documented surgical sterilization ≥2 years prior to screening, or be practicing adequate birth control. All female patients 9 years of age and older, and also any who have reached menarche before age 9 years, must have a negative serum pregnancy test during screening. It is the investigator's responsibility to determine whether the patient has adequate birth control for study participation.

4.2. Exclusion Criteria

A patient will not be eligible for inclusion in the study if any of the following criteria apply:

1. Patient has had IV or oral iron supplements within 2 weeks prior to Visit 2.
2. Patient has had a blood transfusion within 3 months prior to Visit 2.
3. Patient is receiving intravenous or oral antibiotics or antifungals for any infectious process. Prophylactic antibiotics administered on a regular basis are allowed. Otherwise-eligible patients may be rescreened when they have recovered from any acute illnesses.
4. Patient has a body weight of <11 lbs (5 kg) at screening.
5. Patient has participated in an investigational drug study within the 30 days prior to Visit 2.
6. Patient has any condition that, in the opinion of the investigator, is likely to prevent the patient from complying with or successfully completing the protocol.

4.3. Removal of Patients from Therapy/Premature Discontinuation

A patient will be discontinued from the study for the following medical or administrative reasons:

- Occurrence of a TEAE that represents an unacceptable risk to the patient and when continued participation in the investigational study is not warranted, in the judgment of the investigator. The investigator must follow the patient until the AE resolves or satisfactorily stabilizes;
- Occurrence of a TEAE of grade ≥3 (Common Terminology Criteria for Adverse Events [CTCAE] v4.0) that the investigator determines to be related to the study drug (Shohl's solution or Triferic). The investigator must follow the patient until the AE resolves or satisfactorily stabilizes;
- Pregnancy;
- Initiation of a prohibited concomitant therapy without medical monitor or sponsor approval; and/or
- Patient request.

The investigator may discontinue individual patients from the study at any time. Patients may voluntarily withdraw at any time. If possible, patients who are withdrawn should complete a Follow-up visit.

Patients who withdraw or are withdrawn prior to Visit 2 will be considered screen failures and will be replaced.

4.4. Study Discontinuation

After 5 patients have completed Period 1, if none of them is a Triferic responder (i.e., no patient has a serum iron C_{max} that is >15 g/dL higher than the Hr 0 serum iron concentration following oral Shohl's solution 0.67 mmol/kg and Triferic 3 mg Fe/kg body weight), then Rockwell Medical will consider discontinuing the study.

In addition, after 5 patients have completed Period 2, if none of them is a hemoglobin responder (i.e., no patient has a Visit 9 Hgb concentration that is ≥1 g/dL higher than the Visit 5 Hgb concentration), then Rockwell Medical will consider discontinuing the study.

5. TREATMENTS

5.1. Treatments Administered

Study drug for Visits 2-4 will be administered by qualified study personnel only in accordance with the procedures described in this protocol. The order in which the different treatment visits are scheduled during Period 1 will be determined by the site. For Periods 2-3, study drugs should be self-administered by the patient, or alternatively by the patient's parent or guardian if the patient is unable to do so.

Ferrous sulfate (Fer-In-Sol®, Mead Johnson, Glenview, IL) will be administered at a dose of 3 mg Fe/kg. When administered in conjunction with Shohl's solution, the dose will be given 5-15 minutes after the dose of Shohl's solution.

Citrate (as Shohl's solution, e.g., Oracit®; CMP Pharma, Farmville, NC) will be administered at 0.67 mmol/kg.

Ferric pyrophosphate citrate (Triferic®; Rockwell Medical, Wixom, MI) will be administered at a dose of 3 mg Fe/kg, 5-15 minutes after the dose of Shohl's solution.

At each of Visits 5, 7, 9, 10, and 11, sufficient Shohl's solution and Triferic to provide at least 60 days of dosing will be dispensed to the patient. On study visit days, patients should not take their Shohl's solution and Triferic doses until after the study visit. Patients are to stop taking Shohl's solution and Triferic after Visit 12.

5.2. Identity of Investigational Products(s)

Triferic is supplied as either a sterile 5-mL ampule or sterile 50-mL ampule, both containing 5.44 mg/mL of iron in water. Each 5-mL ampule contains 27.2 mg of Triferic iron and each 50-mL ampule contains 272 mg of Triferic iron.

Citrate (as Shohl's solution, e.g., Oracit®; CMP Pharma, Farmville, NC) is supplied as 500-mL bottles containing citric acid USP 640 mg/5 mL and hydrous sodium citrate USP 490 mg/5 mL. Oracit will be used for dosing in the US. Other

commercially-available preparations of Shohl's solution that contain sodium citrate may also be used (e.g., in the EU, if the protocol is amended to add EU sites) if Oracit is not available.

Ferrous sulfate (Fer-In-Sol®, Mead Johnson, Glenview, IL) is supplied as 50-mL bottles containing 15 mg Fe/mL.

5.2.1. Labeling

Triferic study drug packaging will bear a label that meets applicable laws for an investigational drug, which includes, but is not limited to, the following information:

- Federal law statement
- Protocol number
- Lot number
- Dosing instructions
- Storage information

Shohl's solution and Fer-In-Sol bottles will be supplied in their currently-available commercial presentations.

5.2.2. Storage and Handling

Prior to being dispensed, all study drugs will be kept in a locked area with limited access.

Triferic ampules will be stored protected from light in an aluminum pouch at controlled room temperature (20° to 25°C [68° to 77°F]; excursions will be permitted to 15°-30°C [59° to 86°F] [See USP Controlled Room Temperature]).

Shohl's solution and Fer-In-Sol bottles will be stored at 15°-30°C [59° to 86°F].

All study drugs should be kept out of reach of children.

5.3. Method of Assigning Patients to Treatment Groups

5.3.1. Treatment Assignment/Randomization

The study is open-label and all patients will be treated in the sequence indicated in Section 3.1. Consequently, randomization is not required.

5.4. Selection and Timing of Dose for Each Patient

For Visits 2-4, in order to help control for the diurnal variation in serum iron parameters, each treatment will be administered at approximately the same time

each day per patient. The order in which the different treatment visits are scheduled during Period 1 will be determined by the site.

During Periods 2 and 3, it is recommended that the patients take the Shohl's solution and Triferic orally at least one hour before or two hours after meals. Initially, the dose of study drug will be Shohl's solution 0.67 mmol/kg followed by Triferic 3 mg/kg 3x/day.

However, if the patient experiences adverse events related to either the Shohl's solution or Triferic, study drug may be withheld for up to 7 days if needed and then resumed 3x/day with Shohl's solution being dosed at 0.67 mmol/kg and Triferic being dosed at 1/3 of the most recent previous dose.

If the adverse event recurs, study drug may be withheld for up to 7 days if needed and then resumed with a decreased frequency of dosing. The frequency of dosing may be decreased from 3x/day to 1x/day.

If a dose of Shohl's solution and Triferic has been well-tolerated for at least 7 days, if the dose frequency is less than 3x/day it may be increased by 1x/day if needed based on Hgb concentrations and serum iron parameters. If a dose of Shohl's solution and Triferic has been well-tolerated for at least 7 days, if the Triferic dose being administered at less than 3 mg/kg, then the dose may be increased by 1 mg/kg per dose if needed based on Hgb concentrations and serum iron parameters. See Appendices 4 and 5 for details regarding study drug dosing.

5.5. Procedures for Blinding

This is an open-label study; no blinding is required.

5.6. Prior and Concomitant Therapy

5.6.1. Prior Therapy

All prescription and non-prescription medications (including multivitamins) taken at screening and/or within 14 days prior to Visit 2 (whichever is earlier) will be documented in source documents and the case report form (CRF) (based on patient report and/or medical records). The date of screening is considered to be the date that the first study-related screening assessment is performed.

5.6.2. Concomitant Therapy

All prescription and non-prescription medications taken over the course of study participation must be documented in the source documents and CRF.

5.6.3. Prohibited Medications

Oral and IV iron products are prohibited from 2 weeks prior to Visit 2 until all blood samples have been collected after the Follow-up/Early Termination Visit. This includes oral multivitamins containing iron.

Blood transfusions are prohibited from 3 months prior to Visit 2. If a patient requires transfusion after enrollment in the study, they should first be discontinued from the study and then transfused. Follow-up/Early Termination Visit procedures may occur prior to or after the blood transfusion.

Aluminum-containing compounds (e.g., Maalox®, Alternagel®, Alu-Cap®, Dialume®, Amphojel®, Alu-Tab®, Aloh-Gel®, etc.) are prohibited from Day 1 of the study through the date of the patient's last dose of Shohl's solution.

5.7. Treatment Compliance

The site is responsible for documenting compliance with study drug administration.

5.7.1. Study Drug Accountability

Study drug will be administered in accordance with the procedures of this protocol. Only authorized site personnel may supply study drug and only patients enrolled in the study may receive study drug, in accordance with applicable regulatory requirements.

Drug accountability information collected may include but is not limited to:

- Receipt of study drug (date and quantity);
- Storage temperature log;
- Dispensation of study drug (date, quantity, and patient number);
- Return of study drug (date, quantity, and patient number); and
- Initials of individual dispensing study drug

At the conclusion of a site's participation in the study, all unused investigational drug shall be returned to Rockwell or destroyed upon Rockwell's request unless otherwise instructed by Rockwell. A copy of the reconciled drug inventory record will be provided to Rockwell or its designee, and the original will be retained at the site.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Study Visits

The study should be conducted as much as possible according to the time and events schedule in **Appendix 1** (Table 2).

6.1.1. Screening (Week -4 through Day -1)

6.1.1.1. Screening Visit (Visit 1)

The Screening Visit (Visit 1) should be conducted within 28 days prior to Visit 2. The date of screening is considered to be the date that the first study-related screening assessment is performed. The following procedures will be performed at screening:

- For adult patients, obtain informed consent. For pediatric patients, obtain informed consent from parent(s)/legal guardian(s) and assent (where applicable) from the patient. This must be done prior to any study procedures, including asking patients to discontinue any prohibited medications;
- Assign study-specific patient number;
- Record patient demographics and medical history;
- Record current medications;
- Record height and weight;
- Record vital signs (blood pressure, pulse, temperature);
- Perform a physical examination;
- Perform serum pregnancy test (for all female patients 9 years of age or older, and also any who have reached menarche prior to age 9 years);
- Collect venous blood for isolation and storage of genomic DNA, if patient has not previously had *TMPRSS6* sequencing done;
- Collect venous blood for hematology, reticulocyte count, reticulocyte hemoglobin concentration (CHr), chemistry, the serum iron profile, and sTfR and hepcidin concentrations. For pediatric patients, results from up to 30 days prior to screening may be used for determination of eligibility;
- Confirm patient meets all eligibility criteria; and
- Schedule next study visit (Visit 2). Remind the patient that they should be NPO except for water after midnight prior to Visit 2.

6.1.2. Period 1: Iron Absorption Testing (Visits 2-4, Weeks 1-3)

6.1.2.1. Study Procedures

The following procedures are to be completed during Visits 2-4:

- Assess and record AEs since last study visit;
- Assess and record medications;
- Collect vital signs (blood pressure, pulse, and temperature);
- Collect blood for serum iron parameters (serum iron, TSAT, TBI [optional], NTBI, and LPI) within 30 minutes prior to the oral iron dose;
- Administer study drug (see Section 6.1.2.2 below, and also Appendices 4 and 5);

- Collect blood for serum iron parameters at 1 hr, 2 hr, and 4 hr following the oral iron dose per Appendix 2, Tables 3, 4, and 5 for Visits 2, 3, and 4, respectively;
- Assess and record AEs; and
- Schedule the patient for their next study visit to take place in approximately 1 week. Remind the patient that they should be NPO except for water after midnight prior to each visit.

It is recommended that sixty (60) minutes after each oral iron dose during Period 1, patients may eat a non-meat breakfast (note: dairy is permitted, but eggs, seafood, and other meats are not); and they may resume a normal diet after collection of the 4-hr blood samples.

Following dosing with oral Shohl's solution 0.67 mmol/kg and Triferic 3 mg Fe/kg body weight, serum iron C_{max} should be compared to the Hr 0 serum iron concentration. If the serum iron C_{max} is >15 g/dL higher than the Hr 0 serum iron concentration, the patient is designated a "Triferic responder" and will proceed to Period 2. If not, the patient will proceed to the early termination visit to occur approximately 1 week after Visit 4.

6.1.2.2. Study Drug

Study drug for Visits 2-4 will be as follows:

- oral $FeSO_4$, 3 mg Fe/kg body weight
- oral Shohl's solution, 0.67 mmol/kg body weight, followed after 5-15 minutes by oral $FeSO_4$, 3 mg Fe/kg body weight
- oral Shohl's solution, 0.67 mmol/kg body weight, followed after 5-15 minutes by oral Triferic (ferric pyrophosphate citrate), 3 mg Fe/kg body weight

The order in which the different treatment visits are scheduled during Period 1 will be determined by the site. Please see Appendices 4 and 5 for details of study drug dosing.

6.1.3. Period 2: Dose Titration (Visits 5-9, Weeks 4-20)

The following procedures are to be completed during Visits 5-9:

- Assess and record AEs since last study visit;
- Assess and record medications;
- Collect vital signs (blood pressure, pulse, temperature) and weight;
- Perform a brief, targeted physical examination (Visit 5 only);
- Collect venous blood for hematology, reticulocyte count, CHr, chemistry, the serum iron profile, and sTfR and hepcidin concentrations;
- Collect study drug and perform compliance assessment (Visits 6-9 only);

- Dispense study drug and dosing syringes and/or dosing cups (Visits 5, 7, and 9 only), and provide instruction on study drug storage and dosing (see Appendices 4 and 5); and
- Schedule the patient for their next study visit to take place in approximately 1 month (Visits 5-8) or 2 months (Visit 9). Remind the patient that they should be NPO except for water after midnight prior to each visit, and they should not take any study drug on visit days until after their visit.

Following Visit 9, the patient's Visit 9 hemoglobin level should be compared to the Visit 5 hemoglobin level. If the Visit 9 hemoglobin level is ≥1 g/dL higher than the Visit 5 level, the patient is designated a "hemoglobin responder" and will proceed to Period 3. If not, the patient will proceed to the early termination visit to occur within approximately 1 week after Visit 9.

6.1.4. Period 3: Hemoglobin Maintenance (Visits 10-12, Weeks 21-44)

The following procedures are to be completed during Visits 10-12:

- Assess and record AEs since last study visit;
- Assess and record medications;
- Collect vital signs (blood pressure, pulse, temperature) and weight;
- Perform a brief, targeted physical examination (Visit 10 only);
- Collect venous blood for hematology, reticulocyte count, CHr, chemistry, the serum iron profile, and sTfR and hepcidin concentrations;
- Collect study drug and perform compliance assessment;
- Dispense study drug (Visits 10 and 11 only) and dosing syringes and/or dosing cups, and provide instruction on study drug storage and dosing (see Appendices 4 and 5); and
- At the conclusion of Visits 10 and 11, schedule the patient for their next study visit to take place in approximately 2 months. Additional unscheduled visits at weeks 24, 32, and 40 may be performed at the discretion of the investigator for assessments of Hgb and/or the serum iron profile to further titrate the dose of study drug. Remind the patient that they should be NPO except for water after midnight prior to each visit, and they should not take any study drug on visit days until after their visit. At the conclusion of Visit 12, advise the patient not to take any more study drug, and schedule the patient for the follow-up visit to take place in approximately 1 week.

6.1.5. Follow-up/Early Termination (Visit 13)

The following procedures are to be completed during the Follow-up/Early Termination visit:

- Assess and record AEs since last study visit;
- Assess and record concomitant medications;
- Collect vital signs (blood pressure, pulse, temperature) and weight;
- Collect blood for hematology, chemistry, the serum iron profile, and a serum pregnancy test (if applicable);
- Collect the reticulocyte count, CHr, and sTfR and hepcidin concentrations only if not collected within the previous 30 days;
- Collect any remaining study drug and perform compliance assessment if applicable; and
- Discharge patient from the study.

6.2. Study Assessments

Serum samples for hepcidin, and the Visits 2-4 serum iron parameters (NTBI, and LPI) will be prepared and shipped to Hepcidinanalysis.com according to the instructions in **Appendix 3**. All other laboratory samples will be sent to the site-specific local clinical laboratory.

6.2.1. Laboratory Assessments

6.2.1.1. Hepcidin

The assay for hepcidin has been validated and will be performed on serum samples by weak cation exchange chromatography in combination with time-of-flight mass spectrometry (WCX-TOF MS) on a Microflex LT MALDI-TOF mass spectrometer (Bruker Daltonics).

6.2.1.2. Non-Transferrin-Bound Iron (NTBI) and Labile Plasma Iron (LPI)

The assays for NTBI and LPI will be performed on serum samples by Hepcidinanalysis.com using a validated method.

6.2.1.3. All Other Laboratory Assessments

All of the other laboratory assessments are routine tests and will be performed by the site-specific local clinical laboratory.

6.2.1.4. Collecting, Processing, and Shipping Samples

Blood samples for serum iron parameters (serum iron, TSAT, TBI [optional], NTBI, and LPI) at Visits 2-4 will be collected as outlined in the Sample Collection Schedule

in **Appendix 2**. An indwelling venous catheter may be inserted for the collection of blood samples if deemed necessary by the investigator. Approximately 3.5-5 mL of whole blood will be collected for each blood draw (1-2 mL blood may be collected instead for smaller patients by syringe and transferred to pediatric vacutainer tubes to avoid exceeding maximum blood collection limits). The total volume of blood collected from each patient will be dependent upon the age and weight of the patient and will be collected in accordance with the limits for blood sampling in **Appendix 2** (if the patient is between body weight categories, the lower weight category should be used).

Blood samples for serum iron parameters at Visits 2-4 will be collected in serum separator tubes with clot activator at the following nominal time points (actual blood sampling times must be recorded in the source documents and CRF) as described in **Appendix 2** (if the patient is between body weight categories, the lower weight category should be used): pre-dose (within 30 minutes before dosing), and 1, 2, and 4 hours after each oral iron dose at Visits 2-4. The time points are listed in the blood sampling schedule for Visits 2-4 (Table 3-5) according to patient body weight.

Additional clinical blood samples can be collected as long as the total volume of blood does not exceed the volumes recommended by the CMRC tables for the maximum allowable blood draws (http://www.ucdmc.ucdavis.edu/clinicaltrials/studytools/documents/Blood_Draws_Maximum_Allowable.doc).

Blood samples for DNA sequencing and for the analysis of and hepcidin will be processed as described in **Appendix 3**. All other samples will be processed per the site-specific local clinical laboratory requirements.

6.2.2. Assessment of Safety

Safety assessments will include the following:

- AEs and SAEs, both reported and observed;
- Clinical laboratory tests;
- Changes in physical examinations;
- Vital sign measurements (blood pressure, pulse, temperature) and weight.

6.2.2.1. Clinical Laboratory Tests

All blood samples other than those for DNA sequencing, NTBI, LPI, and hepcidin will be analyzed by the site's local licensed clinical laboratory. For pediatric patients, recent (within 30 days of screening) tests are sufficient for determining study eligibility. For all patients, *TMPRSS6* sequencing results obtained at any time prior to enrollment may be used for determination of eligibility. The clinical laboratory tests that may be conducted at local labs are as follows:

- **Hematology**: complete blood count with platelet count, white blood cell (WBC) count and WBC differential.
- **Blood Chemistry**: routine Chemistry 20 analysis
- **Serum Iron Profile:** serum iron, ferritin, transferrin, TSAT, and TIBC. Optional TBI and UIBC if laboratory can perform that test.
- **Other:** reticulocyte count, CHr, and sTfR.

The investigator is responsible for determining whether out-of-range laboratory values are clinically significantly changed or not. If the investigator determines that additional laboratory examinations are needed for a patient in screening, then the patient is not considered eligible for the study until such values are considered clinically stable. All clinically significantly changed values of enrolled patients will be followed until resolution or stabilization.

6.2.2.2. Physical Examinations

A physical examination will be performed during the screening period any time prior to Visit 2 and will consist of assessments of the following: skin, ENT (ears, nose, and throat), head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, and neurologic. Brief, targeted physical examinations will be performed at Visits 5 and 10.

6.2.2.3. Vital Signs

Vital signs will include supine or sitting blood pressure (mm Hg), heart rate (beats per minute [bpm]), and tympanic or oral temperature. A consistent body position (supine or sitting) should be used for all routine vital sign assessments. Vital sign measurements will be collected at specified intervals as per Section 6.1 and Appendix 1.

7. ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

7.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this product.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events will be recorded on the adverse events CRF from the start of the first dose of oral iron ($FeSO_4$) through the end of study participation or 7 days after the last dose of oral iron ($FeSO_4$ or Triferic), whichever is later. Pre-treatment-emergent medical conditions will be captured on the medical history CRF, unless they meet seriousness criteria (Section 7.2).

An AE **does** include any:

- Exacerbation of a pre-existing illness;
- Increase in frequency or intensity of a pre-existing episodic event or condition;
- Condition detected or diagnosed after the start of study drug administration even though it may have been present prior to the start of the study; or
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

Symptoms associated with a disease not previously reported by the patient will be recorded as an AE.

An AE **does not** include a/an:

- Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion). Rather, the underlying condition that leads to the procedure is the AE that should be reported, unless the condition did not worsen during the study;
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen;
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions).

7.2. Definition of a Serious Adverse Event

Any SAE that occurs from the date of Screening to the date of the Follow-up visit or 7 days after the last dose of Triferic, whichever is later, will be reported on an SAE report form. For enrolled patients, SAEs are also recorded on the AE CRF page. An SAE is any AE occurring at any dose that results in any of the following outcomes:

a. Death;

b. A life-threatening AE;

- *NOTE: Life-threatening means that the patient was, in the view of the investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.*

c. Inpatient hospitalization or prolongation of an existing hospitalization;

- *NOTE: Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE or SAE.*
- *NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, or otherwise meets seriousness criteria, the event is an SAE.*
- *NOTE: "Inpatient" hospitalization means the patient has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.*

d. A disability/incapacity;

- *NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.*

e. A congenital anomaly in the offspring of a patient who received drug; or

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

- Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

7.3. Method, Frequency, and Time Period for Detecting Adverse Events and Serious Adverse Events

At appropriate intervals, patients should be assessed for AEs and SAEs. After the patient has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking a non-leading question such as the following:

1. “How are you feeling?”
2. “Have you had any medical problems since your last assessment/visit?”
3. “Have you taken any new medicines since your last assessment/visit?”

7.4. Reporting SAEs

CONTACT THE MEDICAL MONITOR BY PHONE, EMAIL, OR FAX (1 866 250 5488) WITHIN THE TIMEFRAME SPECIFIED IN SECTION 7.4.1 TO NOTIFY ROCKWELL MEDICAL OF ANY SAEs.

All SAEs (related and unrelated) will be recorded from the time of the Screening visit until the date of the Follow-up visit or 7 days following the last dose of Triferic, whichever is later. Any SAEs considered possibly, probably, or definitely related to the investigational product and discovered by the investigator or site personnel at any interval after completion of the study should also be reported. All SAEs must be reported to Rockwell Medical within 48 hours of the site’s first awareness of the event. If the SAE is fatal or life-threatening, it must be reported to Rockwell Medical within 24 hours of the site’s first awareness of the event. The investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax (1 866 250 5488) or email to Rockwell Medical.

At a minimum, the event name, the reporter’s name and contact information, and the patient’s study identifier must be provided at the time of the initial report. Optimally, a description of the event and the investigator’s preliminary assessment of causality would also be provided. Additional follow-up information, if required or available, should be sent to Rockwell Medical within 48 hours of receipt. Follow-up information should be provided using a follow up SAE report, and the follow-up SAE report should be placed with the original report in the appropriate section of the CRF/study file.

The investigator is encouraged to discuss with Rockwell Medical any AEs for which the issue of seriousness is unclear or questioned.

Rockwell Medical is responsible for notifying the relevant regulatory authorities of certain events. Multiple inquiries between Rockwell Medical and the study site may be necessary for report preparation.

It is the Principal Investigator’s responsibility to notify the Institutional Review Board (IRB), Ethics Committee (EC) or the relevant local regulatory authority of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7- and 15-Day Safety Reports) that occur during any clinical trials of Triferic. Each site is responsible for notifying their IRB, EC or the relevant local regulatory authority of these additional SAEs.

7.4.1. Timeframes for Reporting SAEs

Prompt notification to Rockwell Medical regarding SAEs is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. The investigator must report SAEs according to the following time frames:

- **Death or Life-Threatening Event:**
  - *Initial notification* must be sent to Rockwell Medical **within 24 hours** of the investigational site learning of the death or life-threatening event (regardless of causality).
  - *Complete SAE information* (i.e., all SAE pages) must be sent to Rockwell Medical **within 48 hours.**
  - Follow-up information must be sent to Rockwell Medical within 48 hours of receipt of the information by the investigational site.
- **All other SAEs**
  - Complete SAE information (i.e., all SAE pages) must be sent to Rockwell Medical within 48 hours of site study personnel learning of the event.
  - Follow-up information must be sent to Rockwell Medical within 48 hours of receipt of the information by the investigational site.

7.4.2. SAE Information to Report

All information available regarding an SAE must be submitted in the timeframes indicated in Section 7.4.1. At a minimum, SAE reports must contain the patient's study identifier, the SAE term, and the name of the person reporting the event to Rockwell Medical. Optimally, a description of the event and the investigator's preliminary assessment of causality would also be provided.

The investigator must record all relevant information regarding an AE/SAE in the applicable sections of the CRF. **It is not acceptable for the investigator to send photocopies of the patient's medical records in lieu of completion of the appropriate AE/SAE pages**. However, there may be instances when copies of medical records for certain cases are requested by Rockwell Medical. If medical records are submitted to Rockwell Medical then all patient personal identifiers must be completely and thoroughly redacted prior to submission. Each page of medical records should be labeled with the patient's study identifier.

7.4.3. Regulatory/Ethics Reporting Requirement

The investigator, or responsible person according to local requirements, must comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/EC.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs

Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a diagnosis, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected before study drug administration and do not worsen after study drug administration, should not be reported as AEs. Instead, the diagnosis with which they are associated should be assessed for whether it constitutes an AE, and reported accordingly. For example, if a patient experiences leukocytosis or hypoxia associated with a diagnosis of pneumonia, it is not necessary to report these in addition to reporting the pneumonia unless they are more severe than expected.

If not known to be associated with a diagnosis, abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the investigator as clinically significant must be recorded as AEs or SAEs if they meet the definition of an adverse event (Section 7.1, Definition of an Adverse Event), and reported as SAEs if they meet the criteria for seriousness (Section 7.2, Definition of an SAE).

The investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.6. Documenting AEs

Adverse events, including SAEs, will be recorded on the adverse events CRF from the start of the first dose of oral iron ($FeSO_4$) through the end of study participation or 7 days after the last dose of oral iron ($FeSO_4$ or Triferic), whichever is later. Pre-treatment-emergent medical conditions will be captured on the medical history CRF, unless they meet seriousness criteria (Section 7.2).

Any SAE that occurs from the date of Screening to the Follow-up visit or 7 days after the last dose of oral iron, whichever is later, will be reported on an SAE report form. For enrolled patients, SAEs are also recorded on the AE CRF page.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or SAE.

7.7. Follow-up of AEs

After the initial AE report, the investigator is required to proactively follow each patient and provide further information to Rockwell Medical on the patient’s condition. All AEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs that are ongoing at the conclusion of the patient's participation will be followed up until resolution, until the condition stabilizes, or until the patient is lost to follow-up. The appropriate AE/SAE source document and CRF page(s) will be updated. If a patient dies during participation in the study or during the 7 days following the patient's last dose of oral iron, a copy of any post-mortem findings, including histopathology, should be obtained, if available, and forwarded to Rockwell Medical.

7.8. Post-study AEs

Investigators are not obligated to actively seek new AEs or SAEs that begin after the Follow-up visit or 7 days after the last dose of oral iron, whichever is later. The investigator should notify Rockwell Medical of any SAEs that begin following study completion only if the event is considered related to study drug.

8. STATISTICS

8.1. General Considerations

A total sample size of approximately 28 patients is planned. Where appropriate, the normality of data will be assessed before analysis by using the Shapiro-Wilk test and graphically by evaluating histograms and Q-Q plots. Data not normally distributed will be log transformed for analysis. Log-transformed data will be back transformed for reporting. Normally distributed data will be presented as means (±SDs, ±95% confidence intervals (CI), or both), data normally distributed after log transformation will be presented as geometric means (±95% CI), and non-normally distributed data will be presented as medians and ranges. The baseline demographic and clinical characteristics of the study population will be presented in tabular form. For the primary and key secondary endpoints, a summary of results with the estimated effect size and its precision will be reported. Differences in changes between baseline and 4-month and subsequent 6-month measurements will be compared.

8.2. Determination of Sample Size

The overall goal of this project is to test the primary study hypothesis that QD-TID administration of Shohl's solution, 0.67 mmol/kg, followed by Triferic, 1 to 3 mg Fe/kg, will produce a sustained increase in hemoglobin concentration of ≥1 g/dL in 80% of patients with IRIDA (termed "hemoglobin responders"). Given that the total number of patients with IRIDA currently reported is only about 75 individuals, for the purpose of sample size calculation for this trial, we determine the number of patients that would need to be examined to determine if the true proportion of hemoglobin responders is within ±10% of our estimate with a 90% confidence interval. Then

$$n = \frac{\left(Z_{\alpha/2}\right)^2 p^*(1-p^*)}{E^2}$$

$$= (1.645^2 \text{ x } 0.8 \text{ x } 0.2)/0.1^2$$

$$= 43.4$$

where n is the unadjusted sample size for an unlimited population, $Z_{\alpha/2}$ is value of the normal distribution at α/2, p* is the hypothesized proportion of hemoglobin responders, and E is the level of precision. Because the population of patients with iron-refractory iron-deficiency anemia currently reported is only about 75 individuals, the sample size is adjusted by

$$n_{adj} = Nn/(N+n-1)$$

$$= (75 \text{ x } 43.4)/(75 + 43.4 - 1)$$

$$= 27.6$$

Accordingly, our sample size estimate for this trial is 28 patients. If our estimate that 80% of patients is an appreciable overestimate, then the need to revise this estimate should become evident early during the course of the trial.

8.3. Analysis Populations

Two analysis populations will be defined as follows:

- **MITT Population** will include all enrolled patients who receive at least 1 dose of study drug and have at least one Hgb assessment following Visit 5.
- **Safety Population** will include all randomized patients who received at least 1 dose of study drug.

The analyses of baseline characteristics will be performed for the Safety Population. All efficacy analyses will be performed for the MITT Population. All safety analyses will be performed for the Safety Population.

8.4. Patient Disposition

Patient disposition will be summarized by Safety Population and for the 4 age strata.

8.5. Baseline Characteristics

Baseline characteristics will be summarized for the Safety Population and for the 4 age strata.

8.6. Concomitant Medications

Concomitant medications will be categorized by World Health Organization (WHO) classification (ATC levels 1-4) and drug name and summarized by number and percentage of patients for the Safety Population.

8.7. Extent of Exposure

Exposure will be calculated for the Safety Population and for the 4 age strata.

8.8. Safety Assessments

8.8.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1 or later. The frequency of treatment-emergent AEs will be calculated for each body system, by preferred term, by treatment, for number of patients and percentage reporting the event. The severity of the AEs and the relationship to the study drug will be summarized for each body system and preferred term by treatment. Withdrawals due to AEs will be summarized for each body system and preferred term by treatment. Adverse events will also be summarized by sex, age stratum (<6 years, 6 to <12 years, 12 to <18 years, ≥18 years) and race (white and nonwhite).

If more than 1 patient experiences an AE grade ≥3 (CTCAE v4.0) that is considered related to study drug by the investigator, then a complete review of all AEs in the study will be initiated. During any such review, no new patients will be enrolled in the study until a determination concerning the AEs is completed.

Narratives will be presented for all deaths, SAEs and patients withdrawn due to AEs.

8.8.2. Clinical Laboratory Assessments

All clinical laboratory assessments will be summarized for the Safety Population. Baseline, time point, and Follow-up values will be summarized separately. Changes from baseline will be summarized by age group.

8.8.3. Vital Signs

Vital signs will be reported by each individual component. Changes from baseline at each time point will be summarized.

8.9. Statistical and Analytical Issues

8.9.1. Statistical Analysis Plan

A study-specific statistical analysis plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will give a detailed description of the summaries and analyses (primary and secondary) that will be performed and clearly describe when these analyses will take place. Included in the SAP will be adjustments for covariates, and handling of dropouts and missing data points.

8.9.2. Handling of Missing Data

Missing data will not be replaced or imputed. All analyses will use available data only.

8.9.3. Interim Analyses and Data Monitoring

An interim analysis will be performed after approximately 5 patients have been studied to assess the frequency of hemoglobin responders at Visit 9. Should the proportion of hemoglobin responders be too high or too low, the protocol may be amended to change the targeted sample size for the remainder of the study.

8.9.4. Criteria for Stopping the Study

The study can be stopped at any time if any of the following circumstances occurs:

- An SAE occurring during Triferic administration and considered related to study drug;
- Signs of potential iron toxicity in 1 or more patients in any cohort as evidenced by any of the following, that is not consistent with the patients' ongoing medical history:

- GI: Nausea, vomiting, diarrhea and abdominal pain;
- CV: Decreased cardiac output leading to hypoperfusion and shock;
- Metabolic: Acute metabolic acidosis; or
- CNS: Depressed sensorium;

- Serum iron levels ≥500 µg/dL regardless of symptomology; or
- Hepatic injury as evidenced by any acute combination of elevated bilirubin, AST or ALT levels.

If any of these events occurs, enrollment may be suspended and a safety review committee will review the entire study's safety data before a decision is made to resume enrollment or terminate the study.

9. STUDY ADMINISTRATION

9.1. Sponsor's and Investigator's Responsibilities

This study will be conducted in accordance with current applicable regulations, ICH and local ethical and legal requirements.

9.2. Sponsor's Responsibilities

9.2.1. GCP Compliance

Rockwell Medical and any third party to whom aspects of the study management or monitoring have been delegated will undertake their roles for this study in compliance with all applicable regulations and ICH GCP Guideline E6.

Visits to investigator sites will be conducted by representatives of Rockwell Medical to inspect study data, patients' medical records and CRFs in accordance with current GCP and the respective local and national government regulations and guidelines. Records and data may additionally be reviewed by auditors, or by regulatory authorities.

9.2.2. Regulatory Approval

Rockwell Medical will ensure that local Regulatory Authority and IRB/EC requirements are met at each site prior to releasing investigational product for shipment to the study site.

9.2.3. Indemnity/Liability and Insurance

Rockwell Medical will ensure that suitable insurance coverage is in place prior to the start of the study.

9.2.4. Protocol Conduct

9.2.4.1. Protocol Compliance and Protocol Deviations

Except for a change that is intended to eliminate an apparent immediate hazard to a study patient, the protocol shall be conducted as specified. Any such change must be reported immediately to Rockwell Medical and to the IRB/EC according to the applicable IRB/EC policy.

The investigator must notify the IRB/EC of any and all protocol deviations according to the applicable IRB/EC policy. Protocol waivers will not be granted.

Written documentation of all protocol deviations must be kept in the study center file and provided to Rockwell Medical. Examples of possible protocol deviations include, but are not limited to:

- Failure to obtain required informed consent,
- Failure to collect, report or file AE reports,
- Performance of an unapproved study procedure,
- Performance of research at an unapproved location,
- Failure to file protocol modifications, and
- Failure to adhere to an approved protocol.

9.2.4.2. Protocol Amendments

All protocols and amendments will be prepared by Rockwell Medical. If it becomes necessary to issue a protocol amendment during the course of the study, Rockwell Medical (or designee) will notify the investigators and collect a documented Investigator Agreement to the amendment.

All protocol amendments must be submitted to the IRB/EC for review and approval must be obtained prior to implementation. However, immediate implementation of a protocol amendment may be necessary if the nature of the amendment concerns the safety of patients and is required to be implemented on an urgent basis to protect the safety of patients. Any such immediate implementation of protocol amendments must be agreed to in advance and in writing by Rockwell. Hard copy documentation of IRB/EC approval must be forwarded to Rockwell.

If an amendment significantly alters the study design, increases potential risk to the patient or otherwise affects statements in the informed consent form (ICF) and assent form, the ICF and assent form must be revised accordingly and submitted to the IRB/EC for review and approval. The approved ICF and assent form must be used to obtain informed consent/assent from new patients/legal guardians prior to enrollment and must be used to re-obtain informed consent/assent from patients/legal guardians already enrolled if they are potentially affected by the amendment and wish to continue participation.

9.3. Investigator's Responsibilities

9.3.1. GCP Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 and the applicable regulatory requirements.

It is the investigator's responsibility to ensure that adequate time and appropriate resources are available at the study site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.

If the patient has a primary physician the investigator should, with the patient's consent, inform them of the patient's participation in the trial.

9.3.2. Protocol Adherence and Investigator Agreement

The investigator must adhere to the protocol as detailed in this document. The investigator will be responsible for enrolling only those patients who have met protocol eligibility criteria. The investigators will be required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

It is the investigator's responsibility to communicate with their local IRB/EC to ensure accurate and timely information is provided at all phases during the study. In particular the appropriate approvals must be in place prior to recruitment, notification of any SAEs during the study must take place and the IRB/EC must be informed of study completion.

9.3.3. Documentation and Retention of Records

9.3.3.1. Case Report Forms

Case report forms (CRFs) will be supplied by Rockwell Medical and should be handled in accordance with instructions from Rockwell Medical.

In accordance with the U.S. 21 CFR 312.62, a CRF, whether paper or electronic, must be completed for each patient enrolled in the study. All data collected for each study patient will be recorded on CRFs provided or approved by Rockwell Medical.

CRFs need not be completed by the investigator, but all entries in CRFs are the responsibility of the investigator and entry of CRF data must be made under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility (if paper), and timeliness of all data reported in the CRFs and all required reports for each study patient. The investigator is also responsible for maintaining any source documentation related to the study, including, but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs, files or tapes. The investigator must retain a copy of all CRFs.

9.3.3.2. Site Visits

Study Initiation, Monitoring and Closeout Visits

Representatives of Rockwell Medical will perform a number of on-site visits to the study center, from prior to initiation of the study at the site until after the study has been completed. These visits will include but not be limited to review of the site for adequacy to conduct the trial, review of study data, CRFs, and supportive source documents, and drug accountability.

Throughout the course of the study, Rockwell Medical representatives will also make frequent contacts with the investigator and designated site personnel. As part of the data review it is expected that source documents (e.g., hospital records, office records) will be made available for review by Rockwell Medical. The study documents may also be similarly evaluated by auditors representing Rockwell Medical. For these purposes, the investigator will make CRFs, source documents and study files available when requested.

At fulfillment of study enrollment, each investigator will be notified in writing by Rockwell Medical. The study will be terminated and the study center will be closed when all completed original CRFs have been collected, all data discrepancies resolved, and drug accountability has been reconciled. It will be the responsibility of the investigator to notify the IRB/EC that the study has been completed.

Rockwell Medical has the right to terminate the study for non-adherence to protocol, unavailability of the investigator or his or her study staff for Rockwell Medical or its representatives, or for administrative reasons, at any time. In that event, Rockwell Medical will notify each investigator in writing that the study is to be discontinued. The investigator will comply with Rockwell Medical's written instructions for study discontinuation, which will include the following:

- Date discontinuation will occur,
- Rationale for discontinuation,
- Instructions on how discontinuation is to be performed,
- Instructions for patients participating in the study, and
- Instructions for retention of study documents.

In addition to monitoring by Rockwell Medical or its designees, the study may be audited by representatives of the U.S. Food and Drug Administration (FDA) or other applicable regulatory agencies, who will also be allowed access to study documents. The investigator should immediately notify Rockwell Medical of any proposed or scheduled audits with any regulatory authorities.

9.3.3.3. Recording, Access and Retention of Source Data

All records of this clinical study must be retained by the investigator, including, but not limited to, the following:

- Protocol and all protocol amendments,

- All signed versions of the Statement of Investigator, Form FDA 1572,
- All drug accountability records,
- All IRB/EC approvals, correspondence and reports,
- Signed and dated informed consent/assent forms for each patient,
- Completed CRFs for each patient,
- Copies of any other material distributed to patients,
- Any advertisements for this study,
- The investigator's final report to the IRB/EC, and
- Source documents pertaining to the study, including, but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs, files or tapes.

The period of time these documents must be maintained is governed by US law and, when applicable, non-US regulations. All records are to be retained by the investigator for a minimum of two (2) years after the FDA has approved the use of Triferic for the treatment of IRIDA, or after Rockwell Medical has notified the investigator in writing that all investigations of the drug have been discontinued. However, because of international regulatory requirements, Rockwell Medical may request retention for a longer period of time. Therefore, Rockwell Medical or its designee will inform the investigator when these documents may be destroyed. The investigator must obtain written approval from Rockwell Medical prior to destruction of any records.

The investigator must advise Rockwell Medical in writing if the records are to be moved to a location other than the investigator's archives. If the investigator leaves the institution or study center, the records shall be transferred to an appropriate designee, at the study center, who assumes the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to Rockwell Medical.

In the event of accidental loss or destruction of any study records, the investigator will immediately notify Rockwell Medical in writing. Rockwell Medical or its designee must be notified in writing at least 30 days prior to the intended date of disposal of any study records related to this protocol.

9.3.4. Investigator's Final Report

Shortly after completion of the investigator's participation in the study, the investigator will submit a written report to Rockwell Medical. This report may be a copy of the investigator's end-of-study report to their IRB/EC, which will include, but not be limited to, notification that the study has concluded, the number of patients enrolled/ treated, and the number of adverse and serious AEs that occurred during the study. The report to the IRB/EC will be consistent with the applicable IRB/EC regulations and time frames.

9.4. Ethical Considerations

This study will be conducted under a US Investigational New Drug (IND) Application. All applicable US regulations governing human subject protection must be followed. All ethical and regulatory requirements necessary to comply with the principles of Good Clinical Practice (GCP) for the conduct and monitoring of clinical investigations must be followed.

9.5. Informed Consent

A copy of the proposed ICF and assent form documents should be submitted to Rockwell Medical for review and comment prior to submission to the reviewing IRB/EC. The ICF/assent forms must be approved by the IRB/EC and contain all elements required by all applicable federal, state, local, and institutional regulations or requirements prior to consenting a patient. Authorization to use or disclose Personal Health Information (PHI) in accordance with requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) should be covered in the ICF/assent form or in a separate document to be signed by the patient.

The investigator will be responsible for obtaining written informed consent from the parent(s)/legal guardian(s) of potential patients and assent from potential patients (where applicable) prior to any study-specific screening and entry into the study. The research study will be completely explained to each prospective study patient. The investigator or designee must explain that the patient is free to refuse to enter the study, and free to withdraw from it at any time for any reason.

9.5.1. Institutional Review Board or Ethics Committee Approval

In accordance with 21 CFR Parts 50 and 56, the investigator agrees to provide the appropriate IRB/EC with all appropriate material, including a copy of the protocol, ICF, and any proposed advertisement for the study prior to the start of the study.

The proposed ICF and any proposed advertisement must also be agreed to by Rockwell Medical. The site may not begin consenting, screening or enrolling patients until the investigator has obtained IRB/EC approval of the protocol and ICF/assent form and Rockwell Medical has received documentation of each.

The investigator will supply to Rockwell Medical a list of the names, professions, and affiliations of IRB/EC members to demonstrate compliance with membership requirements. If the investigator or a sub-investigator is a routine voting member of the IRB/EC, Rockwell Medical will be provided with a statement from the IRB/EC that the investigator/sub-investigator did not and will not vote on any IRB/EC decisions pertaining to this clinical investigation.

During the course of the study, the investigator shall make timely and accurate reports to the IRB/EC on the progress of the trial, at intervals not exceeding one year, as well as satisfying any other local IRB/EC regulations regarding reporting. Furthermore, at the completion or early termination of the study, a final report should be made to the IRB/EC by the investigator within the applicable IRB/EC time frames.

Any significant changes or revisions in the study protocol or any changes that may alter patient risk must be approved by Rockwell Medical (and may require FDA/other regulatory agency review and/or approval) and must be approved in writing by the IRB/EC prior to implementation. The investigator must also receive a written notice of approval from Rockwell Medical prior to initiating the revised changes to the study protocol. A protocol change intended to eliminate an apparent immediate hazard may be implemented immediately, provided that Rockwell Medical is immediately notified and an amendment is subsequently provided by Rockwell Medical and approved by the IRB/EC.

It is the investigator's obligation to maintain an IRB/EC correspondence file, to provide copies of all documents to Rockwell Medical, and to make this available for review by Rockwell Medical or its designated representatives as part of the study monitoring process.

9.6. Confidentiality

All US-based investigational sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA. An investigational site that is not a Covered Entity, as defined by HIPAA, must provide documentation of this fact to Rockwell Medical.

10. DISCLOSURE OF DATA AND PUBLICATION

All information obtained as a result of this study or during the conduct of this study will be regarded as confidential. All unpublished information relating to this drug or to the operations of Rockwell Medical, including clinical indications, formula, methods of manufacture, and any other related scientific data provided to or developed by the investigator, is confidential and shall remain the sole property of Rockwell Medical. The investigator agrees to use the information for the purpose of carrying out this study and for no other purpose, unless prior written permission from Rockwell Medical is obtained. Rockwell Medical has full ownership of the CRFs and database resulting from this study.

The investigator agrees that results from this study may be used by Rockwell Medical for purposes of domestic and international new drug registration, for publication, and to inform medical and pharmaceutical professionals. Regulatory authorities will be notified of the investigator’s name, address, qualifications, and extent of involvement.

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APPENDIX 1. TIME AND EVENTS SCHEDULE

Table 2: Time and Events Schedule

Assessments	Screen	Period 1: Iron Absorption Testing			Period 2: Dose Titration§					Period 3: Hemoglobin Maintenance§			Follow-up
Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Target study week*	-4 to -1	1	2	3	4	8	12	16	20	28	36	44	45
Informed consent/ patient assent	X												
Inclusion/exclusion criteria	X												
Demographics and medical history	X												
Height and weight[a]	X				X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X				X					X			
DNA sample[c]	X												
Hematology[b,c]	X				X	X	X	X	X	X	X	X	X
Reticulocyte count, CHr, and sTfR and hepcidin[d]	X				X	X	X	X	X	X	X	X	(X)[d]
Chemistry[b,c]	X				X		X		X	X	X	X	X
Serum iron profile[b,c]	X				X	X	X	X	X	X	X	X	X
Serum iron, TSAT, TBI, NTBI, and LPI[e]		X	X	X									
Serum pregnancy test (if applicable)[b,c]	X												X
Enroll patient§		X			X					X			
Administer study drug		X	X	X									
Dispense study drug					X		X		X	X	X		
Collect study drug and assess compliance						X	X	X	X	X	X	X	(X)
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X

§ Period 1 Triferic responders will progress to Period 2. Period 2 Hgb responders will progress to Period 3. During Period 3, additional unscheduled visits at weeks 24, 32, and 40 may be performed at the discretion of the investigator for assessments of Hgb and/or the serum iron profile to further titrate the dose of study drug.

* A visit window of ±1 week is permitted for each study visit; however, study visits 3-5 and 13 should occur at least 2 days after the previous study visit.

[a] Height will be recorded at Screening Visit only.

[b] All blood draws for pediatric patients to use pediatric tubes. Blood draws for adult patients may use standard adult tubes.

[c] For pediatric patients, hematology, chemistry, and serum iron profile results from up to 30 days prior to screening may be used for determination of eligibility. For all patients, *TMPRSS6* sequencing results obtained at any time prior to enrollment may be used for determination of eligibility.

[d] Collect only if not obtained within the previous 30 days.

[e] See Appendix 2, Tables 3, 4, and 5 for the schedule for obtaining these serum iron parameter samples at Visits 2, 3, and 4, respectively.

APPENDIX 2. SERUM IRON PARAMETER SAMPLE COLLECTION SCHEDULE, VISITS 2-4

Table 3: Sample Collection Schedule, Visit 2

Body weight (kg)	***5***	***6***	***7***	***8***	***9***	***10***	***11-15***	***16-20***	***21-25***	***>25***
Body weight (lbs)	***11***	***13.2***	***15.4***	***17.6***	***19.8***	***22***	***24.2-33***	***35.2-44***	***46.2-55***	***>55***
Total blood volume (mL)	***400***	***480***	***560***	***640***	***720***	***800***	***880-1200***	***1280 1600***	***1680 2000***	***>2000***
Maximum allowable volume (mL) in one blood draw (2.5% TBV)	***10***	***12***	***14***	***16***	***18***	***20***	***22-30***	***32-40***	***42-50***	***>50***
Total (clinical + research) maximum allowable volume (mL) in a 30-day period	***20***	***24***	***28***	***32***	***36***	***40***	***44-60***	***64-80***	***84-100***	***>100***
Nominal Time hr§	**Serum Iron Parameter Collection Schedule for Visit 2**									
0	a†	a†	a†	a†	a	a	a	a	a	a
1	a†	a†	a†	a†	a†	a†	a	a	a	a
2	a†	a†	a†	a	a	a	a	a	a	a
4	a†	a†	a†	a†	a†	a†	a	a	a	a
Total Blood Draw for Visit 2 (mL)	4	4	4	6.5	11	11	14	14	14	14

§ The time of the 3 mg Fe/kg oral dose (as $FeSO_4$) is time 0. Sample collection for the 0-hr nominal time point should occur within 30 minutes prior to the iron dose.

† For patients <9 kg (19.8 lb), 1 mL blood may be drawn using a syringe and put into a 2.5 - 3.5 mL serum separator tube (e.g., BD #367983 [gold top] or Vacuette #454243 [red cap with white ring, non-ridged]) to remain within collection volume limits. For patients 9 - ≤10 kg (22 pounds), 2 mL blood may be drawn and put into a 2.5 - 3.5 mL serum separator tube to remain within collection volume limits. Tubes may also be underfilled at additional time points if needed for any patient to remain within collection volume limits.

a Collect samples for assessment of serum iron, TSAT, TBI, NTBI, and LPI. Process according to the instructions in Appendix 3.

Table 4: Sample Collection Schedule, Visit 3

Body weight (kg)	***5***	***6***	***7***	***8***	***9***	***10***	***11-15***	***16-20***	***21-25***	***>25***
Body weight (lbs)	***11***	***13.2***	***15.4***	***17.6***	***19.8***	***22***	***24.2-33***	***35.2-44***	***46.2-55***	***>55***
Total blood volume (mL)	***400***	***480***	***560***	***640***	***720***	***800***	***880-1200***	***1280 1600***	***1680 2000***	***>2000***
Maximum allowable volume (mL) in one blood draw (2.5% TBV)	***10***	***12***	***14***	***16***	***18***	***20***	***22-30***	***32-40***	***42-50***	***>50***
Total (clinical + research) maximum allowable volume (mL) in a 30-day period	***20***	***24***	***28***	***32***	***36***	***40***	***44-60***	***64-80***	***84-100***	***>100***
Nominal Time hr§	**Serum Iron Parameter Collection Schedule for Visit 3**									
0	a†	a†	a	a	a	a	a	a	a	a
1	a†	a†	a†	a†	a†	a†	a	a	a	a
2	a†	a†	a	a	a	a	a	a	a	a
4	a†	a†	a†	a†	a†	a†	a	a	a	a
Total Blood Draw for Visit 3 (mL)	4	4	11	11	11	11	14	14	14	14
Total Blood Draw Visits 2 + 3 (mL)	8	8	15	17.5	22	22	28	28	28	28

§ The time of the 3 mg Fe/kg oral dose (as $FeSO_4$) is time 0. At Visit 3, the iron dose should occur approximately 5 minutes after administration of Shohl's solution, 0.67 mmol/kg. Sample collection for the 0-hr nominal time point should occur within 30 minutes prior to the iron dose.

† For patients <9 kg (19.8 lb), 1 mL blood may be drawn using a syringe and put into a 2.5 - 3.5 mL serum separator tube (e.g., BD #367983 [gold top] or Vacuette #454243 [red cap with white ring, non-ridged]) to remain within collection volume limits. For patients 9 - ≤10 kg (22 pounds), 2 mL blood may be drawn and put into a 2.5 - 3.5 mL serum separator tube to remain within collection volume limits. Tubes may also be underfilled at additional time points if needed for any patient to remain within collection volume limits.

a Collect samples for assessment of serum iron, TSAT, TBI, NTBI, and LPI. Process according to the instructions in Appendix 3.

Table 5: Sample Collection Schedule, Visit 4

Body weight (kg)	***5***	***6***	***7***	***8***	***9***	***10***	***11-15***	***16-20***	***21-25***	***>25***
Body weight (lbs)	***11***	***13.2***	***15.4***	***17.6***	***19.8***	***22***	***24.2-33***	***35.2-44***	***46.2-55***	***>55***
Total blood volume (mL)	***400***	***480***	***560***	***640***	***720***	***800***	***880-1200***	***1280 1600***	***1680 2000***	***>2000***
Maximum allowable volume (mL) in one blood draw (2.5% TBV)	***10***	***12***	***14***	***16***	***18***	***20***	***22-30***	***32-40***	***42-50***	***>50***
Total (clinical + research) maximum allowable volume (mL) in a 30-day period	***20***	***24***	***28***	***32***	***36***	***40***	***44-60***	***64-80***	***84-100***	***>100***
Nominal Time hr§	**Serum Iron Parameter Collection Schedule for Visit 4**									
0	a†	a	a	a	a	a	a	a	a	a
1	a†	a†	a†	a†	a†	a†	a	a	a	a
2	a	a	a	a	a	a	a	a	a	a
4	a†	a†	a†	a†	a†	a†	a	a	a	a
Total Blood Draw for Visit 4 (mL)	6.5	11	11	11	11	11	14	14	14	14
Total Blood Draw Visits 2 + 3 + 4 (mL)	14.5	19	26	28.5	33	33	42	42	42	42

§ The time of the 3 mg Fe/kg oral dose (as Triferic, ferric pyrophosphate citrate) is time 0. At Visit 4, the iron dose should occur approximately 5 minutes after administration of Shohl's solution, 0.67 mmol/kg. Sample collection for the 0-hr nominal time point should occur within 30 minutes prior to the iron dose.

† For patients <9 kg (19.8 lb), 1 mL blood may be drawn using a syringe and put into a 2.5 - 3.5 mL serum separator tube (e.g., BD #367983 [gold top] or Vacuette #454243 [red cap with white ring, non-ridged]) to remain within collection volume limits. For patients 9 - ≤10 kg (22 pounds), 2 mL blood may be drawn and put into a 2.5 - 3.5 mL serum separator tube to remain within collection volume limits. Tubes may also be underfilled at additional time points if needed for any patient to remain within collection volume limits.

a Collect samples for assessment of serum iron, TSAT, TBI, NTBI, and LPI. Process according to the instructions in Appendix 3.

APPENDIX 3. SAMPLE HANDLING, STORAGE & SHIPPING

Supplies for the Study

2.5 - 3.5-mL serum separator vacutainer tubes (pediatric) and 5-mL serum separator vacutainer tubes (adults)

3-mL syringes for blood sampling

Screw-top plastic sample transport tubes

Sample Collection and Processing Instructions

a) Serum iron, TSAT, TBI: follow the site-specific local clinical laboratory requirements.
b) NTBI, and LPI samples: After allowing the samples to clot at controlled room temperature (22°C nominal temperature) for 30 minutes, separate the serum by centrifuging at controlled room temperature at 1500x*g* for 10 minutes. Gently transfer into plastic sample transport tubes. Store frozen at -80°C until shipped to Hepcidinanalysis.com on dry ice for analysis of NTBI and LPI.
c) Hepcidin samples: After allowing the samples to clot at controlled room temperature (22°C nominal temperature) for 30 minutes, separate the serum by centrifuging at controlled room temperature (22°C nominal temperature) at 1500x*g* for 10 minutes and gently transfer two 400-µL aliquots into plastic sample transport tubes. Store aliquot #1 frozen at -80°C until shipped to Hepcidinanalysis.com on dry ice. Store aliquot #2 frozen at -80°C until shipped as directed by Rockwell Medical.
d) CHr samples: follow the site-specific local clinical laboratory requirements.
e) sTfR samples: follow the site-specific local clinical laboratory requirements.
f) DNA samples: TBD
g) All other samples: follow the site-specific local clinical laboratory requirements.

See site instructions for further details on sample collection, processing, and shipping, particularly for pediatric samples.

APPENDIX 4. DETAILED INSTRUCTIONS FOR STUDY DRUG DOSING

Note: For Visits 2-4, study drugs should only be administered by qualified site personnel. For Periods 2-3, study drugs should be self-administered by the patient, or alternatively by the patient's parent or guardian if the patient is unable to do so.

Materials required:

1-, 3-, 5-, and 10-mL medication dosing syringes

30-mL graduated plastic medication dosing cups

Procedure:

Fer-In-Sol (Visit 2, 3, or 4)

1. Shake the bottle of Fer-In-Sol well.

2. Determine the volume of Fer-In-Sol to be dosed (see Appendix 5, Table 6).

3. Select the most appropriate dosing device (1-, 3-, 5-, or 10-mL medication dosing syringe; or 30-mL graduated plastic medication dosing cup) based on the volume to be dosed and the age of the patient.

4. Dispense the correct amount of Fer-In-Sol according to Appendix 5, Table 6. If the Fer-In-Sol is to be administered via syringe, draw up the indicated volume of Fer-In-Sol in the appropriate syringe. If the Fer-In-Sol is to be administered via dosing cup, pour the indicated volume of Fer-In-Sol into a dosing cup.

5. Administer the Fer-In-Sol. For dosing via syringe, dispense the Fer-In-Sol slowly towards the patient's inner cheek. For dosing via dosing cup, have the patient drink all of the contents of the cup.

Shohl's Solution Followed by Fer-In-Sol (Visit 2, 3, or 4)

1. Determine the volume of Shohl's solution to be dosed (see Appendix 5, Table 7).

2. Select the most appropriate dosing device (1-, 3-, 5-, or 10-mL medication dosing syringe; or 30-mL graduated plastic medication dosing cup) based on the volume to be dosed and the age of the patient.

3. Dispense the correct amount of Shohl's solution according to Appendix 5, Table 7. If the Shohl's solution is to be administered via syringe, draw up the indicated volume of Shohl's solution in the appropriate syringe. If the Shohl's solution is to be administered via dosing cup, pour the indicated volume of Shohl's solution into a dosing cup.

4. Administer the Shohl's solution. For dosing via syringe, dispense the Shohl's solution slowly towards the patient's inner cheek. For dosing via dosing cup, have the patient drink all of the contents of the cup.

5. Shake the bottle of Fer-In-Sol well.

6. Determine the volume of Fer-In-Sol to be dosed (see Appendix 5, Table 7).

7. Select the most appropriate dosing device (1-, 3-, 5-, or 10-mL medication dosing syringe; or 30-mL graduated plastic medication dosing cup) based on the volume to be dosed and the age of the patient.

8. 5-15 minutes after the dose of Shohl's solution, dispense the correct amount of Fer-In-Sol according to Appendix 5, Table 7. If the Fer-In-Sol is to be administered via syringe, draw up the indicated volume of Fer-In-Sol in the appropriate syringe. If the Fer-In-Sol is to be administered via dosing cup, pour the indicated volume of Fer-In-Sol into a dosing cup.

9. Administer the Fer-In-Sol. For dosing via syringe, dispense the Fer-In-Sol slowly towards the patient's inner cheek. For dosing via dosing cup, have the patient drink all of the contents of the cup.

Shohl's Solution Followed by Triferic (Visit 2, 3, or 4)

1. Determine the volume of Shohl's solution to be dosed (see Appendix 5, Table 8).

2. Select the most appropriate dosing device (1-, 3-, 5-, or 10-mL medication dosing syringe; or 30-mL graduated plastic medication dosing cup) based on the volume to be dosed and the age of the patient.

3. Dispense the correct amount of Shohl's solution according to Appendix 5, Table 8. If the Shohl's solution is to be administered via syringe, draw up the indicated volume of Shohl's solution in the appropriate syringe. If the Shohl's solution is to be administered via dosing cup, pour the indicated volume of Shohl's solution into a dosing cup.

4. Administer the Shohl's solution. For dosing via syringe, dispense the Shohl's solution slowly towards the patient's inner cheek. For dosing via dosing cup, have the patient drink all of the contents of the cup.

5. Determine the volume of Triferic to be dosed (see Appendix 5, Table 8).

6. Select the most appropriate dosing device (1-, 3-, 5-, or 10-mL medication dosing syringe; or 30-mL graduated plastic medication dosing cup) based on the volume to be dosed and the age of the patient.

7. Open the Triferic ampule(s) by twisting off the plastic top. Use a new ampule(s) for each dose.

8. 5-15 minutes after the dose of Shohl's solution, dispense the correct amount of Triferic according to Appendix 5, Table 8. If the Triferic is to be administered via syringe, draw up the indicated volume of Triferic in the appropriate syringe. If the Triferic is to be administered via dosing cup, pour the indicated volume of Triferic into a dosing cup.

9. Administer the Triferic. For dosing via syringe, dispense the Triferic slowly towards the patient's inner cheek. For dosing via dosing cup, have the patient drink all of the contents of the cup.

Periods 2-3, Shohl's Solution Followed by Triferic

For Periods 2 and 3, each time study drug is dispensed and each time the investigator puts the patient on a different dose of Triferic, site personnel should:

1. Determine the volume of Shohl's solution and Triferic to be dosed (see Appendix 5, Table 9).

2. Select the most appropriate dosing device(s) (1-, 3-, 5-, or 10-mL medication dosing syringe; or 30-mL graduated plastic medication dosing cup) based on the volumes to be dosed and the age of the patient.

3. Show the patient (and/or the patient's parent or guardian, if appropriate) the volumes of Shohl's solution and Triferic to be dosed for each administration on the dosing device(s).

4. Write down the volumes of Shohl's solution and Triferic to be dosed for each administration on the Study Drug Administration Sheet and provide this to the patient (and/or the patient's parent or guardian, if appropriate).

5. Provide the patient with enough study drug (Shohl's solution and Triferic) and dosing devices to last until the next time the patient is scheduled to be dispensed study drug.

The Study Drug Administration Sheet will include the following instructions:

1. Check the Study Drug Administration Sheet for the amount of Shohl's solution to be dosed and how many times per day it should be dosed.

2. If the Shohl's solution is to be given by syringe, draw up the correct volume of Shohl's solution into the syringe. If the Shohl's solution is to be given by dosing cup, pour the correct amount of Shohl's solution into a dosing cup(s).

3. For dosing via syringe, dispense the Shohl's solution slowly towards your inner cheek. For dosing via dosing cup, drink all of the contents of the cup(s).

4. Check the Study Drug Administration Sheet for the amount of Triferic to be dosed and how many times per day it should be dosed.

5. Open the needed number of Triferic ampules by twisting off the plastic top. Use new ampules for each dose.

6. 5-15 minutes after the dose of Shohl's solution, give yourself the correct amount of Triferic. If the Triferic is to be given by syringe, draw up the correct volume of Triferic into the syringe. If the Triferic is to be given by dosing cup, pour the correct amount of Triferic into a dosing cup(s).

7. For dosing via syringe, dispense the Triferic solution slowly towards your inner cheek. For dosing via dosing cup, drink all of the contents of the cup(s).

8. If you have side effects from either the Shohl's solution or the Triferic, be sure to tell your study doctor. Your study doctor may be able to adjust the dose of your study medication so that it is less bothersome to you.

9. You may stop taking the study medication any time you want. Please tell the study doctor if you stop taking the study medication and why.

APPENDIX 5. STUDY DRUG DOSING SCHEDULES

Ferrous sulfate (Fer-In-Sol®, Mead Johnson, Glenview, IL; 15 mg Fe(II)/mL) will be administered at a dose of 3 mg Fe/kg at two visits during Period 1. When given in conjunction with Shohl's solution, the dose will be given 5-15 minutes after the dose of Shohl's solution.

Citrate (as Shohl's solution, e.g., Oracit®; CMP Pharma, Farmville, NC; hydrous sodium citrate 490 mg/5 mL and citric acid 640 mg/5 mL; 1 mmol citrate/mL) will be administered at 0.67 mmol/kg at two visits during Period 1.

Ferric pyrophosphate citrate (Triferic®; Rockwell Medical, Wixom, MI; 5.44 mg Fe(III)/mL) will be administered at a dose of 3 mg Fe/kg at one visit during Period 1, 5-15 minutes after the dose of Shohl's solution.

Fer-In-Sol

Fer-In-Sol should be administered at a dose of 3 mg Fe/kg body weight according to the following table. If the patient is between body weight categories, use the lower weight category. The dose may be rounded down to the nearest whole mL.

Table 6: Study Drug Dosing

Weight (kg)	Fer-In-Sol (mL)
5.0	1.0
6.0	1.2
7.0	1.4
8.0	1.6
9.0	1.8
10.0	2.0
11.0	2.2
12.0	2.4
13.0	2.6
14.0	2.8
15.0	3.0
20.0	4.0
25.0	5.0
30.0	6.0
35.0	7.0
40.0	8.0
45.0	9.0
50.0	10
55.0	11
60.0	12
65.0	13
70.0	14
75.0	15
80.0	16
85.0	17
90.0	18
95.0	19
≥100.0	20

Shohl's Solution Followed by Fer-In-Sol

Shohl's solution (1 mmol citrate/mL) will be administered at a dose of 0.67 mmol/kg body weight followed 5-15 minutes later by Fer-In-Sol administered at a dose of 3 mg Fe/kg body weight according to the following table. If the patient is between body weight categories, use the lower weight category. The dose may be rounded down to the nearest whole mL.

Table 7: Study Drug Dosing

Weight (kg)	Shohl's Solution (mL)	Fer-In-Sol (mL)
5.0	3.4	1.0
6.0	4.0	1.2
7.0	4.7	1.4
8.0	5.4	1.6
9.0	6.0	1.8
10.0	6.7	2.0
11.0	7.4	2.2
12.0	8.0	2.4
13.0	8.7	2.6
14.0	9.4	2.8
15.0	10	3.0
20.0	13	4.0
25.0	17	5.0
30.0	20	6.0
35.0	24	7.0
40.0	27	8.0
45.0	30	9.0
50.0	34	10
55.0	37	11
60.0	40	12
65.0	44	13
70.0	47	14
75.0	50	15
80.0	54	16
85.0	57	17
90.0	60	18
95.0	64	19
≥100.0	67	20

Shohl's Solution Followed by Triferic

Shohl's solution (1 mmol citrate/mL) will be administered at a dose of 0.67 mmol/kg body weight followed 5-15 minutes later by Triferic administered at a dose of 3 mg Fe/kg body weight according to the following table. If the patient is between body weight categories, use the lower weight category. The dose may be rounded down to the nearest whole mL.

Table 8: Study Drug Dosing

Weight (kg)	Shohl's Solution (mL)	Triferic (mL)
5.0	3.4	2.8
6.0	4.0	3.3
7.0	4.7	3.9
8.0	5.4	4.4
9.0	6.0	5.0
10.0	6.7	5.5
11.0	7.4	6.1
12.0	8.0	6.6
13.0	8.7	7.2
14.0	9.4	7.7
15.0	10	8.3
20.0	13	11
25.0	17	14
30.0	20	17
35.0	24	19
40.0	27	22
45.0	30	25
50.0	34	28
55.0	37	30
60.0	40	33
65.0	44	36
70.0	47	39
75.0	50	41
80.0	54	44
85.0	57	47
90.0	60	50
95.0	64	52
≥100.0	67	55

Periods 2 and 3

During Periods 2 and 3, Shohl's solution (1 mmol citrate/mL) will be administered 3x per day at a dose of 0.67 mmol/kg body weight followed 5-15 minutes later by Triferic according to the following table. If the patient is between body weight categories, use the lower weight category. The dose may be rounded down to the nearest whole mL.

Initially, the dose of study drug will be Shohl's solution 0.67 mmol/kg followed by Triferic 3 mg/kg 3x/day. However, the Triferic dose may be titrated to 2 mg/kg or 1 mg/kg if needed. In addition, the number of doses of study drug may be decreased to 2x/day or 1x/day.

Table 9: Study Drug Dosing, Periods 2 and 3

Weight (kg)	Shohl's Solution (mL)	Triferic 3 mg/kg (mL)	Triferic 2 mg/kg (mL)	Triferic 1 mg/kg (mL)
5.0	3.4	2.8	1.8	0.9
6.0	4.0	3.3	2.2	1.1
7.0	4.7	3.9	2.6	1.3
8.0	5.4	4.4	2.9	1.5
9.0	6.0	5.0	3.3	1.7
10.0	6.7	5.5	3.7	1.8
11.0	7.4	6.1	4.0	2.0
12.0	8.0	6.6	4.4	2.2
13.0	8.7	7.2	4.8	2.4
14.0	9.4	7.7	5.1	2.6
15.0	10	8.3	5.5	2.8
20.0	13	11	7.4	3.7
25.0	17	14	9.2	4.5
30.0	20	17	11	5.5
35.0	24	19	13	6.4
40.0	27	22	15	7.4
45.0	30	25	17	8.3
50.0	34	28	18	9.2
55.0	37	30	20	10
60.0	40	33	22	11
65.0	44	36	24	12
70.0	47	39	26	13
75.0	50	41	28	14
80.0	54	44	29	15
85.0	57	47	31	16
90.0	60	50	33	17
95.0	64	52	35	17
≥100.0	67	55	37	18