Clinical Research Protocol

Single Ascending Dose Study of Intraperitoneal Triferic (Ferric Pyrophosphate Citrate) in Patients on Chronic Peritoneal Dialysis

IND Number:	51,290
Protocol Number:	RMFPC-17
Version:	1.0
Clinical Phase:	1
Investigational Drug:	Triferic (Ferric Pyrophosphate Citrate)
Indication:	Maintenance of Iron and Hemoglobin in CKD-5PD Patients
Sponsor Signatory:	Raymond D. Pratt, MD FACP Chief Medical Officer Rockwell Medical, Inc.
Principal Investigator:	
Original Protocol Date:	21 November 2016

PROTOCOL APPROVAL PAGE

Study Title:	Single Ascending Dose Study of Intraperitoneal Triferic (Ferric Pyrophosphate Citrate) in Patients on Chronic Peritoneal Dialysis
Protocol Number:	RMFPC-17
Version:	1.0
Date of Issue:	21 November 2016
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 (Date)
Chief Medical Officer

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title:	Single Ascending Dose Study of Intraperitoneal Triferic (Ferric Pyrophosphate Citrate) in Patients on Chronic Peritoneal Dialysis
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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 US Food and Drug Administration (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 subjects.
- 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 subjects, 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 FDA, local governing regulatory bodies, and IRB/EC inspectors.

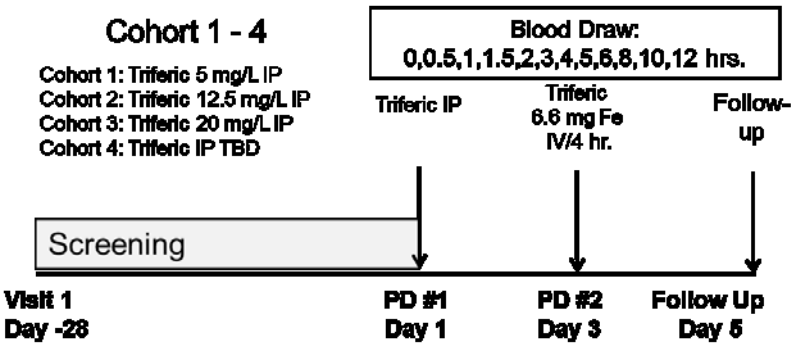
_____ _____

Investigator's Signature Date

_____

Print Name

SYNOPSIS	
PROTOCOL TITLE	Single Ascending Dose Study of Intraperitoneal Triferic (Ferric Pyrophosphate Citrate) in Patients on Chronic Peritoneal Dialysis
PROTOCOL NUMBER	RMFPC-17
SPONSOR	Rockwell Medical, Inc.
INVESTIGATIONAL PRODUCT	Triferic (ferric pyrophosphate citrate)
STUDY OBJECTIVES	**Primary Objective** Determine the pharmacokinetic profile, C_{max} and AUC_{0-t} of Triferic iron administered intraperitoneally in patients with end-stage chronic kidney disease on peritoneal dialysis (CKD-5 PD). **Secondary Objectives** The secondary objectives are: • To determine the dose proportionality of Triferic iron administered via peritoneal dialysate • To estimate the absolute bioavailability Triferic iron administered via peritoneal dialysate • To explore the safety of intraperitoneal Triferic administration in adult CKD-5 PD patients
STUDY DESIGN & DURATION	• Open-label, single ascending dose study. • Up to 4 Cohorts of 6 patients receiving ascending doses of Triferic Intraperitoneally in the PD solution. • Patients on Continuous Cycling Peritoneal Dialysis (CCPD) or Continuous Ambulatory Peritoneal Dialysis (CAPD). • At each treatment visit, the patients will be randomly assigned to receive either a single ascending dose of Triferic administered IP during a long (12 hr.) peritoneal dialysis dwell or a single 6.6 mg dose of Triferic administered IV over 4 hrs. • Blood samples will be obtained at defined times over 12 hours to establish the total serum iron PK of IP Triferic as well as the clinical serum iron profile (sFe, ferritin, TIBC and TSAT). • Peritoneal dialysate samples will be collected prior to and after IP Triferic administration for biocompatibility studies. • Patients will undergo a follow-up visit approximately 1 week after their last dose of study drug. • After analysis of data for Cohort 1 and 2, the blood draw schedule for the remaining cohorts may be changed to reflect the time course of iron absorption and clearance, as well as for patient retention. • Additional cohorts may be added or a cohort deleted based on the serum iron profiles and or safety parameters. • Duration of Study: Each Cohort up to 5 weeks including

	Screening, Treatment and Follow-up. Study Design Schematic: 
NUMBER OF PLANNED SUBJECTS	Approximately 24 Patients will be stratified based on PET tests administered within 6 months of enrollment. Approximately 12 patients with average to high transport and 12 with low average to low transport will be enrolled.
INVESTIGATIONAL SITE	Multicenter
PARTICIPATING COUNTRIES	United States
PATIENT POPULATION	Stable adults with CKD-5 PD
INCLUSION AND EXCLUSION CRITERIA	**Inclusion Criteria** Patients must meet <u>all</u> of the following criteria to be eligible for inclusion in the study: 1. The patient must be able to provide informed consent and have personally signed and dated the study written informed consent document before completing any study-related procedures. 2. The patient must be 18-75 years of age inclusive at the time of consent. 3. The patient must have a diagnosis of End Stage Renal Disease and have been on stable Peritoneal Dialysis for at least 3 months (CAPD or CCPD) prior to Screening using standard PD solution. 4. The patient must be in a stable clinical condition during the four weeks immediately prior to Screening Period as demonstrated by medical history, physical examination and laboratory testing. 5. The patient must have a blood hemoglobin concentration above 9.5 g/dL. 6. The patient must have a TIBC of ≥ 175 µg/dL.

	7. The patient must not have experienced peritonitis episodes in the last 3 months prior to Screening. 8. The patient must agree to discontinue all iron preparations for 14 days prior to Study PD #1/Day 1. 9. Female patients must be nonpregnant and not breastfeeding. They must either have been amenorrheic for the past year or agree to not become pregnant by continuous use of an effective birth control method acceptable to the Investigator for the duration of their participation in the study. **Exclusion Criteria** Patients will <u>not</u> be eligible for inclusion in the study if <u>any</u> of the following criteria apply: 1. The patient has had an RBC or whole blood transfusion within 4 weeks prior to Screening. 2. The patient has had administration of IV or oral iron supplements (including multivitamins with iron) within 14 days prior to Study PD #1/Day 1. 3. The patient has known active bleeding from any site (e.g., gastrointestinal, hemorrhoidal, nasal, pulmonary, etc.). 4. The patient has a living kidney donor identified or living-donor kidney transplant scheduled to occur during study participation. (Note: Patients awaiting deceased-donor transplant need not be excluded.) 5. The patient is scheduled to have a surgical procedure during the study. 6. The patient has had a hospitalization within the 4 weeks prior to Screening (except for vascular access surgery) that, in the opinion of the Investigator, confers a significant risk of hospitalization during the course of the study. 7. The patient has a history of noncompliance with the dialysis regimen in the opinion of the Investigator. 8. The patient has a known active ongoing inflammatory disorder (other than CKD), such as systemic lupus erythematosus, rheumatoid arthritis, or other collagen-vascular disease, that currently requires systemic anti-inflammatory or immunomodulatory therapy. 9. The patient has any current febrile illness (e.g., oral temperature ≥100.4°F, 38.0°C). (The patient may subsequently become eligible at least 1 week after resolution of the illness.) 10. The patient has known bacterial, tuberculosis, fungal, viral, or parasitic infection requiring anti-microbial therapy or anticipated to require anti-microbial therapy during the patient's participation in this study. 11. The patient is known to be positive for HIV, hepatitis B, or

	hepatitis C (viral testing is not required as part of this protocol). 12. The patient has cirrhosis of the liver based on histological criteria or clinical criteria (e.g., presence of ascites, esophageal varices, multiple spider nevi, or history of hepatic encephalopathy). 13. The patient has ALT and/or AST levels consistently greater than twice the upper limit of normal at any time during the two months prior to Study PD #1/Day 1. 14. The patient currently has any malignancy other than basal or squamous cell skin cancer. 15. The patient has a history of drug or alcohol abuse within the 6 months prior to Screening. 16. The patient participated in an investigational drug study within 30 days prior to Study PD #1/Day 1. 17. The patient has any condition that, in the opinion of the Investigator, would make it unlikely for the patient to complete the study.
PLANNED ANALYSES	• Pharmacokinetics (PK) of serum iron following Triferic administration IP • Estimate absolute bioavailability of iron via PD ○ By proportionality of IP (C_{max} and AUC_{0-t}) to IV (C_{max} and AUC_{0-t}) ○ By quantitating iron remaining in the PD solution compared to that infused.
SAFETY ENDPOINTS	• The incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious AEs (TESAEs)
PHARMACOKINETIC ENDPOINTS	The primary PK analysis will be performed on the total serum iron (sFe). Non-compartmental PK parameters will be estimated for total serum iron. Pharmacokinetic parameters will be determined using all appropriate available data from each Cohort. The key PK parameters listed below will be calculated for total serum iron as data permit and as appropriate. The following iron parameters will be determined by obtaining blood at various times after Triferic administration: • Total serum iron (sFe) The key PK parameters listed below will be calculated for total serum iron as data permit and as appropriate. Additional details of the PK analysis will be provided in the PK analysis plan.
	C_{max} — The maximum drug concentration in serum determined directly from individual

		concentration-time data
	T_{max}	The observed time to reach maximum concentration
	$AUC_{(0-t)}$	The area under the serum concentration-time curve from time zero to the time of the last quantified concentration, calculated using the linear-up/log-down trapezoidal rule
	$AUC_{(0-end)}$	The area under the serum concentration-time curve from time zero to the end of each study drug infusion, calculated using the linear-up/log-down trapezoidal rule
	λz	The terminal phase rate constant, estimated by linear regression through the terminal phase of the log concentration-time profile
	$t_{½}$	The terminal phase half-life, calculated as: $t½ = \frac{\ln(2)}{\lambda z}$
	AUC_{inf}	The area under the serum concentration-time curve from time zero extrapolated to infinity, calculated using the linear-up/log-down trapezoidal rule
	CL or CL/F	Total systemic clearance, calculated as: Total Dose/AUC_{last}

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ABBREVIATIONS

AE	adverse event
ALT	alanine transaminase (SGPT)
AST	aspartate transaminase (SGOT)
ATC	anatomical therapeutic chemical
AUC	area under the curve
AV	arteriovenous
BMI	body mass index
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CCPD	Continuous cycling peritoneal dialysis
CFR	Code of Federal Regulations
Chem-20	standard comprehensive metabolic panel laboratory test
CKD	chronic kidney disease
CKD-5HD	chronic kidney disease stage 5, hemodialysis-dependent
CKD-5 PD	chronic kidney disease stage 5, peritoneal dialysis-dependent
CL	total systemic clearance
C_{max}	peak serum concentration, observed
CNS	central nervous system
CRF	case report form
CRP	C-reactive protein
CV	cardiovascular
D5W	dextrose 5% in water
EC	ethics committee
ECG	electrocardiogram
ENT	ear, nose, and throat
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
Fe	Iron
FPC	Triferic (ferric pyrophosphate citrate)
GCP	Good Clinical Practice
GI	gastrointestinal
HD	hemodialysis
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act (of 1996)
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IND	investigational new drug
IP	intra-peritoneal

IRB	institutional review board
IV	intravenous/intravenously
Kt/V	dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water
$K_{ID}t/V$	online dialyzer clearance measured using ionic dialysance multiplied by dialysis time, divided by patient's total body water
LPI	labile plasma iron
λz	terminal phase rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NTBI	non-transferrin-bound Iron
PD	peritoneal dialysis
PHI	protected health information
PK	pharmacokinetic(s)
RBC	red blood cell/red blood cell count
RE	reticuloendothelial
RES	reticuloendothelial system
SAE	serious adverse event
SAP	statistical analysis plan
$t_{½}$	terminal phase half-life
TBD	to be determined
TBI	transferrin-bound iron
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Tf	transferrin
TIBC	total iron-binding capacity
$TIBC_{Tf}$	total iron-binding capacity based on transferrin
$TIBC_{UIBC}$	total iron-binding capacity based on UIBC
T_{max}	time to peak serum concentration, observed
TSAT	transferrin saturation
$TSAT_{Tf}$	transferrin saturation based on transferrin
$TSAT_{UIBC}$	transferrin saturation based on UIBC
UIBC	unsaturated iron-binding capacity
US	United States
USP	United States Pharmacopeia
Vz/F	volume of distribution
WBC	white blood cell/white blood cell count
WHO	World Health Organization

1. INTRODUCTION

1.1. Current Therapies/Treatments

The goals of iron therapy in adult patients with chronic kidney disease receiving chronic dialysis are to avoid depletion of iron stores, prevent iron-restricted erythropoiesis and maintain hemoglobin levels while minimizing erythropoiesis-stimulating agent (ESA) therapy and avoiding blood transfusions that may sensitize patients and limit chances for a kidney transplant[1].

Iron supplementation is provided to patients receiving maintenance peritoneal dialysis (PD) with intravenous (IV) iron. However, these IV iron products are ferric-hydroxide cores within a carbohydrate shell that do not donate iron directly to transferrin. Instead, the complexes must first be taken up by reticuloendothelial (RE) macrophages that free the iron from the carbohydrate shell for subsequent export via ferroportin. As a result, a considerable portion of the iron derived from these iron-carbohydrate complexes is sequestered within macrophages and is not readily available for transport to the erythroid marrow for use in hemoglobin synthesis. Patients receiving PD generally do not have high flow vascular access. Thus, administration of IV iron via peripheral veins can be challenging and may also contribute to venous sclerosis.

Compared to hemodialysis (HD) patients, PD patients have less blood loss; however, they do require iron supplementation along with ESA administration to maintain hemoglobin concentrations. Currently, PD patients must attend the clinic periodically for IV iron administration. If an iron preparation is available for intraperitoneal (IP) administration, this would allow patients to receive needed iron and avoid the potential risks of IV iron administration including anaphylaxis and injection site reactions.

There are no specific guidelines for the administration of iron to PD patients. Recent trends indicate an increase in the use of IV iron in PD patients. PD patients received an average of 1 dose IV iron /month with a mean value of 127 to 151 mg Fe per dose.[2] Patients receiving PD also have elevated hepcidin concentrations which result in the impairment of iron absorption from the duodenum and the release of iron from the reticuloendothelial system. This hepcidin elevation impairs the utilization of IV iron from stores due to the block of ferroportin, the sole iron transporter in macrophages of the RES.

Triferic has been developed as a maintenance iron therapy. Triferic is a form of protected iron, and can be added to the PD solution. Triferic can diffuse across the peritoneal membrane to the systemic circulation. Triferic administered parenterally does not require processing by macrophages, and it donates iron directly to transferrin for optimal utilization in erythropoiesis, avoiding sequestration within the RES.

In adults, Triferic, administered at each HD session via dialysate, has been shown to maintain hemoglobin concentrations without increasing iron stores. Triferic does this by delivering 5-7 mg of elemental iron with each HD session, the amount typically lost as a consequence of retained blood in the dialyzer circuit plus other HD- and uremia-associated blood losses.

The safety profile of Triferic in controlled clinical studies is similar to that of patients receiving placebo. There were few related adverse events (AEs) and no anaphylaxis in over 100,000 individual patient administrations. Safety data are included in the approved US package insert and in the Investigator's Brochure. Triferic added to the bicarbonate concentrate for hemodialysis has been approved as the first maintenance iron therapy in adult CKD-5HD patients.

1.2. Description of Drug

Triferic (ferric pyrophosphate citrate; FPC) is a water-soluble, mixed-ligand iron salt in which iron(III) is bound to pyrophosphate and citrate. It has a molecular formula of $Fe_4(C_6H_4O_7)_3(H_2P_2O_7)_2(P_2O_7)$ and a relative molecular weight of approximately 1313 Da. Triferic solution is a clear, slightly yellow-green sterile solution containing 27.2 mg iron(III) per 5 mL (5.44 mg iron (III) per mL) filled in low density polyethylene (LDPE) ampules.

1.3. 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	Number of Subjects /Treatment Duration
SFP-8	US 1 site	Phase 1/2, 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 7.5 mg/4 hr 10 mg/4 hr 15 mg/12 hr 20 mg/12 hr Placebo	48 Single ascending dose
FPC-12	US 1 site	Phase 1, two sequential doses in healthy volunteers	Triferic 6 mg IV over 3 hrs Triferic 35 µg/kg IV push	12 2 days (1 dose per day)

Protocol Number	Country (# sites)	Study Design and Phase	Treatment Groups	Number of Subjects /Treatment Duration
FPC-16	US 1 Site	Phase 1, 3 period crossover Preliminary BE study	Triferic 2 µM (110 µg/L) via HD Triferic 6.6mg/3 hr IV pre-dialyzer Triferic 6.6 mg/3 hr post dialyzer	13 3 day (1 dose/day)
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, randomized 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 1 site	Phase 2, randomized, double-blind, parallel group, placebo-controlled	Triferic 2 µM (110 µg/L) Placebo	11 36 weeks
SFP-4-RC	NA 44 sites	Phase 3, randomized, single-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, single-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, randomized, 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

1.4. Non-Clinical Studies of Peritoneal Administration of Triferic

1.4.1. *In-vitro* Compatibility Study:

The compatibility study was designed to evaluate the physical compatibility and stability of Triferic added to dextrose and icodextrin containing peritoneal dialysate solutions over a 30 day time period.

The compatibility study was performed on two different peritoneal dialysis solutions. Dianeal contains dextrose as an osmotic agent and Extraneal contains icodextrin as an osmotic agent. All peritoneal dialysis fluids are non-pyrogenic, contain no bacteriostatic or antimicrobial agents and are packaged in polyvinyl chloride containers. A summary of the study conditions are listed in Table 2.

Table 2: Compatibility Study Materials

					mEq/L				
	Dextrose g/dL	Icodextrin g/dL	Triferic	pH	Na	Ca	Mg	Cl	Lactate
Dianeal 1.5%	1.5		10 mg Fe/2 L 50 mg Fe/2L	5.2	132	3.5	0.5	96	40
Dianeal 4.5%	4.5		10 mg Fe/2 L 50 mg Fe/2L	5.2	132	3.5	0.5	96	40
Extraneal 7.5%		7.5	10 mg Fe/2 L 50 mg Fe/2L	5.0	132	3.5	0.5	96	40

Triferic was compatible with all PD solutions at 5 mg/L and 25 mg/L ferric iron concentrations. All testing over the 30 day period indicated stability of Triferic in PD solutions. The iron concentrations and pyrophosphate concentrations were stable at target for up to 30 days.

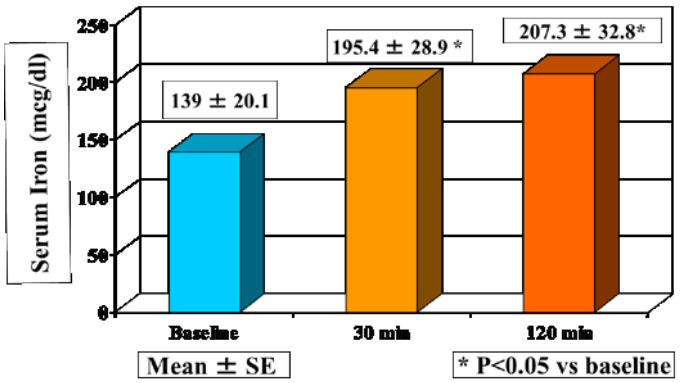
1.4.2. Animal Studies:

1.4.2.1. Study 1: Intraperitoneal administration of soluble ferric pyrophosphate (SFP) in rabbits.

The results of Study 1 demonstrated that SFP (5 mg Fe/L in 2.5% Dianeal) was absorbed from the peritoneum resulting in an increase in in serum Fe from 139.6 ± 20.1 µg/dL to 195.4 ± 28.9 µg/dL after 30 minutes. Concomitantly, the TSAT increased from 53.2% to 73.1% over the same time interval (refer to

Figure 1). Results at 2 hours were similar to the results at 30 minutes indicating a continued transfer of iron from peritoneum to blood.

Figure 1: Serum iron concentrations after administration of PD fluid in Rabbits.



1.4.2.2. Study 2: Four week intraperitoneal GLP toxicity study of Triferic administered to rats.

Study 2 evaluated the toxicity and toxicokinetics of Triferic when administered to iron-replete rats for four weeks as three weekly intraperitoneal doses via a targeted 1-hour infusion. Reversibility of toxicity was evaluated during a four-week recovery period following the final dose Triferic, and effects on serum iron parameters were evaluated. The study was conducted under GLP conditions. Three (3) different concentrations of Triferic iron in 1.5% Dianeal PD fluid were studied and compared to a control group receiving 1.5% Dianeal alone.

Results:

Rats tolerated intraperitoneal doses of Triferic three times a week for four weeks at all dose levels (i.e., at up to 450 µg Fe/kg). There were no clinical signs of toxicity and no effects on body weight gain (growth), food consumption, or hematology, coagulation, clinical chemistry, or urinalysis parameters. Administration of Triferic did not produce macroscopic pathologic findings or affect organ weights at necropsy. The only findings were swellings in the area of the subcutaneous access port and entanglement of the catheter tip in the omentum and/or abdominal fat, which were present in all groups, including the vehicle control group.

No test article-related findings were present in this study. The majority of histologic findings were confined to the region of the treatment site, in addition to immediately adjacent tissues (omentum and/or testicular/ovarian adipose tissue). Findings included chronic active inflammation of the peritoneum and adjacent fascia, variable stages of fibroplasia/fibrosis, and neovascularization. These findings are consistent with a foreign body reaction secondary to catheter/port placement and were recorded collectively as “mixed cell inflammation” with severity grades reflecting the density of the inflammatory infiltrate, amount and maturity of fibrosis, and/or degree of tissue involvement. Findings were relatively localized to the region of the treatment site with only rare incidences of distant involvement of the peritoneum or omentum. No dose-related increases in incidence or severity of any of the findings

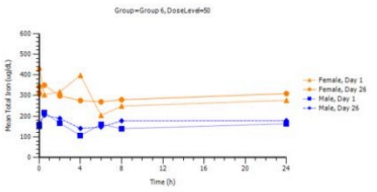
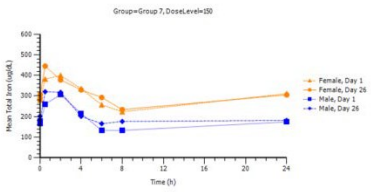
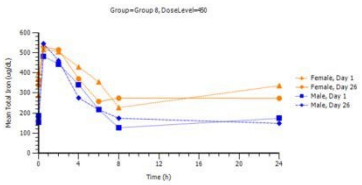
were noted. Findings at the treatment sites of the recovery groups were similar in incidence and severity, as compared to the main study groups.

Toxicokinetic Findings

Intraperitoneal administration of Triferic increased total serum iron concentration in a dose-related manner, and the effects were similar in both sexes and after the first and last doses. At Triferic dose levels of 50, 150, and 450 µg Fe/kg, baseline-adjusted AUC values increased proportionally with dose level after the first dose (162, 489, and 1450 h*µg/dL, respectively) and somewhat less than proportionally after the last dose (142, 362, and 778 h*µg/dL, respectively).

Transferrin saturation also increased in parallel with total serum iron concentration, reaching peak values of 55%, 65%, and 88%, respectively, after the first dose and 51%, 71%, and 78%, respectively, after the last dose. Toxicokinetic findings indicate that C_{max} is reached between 1 and 3 hours and returns to baseline by 8-10 hours after the start of the infusion at the first and last study period as shown in Figure 2. The rapid clearance of iron is similar to that observed after the dialytic infusion of Triferic iron and the IV infusion of Triferic to healthy volunteers (t½ ≅1.7 hr).

Figure 2: Total Serum Iron on Day 1 and 26 According to Dose Group

Dose 50 µg/kg 5 mg Fe/L PD Fluid	Dose 150 µg/kg 15 mg Fe/L PD Fluid	450 µg/kg 45 mg Fe/L PD Fluid
		

Conclusions:

This GLP peritoneal toxicology study demonstrated that Triferic administered in peritoneal dialysis fluid is able to cross the peritoneal membrane and donate iron to the systemic circulation in rats. Triferic demonstrated no adverse effects on peritoneal or omental histopathology. The toxicokinetic analysis demonstrated a dose proportional absorption of Triferic iron which was essentially unchanged after 30 days of repeated administration. The results of this study support administration of Triferic via the peritoneal dialysate in humans.

1.5. Rationale for the Current Study

Peritoneal dialysis patients have need of a convenient and safer alternative to IV iron for the management of their anemia. This study will examine different doses of Triferic administered via the PD fluid to assess the transfer of iron to the systemic circulation.

1.6. Justification for Dose

The doses chosen for this study are within the range studied in the GLP peritoneal toxicity study and are expected to result in sufficient mass transfer of iron from peritoneum to the circulation.

2. STUDY OBJECTIVES

2.1. Primary Objective

Determine the pharmacokinetic profile, C_{max} and AUC_{0-t} of Triferic administered intraperitoneally.

2.2. Secondary Objectives

The secondary objectives are:

- To determine the dose proportionality of Triferic iron administered via peritoneal dialysate
- Estimate absolute bioavailability of iron via PD
    - By proportionality of IP (C_{max} and AUC_{0-t}) to IV (C_{max} and AUC_{0-t})
    - By quantitating iron remaining in PD the PD solution compared to that infused corrected To explore the safety of intraperitoneal Triferic administration in adult CKD-5 PD patients
- To investigate the safety of intraperitoneal Triferic administration in adult CKD-5 PD patients

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

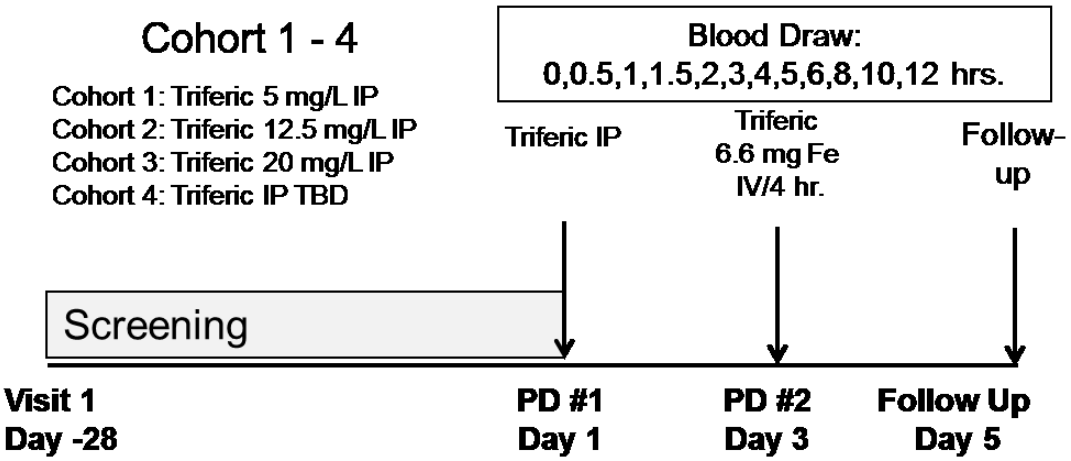
This is a Phase 1, open-label, single ascending dose study to assess the safety and pharmacokinetics of Triferic administered via PD to iron-replete adult end-stage renal disease patients on maintenance peritoneal dialysis (CKD-5PD). Approximately 24 patients will be studied.

Patients will be screened within 28 days of Baseline. All patients must provide informed consent to enter Screening. Patients will be advised to discontinue all iron supplements including multivitamins with iron. The study will be conducted as an outpatient study. Patients will attend the clinic for two (2) 12 hour treatment periods with a 48 hour interval between test article administrations. Patients will be randomly assigned to receive either a single dose of Triferic in the peritoneal dialysis solution or a single IV dose of Triferic 6.6 mg over a 4 hour period.

Patients begin a long dwell time (12 hours) from approximately 08:00 to 20:00 hours on each day of dosing. After completion of PK measurements patient resume their usual dialysis prescription until the next scheduled administration of test article.

A follow-up assessment will be conducted within 1 week after the last administration of test article to assess safety parameters.

Figure 3: Study Design Schematic



3.2. Endpoints

3.2.1. Pharmacokinetic Endpoints

3.2.1.1. Primary Endpoints

This is an exploratory PK study. The primary objective is to characterize the PK of Triferic iron following PD administration. This will be done by assessing the mean absolute C_{max}, AUC_{0-t}, AUC_{0-end} and AUC_{inf} of serum iron obtained with administration of Triferic via PD and IV. Additional parameters to be determined may include T_{max}, CL, λ_z, and $t_{½}$.

3.2.1.2. Secondary Endpoints

The secondary endpoints are as follows:

- Dose proportionality of Triferic iron will be determined using the C_{max} and AUC parameters for serum iron.
- The mass balance of iron absorbed from the PD fluid will be determined by two methods:
    - The absolute bioavailability of iron from Triferic administered via PD.

- The difference in mass of Triferic iron in the PD fluid infused and removed at the end of the dwell will be measured to determine the mass balance.

3.2.2. Safety Endpoints

The safety endpoints are as follows:

- The incidence of treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (TESAEs)

4. SELECTION OF STUDY POPULATION

A total of 18 completed subjects will be required if only 3 doses are studied. Up to 30 completed subjects may be required if two additional cohorts are needed after assessment of safety and tolerability of planned doses. Depending on the safety profile the study may be terminated at the discretion of the Sponsor after the first cohort has completed the study. Doses may be changed depending on the PK or safety results, to be assessed after each cohort completes the study. The Sponsor may change the times for the PK draws after cohort 1 or 2 have completed for patient convenience and compliance.

4.1. Inclusion Criteria

Patients must meet <u>all</u> of the following criteria to be eligible for inclusion in the study:

1. The patient must be able to provide informed consent and have personally signed and dated the study written informed consent document before completing any study-related procedures.
2. The patient must be 18-75 years of age inclusive at the time of consent.
3. Have a diagnosis of End Stage Renal Disease and have been on stable Peritoneal Dialysis for at least 3 months (CAPD or CCPD) prior to Screening using standard PD solution.
4. Be in a stable clinical condition during the four weeks immediately prior to Screening Period as demonstrated by medical history, physical examination and laboratory testing
5. Have a blood hemoglobin concentration above 9.5 g/dL.
6. Have a TIBC of ≥ 175 µg/dL.
7. Have not experienced peritonitis episodes in the last 3 months prior to Screening.
8. The patient must agree to discontinue all iron preparations for 14 days prior to Study PD #1/Day 1.
9. Female patients must be nonpregnant and not breastfeeding. They must either have been amenorrheic for the past year or agree to not become pregnant by continuous use of an effective birth control method acceptable to the Investigator for the duration of their participation in the study.

4.2. Exclusion Criteria

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

1. The patient has had an RBC or whole blood transfusion within 4 weeks prior to Screening.
2. The patient has had administration of IV or oral iron supplements (including multivitamins with iron) within 14 days prior to Study PD #1/Day 1.
3. The patient has known active bleeding from any site (e.g., gastrointestinal, hemorrhoid, nasal, pulmonary, etc.).
4. The patient has a living kidney donor identified or living-donor kidney transplant scheduled to occur during study participation. (Note: Patients awaiting deceased-donor transplant need not be excluded.)
5. The patient is scheduled to have a surgical procedure during the study.
6. The patient has had a hospitalization within the 4 weeks prior to Screening (except for vascular access surgery) that, in the opinion of the Investigator, confers a significant risk of hospitalization during the course of the study.
7. The patient has a history of noncompliance with the dialysis regimen in the opinion of the Investigator.
8. The patient has a known ongoing inflammatory disorder (other than CKD), such as systemic lupus erythematosus, rheumatoid arthritis, or other collagen-vascular disease, that currently requires systemic anti-inflammatory or immunomodulatory therapy.
9. The patient has any current febrile illness (e.g., oral temperature ≥100.4°F, 38.0°C). (Patients may subsequently become eligible at least 1 week after resolution of the illness.)
10. The patient has known bacterial, tuberculosis, fungal, viral, or parasitic infection requiring anti-microbial therapy or anticipated to require anti-microbial therapy during the patient's participation in this study.
11. The patient is known to be positive for HIV, hepatitis B, or hepatitis C (viral testing is not required as part of this protocol).
12. The patient has cirrhosis of the liver based on histological criteria or clinical criteria (e.g., presence of ascites, esophageal varices, multiple spider nevi, or history of hepatic encephalopathy).
13. The patient has ALT and/or AST levels consistently greater than twice the upper limit of normal at any time during the two months prior to Study PD #1/Day 1.

14. The patient currently has any malignancy other than basal or squamous cell skin cancer.
15. The patient has a history of drug or alcohol abuse within the 6 months prior to Screening.
16. The patient participated in an investigational drug study within 30 days prior to Study PD #1/Day 1.
17. The patient has any condition that, in the opinion of the Investigator, would make it unlikely for the patient to complete the study.

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 treatment-emergent AE (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 TEAE 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 after enrollment will not be replaced under this protocol. Patients who withdraw or are withdrawn prior to enrollment will be considered screen failures and will be replaced.

5. TREATMENTS

5.1. Treatments Administered

Triferic will be administered by qualified study personnel only in accordance with the procedures described in this protocol.

5.2. Identity of Investigational Products(s)

Triferic is supplied as sterile 5 mL or 50 mL ampules containing 5.44 mg/mL of iron in water for injection. The actual content of Triferic iron from the COA will be used to calculate the dose to be administered.

5.2.1. Labeling

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
- Storage information

5.2.2. Storage and Handling

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° to 30°C [59° to 86°F] [See USP Controlled Room Temperature]).

5.3. Method of Assigning Patients to Treatment Groups

5.3.1. Treatment Assignment/Randomization

This is a multiple period cohort study. Each patient within a cohort will be randomized to receive either a single dose of Triferic in the peritoneal dialysis solution, or a single IV dose of Triferic 6.6 mg over a 4 hour period. The anticipated doses of Triferic IP are:

Cohort 1: Triferic 5 mg/L in peritoneal dialysis solution

Cohort 2: Triferic 12.5 mg/L in peritoneal dialysis solution

Cohort 3: Triferic 20 mg/L in peritoneal dialysis solution

Cohort 4: Triferic XX mg/L in peritoneal dialysis solution depending on the results from previous cohorts iron profiles and safety findings. The IP dose of Triferic in Cohort 4 may be higher or lower than the proposed doses in Cohorts 2 and 3 and will be determined by the Sponsor after consultation with the study investigators.

Cohort 5: (If needed) Triferic XX mg/L in peritoneal dialysis solution depending on the results from previous cohorts iron profiles and safety findings. The IP dose of Triferic in Cohort 5 may be higher or lower than the proposed doses in Cohorts 2, 3 and 4 and will be determined by the Sponsor after consultation with the study investigators.

See Appendix 4: Triferic Dosing Solution Preparation.

5.4. Selection of Doses in the Study

The rationale for the doses chosen in this study has been presented in Section 1.5. This is an exploratory study to determine the dose range and PK of Triferic administered IP to adult patients with CKD-5 PD. The doses chosen are within the

range of those studies in the rat GLP toxicology study and have been found to not induce any local toxicity and are lower than doses that are well tolerated.

5.5. Selection and Timing of Dose for Each Patient

Each treatment will be administered starting at approximately 8 AM on the applicable study day for each patient.

5.6. Procedures for Blinding

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

5.7. Procedures for Randomization

The order of administration of test article will be determined by a pre-prepared randomization table.

5.8. Prior and Concomitant Therapy

5.8.1. Prior Therapy

All prescription and non-prescription medications (including multivitamins and oral and IV iron products) taken within 28 days prior to Study PD #1/Day 1 will be documented in source documents and the case report form (CRF) (based on patient report and/or medical records).

Red blood cell and whole blood transfusions are prohibited from 4 weeks prior to Screening and during the study. The date of Screening is considered to be the date that the first study-related Screening assessment is performed. Should a patient require a red blood cell or whole blood transfusion during the study, they will be removed from participation.

5.8.2. Concomitant Therapy

All prescription and non-prescription medications taken from 28 days prior to Study PD #1/Day 1 to Follow-up must be documented in the source documents and CRF.

5.8.3. Prohibited Medications

Oral and IV iron products are prohibited from 14 days prior to Study PD #1/Day 1 until all blood samples have been collected for each subject at Study PD #2. This includes oral multivitamins containing iron.

5.9. Treatment Compliance

Because this is a parenteral administration study, the site is responsible for documenting compliance with study drug administration.

5.9.1. Study Drug Accountability

Study drug will be administered in accordance with the procedures of this protocol. Only authorized site personnel may supply or administer 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);
- Initials of individual dispensing study drug; and
- Compliance assessment.

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 PROCEDURES

6.1. Study Periods and Procedures

A time and events schedule is provided in **Appendix 1** (Table 3).

Screening will occur on Study Day -28 through Study Day -1.

The first dose of study drug will be administered on Day 1. The second dose of study drug will be administered on Day 3. The Follow-up visit is expected to occur within 1 week following Day 3.

Please note that for any visit, if the visit is missed, or if the patient shows up too late to begin PD at 8 AM and/or the Triferic infusion is interrupted for more than 15 minutes, then the visit may be rescheduled to occur within the next 30 days. If Triferic was being administered, the administration should be discontinued and PK and serum iron profile samples should be drawn immediately, and no further PK or serum iron profile samples should be collected for that day.

6.1.1. Screening Period (Study Day -28 through Study Day -1)

The Screening Visit (Day -28) should be conducted within 28 days prior to admission to the clinical research center (Study Day -1). 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:

- Obtain informed consent from the patient (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 all current medications, and also record any other medications taken within 28 days prior to Study PD #1/Day 1
- Record the date of the patient's last RBC or whole blood transfusion
- Record height and weight
- Record vital signs (blood pressure, pulse, and temperature)
- Perform a physical examination
- Record ECG
- Collect laboratory samples (including hematology, Chem-14, CRP, pregnancy test (if applicable) and the serum iron profile) if not available within the last 30 days.
- Confirm patient meets all assessable eligibility criteria
- Schedule the next study visit (clinical research center admission Day -1) to occur within 28 days after Screening. Provide instruction to patients to discontinue any prohibited medications such as oral iron supplements and multivitamins with iron.

6.1.2. Day -1 Enrollment

- Assess and record medical conditions
- Record medications
- Perform a final review of inclusion/exclusion criteria and enroll eligible patients into the study
- Schedule the next visit for administration of test article.

6.1.3. Triferic IP (Day 1 or Day 3, depending on randomization)

The exact time (clock time) of infusion start and stop as well as each blood sample collection must be recorded.

PRE-DIALYSIS

- The site pharmacist will prepare the peritoneal dialysis solution under aseptic conditions (Appendix 4: Triferic Dosing Solution Preparation) at the appropriate dose for the cohort.
- Retain a 50 mL sample of PD fluid for analysis of iron content.
- Weigh the bag of dialysate after removal of the baseline 50 mL sample and record to the nearest gram.
- Record vital signs (blood pressure and pulse) within 10 minutes of starting PD.
- Collect a serum iron profile (sFe, ferritin, TIBC, and TSAT) to be sent to the clinical laboratory, a time = 0 PK blood sample, and a hepcidin sample at approximately 8 AM (within 5 minutes prior to the start of PD) as indicated in Appendix 3.

- The patient will drain the PD fluid from the abdomen and infuse the PD fluid containing Triferic according to their standard routine.
- Weigh the patient after the dialysis fluid is drained and prior to infusing the PD fluid with test article.
- The following samples will be collected from the drained baseline bag of PD fluid that does not contain Triferic:
    - 50 mL to send to the lab for a cell count and differential
    - 50 mL to be stored according to the instructions in Appendix 4 for analysis of fluid iron content, and
    - Six (6) 15-mL samples to be frozen at -80 for future analysis.

DURING DIALYSIS

- Collect blood samples for PK and serum iron profile as indicated in Appendix 2 (PK, Serum Iron Profile, and Hepcidin Sample Collection Schedule).
- Record vital signs (blood pressure, pulse) every 2 hours during PD.
- Assess and record AEs
- At the end of the 12 hour dwell, the patient will drain the PD fluid and cap off or infuse the next bag of PD solution per their standard routine.
- Weigh the drained peritoneal dialysis solution and record to the nearest gram.
- The following samples will be collected from the drained bag of PD fluid that contains Triferic:
    - 50 mL to send to the lab for a cell count and differential
    - 50 mL to be stored according to the instructions in Appendix 4 for analysis of fluid iron content, and
    - Six (6) 15-mL samples to be frozen at -80 for future analysis.
- Remind patients to continue not to take any prohibited medications, such as oral iron supplements and multivitamins with iron.
- Schedule the next visit.

6.1.4. Triferic 6.6 mg IV/4 hours (Day 1 or Day 3, depending on randomization)

PRE-DIALYSIS

- Assess and record AEs
- Record medications
- Insert an IV in a peripheral vein and keep open with an infusion of D5/W.
- The patient should then drain the PD fluid from the abdomen and infuse standard PD fluid according to their usual routine.
- Weigh the patient after the dialysis fluid is drained and prior to infusing the standard PD fluid.
- The following samples will be collected from the drained baseline bag of PD fluid that does not contain Triferic:

  - 50 mL to send to the lab for a cell count and differential
  - 50 mL to be stored according to the instructions in Appendix 4 for analysis of fluid iron content, and
  - Six (6) 15-mL samples to be frozen at -80 for future analysis.
- Record vital signs (blood pressure and pulse) within 10 minutes of starting PD.
- Collect a serum iron profile (sFe, ferritin, TIBC, and TSAT) to be sent to the clinical laboratory, a time=0 PK blood sample, and a t = 0 hepcidin sample at approximately 8 AM (within 5 minutes prior to the start of PD) as indicated in Appendix 3.

DURING DIALYSIS

- Begin the patient's usual PD at approximately 08:00.
- At the same time that PD is started, begin administration of Triferic 6.6 mg intravenously over 4 hours. See Appendix 4 for details of the preparation of Triferic dosing solutions. The rate of infusion should be adjusted to complete the infusion of 6.6 mg Triferic iron over 4 hours. Record the actual start time and stop time of the Triferic IV infusion.
- Collect blood samples for PK and serum iron profile as indicated in Appendix 2 (PK, Serum Iron Profile, and Hepcidin Sample Collection Schedule).
- Record vital signs (blood pressure, pulse) every 2 hours during PD.
- Assess and record AEs.
- At the end of the infusion, drain the PD fluid and reinfuse new fluid per the patient's usual routine.
- The following samples will be collected from the drained bag of PD fluid:
  - 50 mL to send to the lab for a cell count and differential
  - 50 mL to be stored according to the instructions in Appendix 4 for analysis of fluid iron content, and
  - Six (6) 15-mL samples to be frozen at -80 for future analysis.
- Confirm the scheduling next visit.

6.1.5. Follow-up (Study Day 5-8)

NOTE: Patients who are discontinued or withdraw from this study prior to Follow-up are to have Follow-up procedures and evaluations performed at the time of discontinuation or withdrawal.

The following assessments are to be completed during Follow-up:

- Assess and record AEs
- Record concomitant medications
- Physical exam
- Record vital signs (blood pressure, pulse, and temperature)
- Collect safety laboratory samples (including hematology, Chem-14, the serum iron profile) if required to assess AEs

- Discharge patient from the study

6.2. Study Measurements and Assessments

PK samples will be prepared and shipped to a central bioanalytical laboratory for analysis of the total serum iron profile. Safety laboratory samples (including serum chemistry, hematology, pregnancy CRP, and serum iron profile) will be sent to a central clinical laboratory. Dosing solution samples will be sent to a central bioanalytical laboratory for analysis. Baseline and post-dose PD fluid samples will be sent to the central clinical laboratory for analysis of cell count and differential. Hepcidin samples will be analyzed by Mass Spectroscopy at the laboratory of Dorine Swinkels (Hepcidinalysis.com).

6.2.1. Assessment of Pharmacokinetics

The primary PK assessment for each dose level will be determined from samples obtained during PD # 1 and PD #2 for each Cohort.

The PK samples will be obtained according to the schedule in **Appendix 2** and will be analyzed for the iron profile at each time point.

The following serum iron profile values will be measured by the central clinical laboratory at the time points indicated in Appendices 1 and 2:

- Total serum iron
- Ferritin
- TIBC
- TSAT

6.2.1.1. Total Serum Iron

The PK of administered Triferic iron will be assessed by measuring total serum iron.

Total serum iron will be measured using a validated Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method.

6.2.1.2. Appropriateness of Iron Parameter Measurements

The determination of total serum iron by ICP-MS has been developed and validated.

Previous studies have demonstrated the concordance of sFe with transferrin bound iron for Triferic administered parenterally. The autoanalyzer method has a lower limit of detection of 5 µg/dL and the ICP-MS assay has a lower limit of detection of 0.2 µg/dL.

6.2.1.3. Collecting, Processing, and Shipping Pharmacokinetic Samples

Blood samples for PK analysis will be collected as outlined in the PK, Serum Iron Profile and Hepcidin 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 10 mL of whole blood will be collected for each blood draw. Including the safety laboratory tests, the total volume collected from each patient will be less than 200mL.

Blood samples will be collected in serum separator tubes with clot activator at the nominal time points listed in Appendix 2. Actual blood sampling times must be recorded in the source documents and CRF.

Blood samples will be drawn and processed for serum as described in **Appendix 3.**

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, and temperature).

6.2.2.1. Clinical Laboratory Tests

All routine and safety blood samples will be analyzed by the site's local licensed clinical laboratory. The clinical laboratory tests that will be conducted at a clinical laboratory are as follows:

- **Hematology**: complete blood count with platelet count, white blood cell (WBC) count and WBC differential.
- **Blood Chemistry**: routine Chem-14 analysis, serum pregnancy test, and CRP (Screening only).
- **Serum Iron Profile:** sFe, ferritin, TIBC, and TSAT.

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

Physical examinations will consist of assessments of the following: skin, ENT (ears, nose, and throat), head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, and neurologic.

6.2.2.3. Vital Signs and Weight

Vital signs will include blood pressure (mm Hg), heart rate (beats per min), and temperature (Screening and Follow-up). Blood pressure and heart rate

measurements will be obtained in the same position (supine or sitting) and in the same arm when possible, after being supine or sitting for at least 5 minutes.

6.3. Assessment to Proceed to Next Dose Levels

The safety findings, serum iron, and iron profile will be reviewed at the conclusion of each cohort and prior to escalating the dose.

Stopping criteria for any dose level:

- Onset of nausea, vomiting, diarrhea or changes in sensorium in at least 1 patient receiving FPC IP.
- Evidence for metabolic acidosis in at least 1 patient receiving FPC IP.
- Evidence for peritoneal irritation as manifest by abdominal pain with tenderness in greater than 1 patient receiving FPC IP.
- Increase in cell count indicative of peritoneal inflammation in greater than 1 patient receiving FPC IP.
- A serious adverse event deemed possibly related in any patient receiving FPC IP.

7. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol.

7.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject 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 AE CRF from the start of the first dose of Triferic through the end of study participation or 7 days after the last dose of 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:

18. “How are you feeling?”

19. “Have you had any medical problems since your last assessment/visit?”

20. “Have you taken any new medicines since your last assessment/visit?”

7.4. Reporting Serious Adverse Events

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 hrs (24 hrs for deaths and life-threatening events) 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, a reporter's name and contact information, the name of the suspected investigational product and patient identifiers, a description of the event and the Investigator's preliminary assessment of causality must be provided at the time of the initial report. Additional follow-up information, if required or available, should be sent to Rockwell Medical within 48 hrs 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), Independent Ethics Committee (IEC) 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. Each site is responsible for notifying their IRB, IEC or the relevant local regulatory authority of these additional SAEs.

7.4.1. Timeframes for Reporting Serious Adverse Events

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 hrs** 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 hrs.**
  - Follow-up information must be sent to Rockwell Medical within 48 hrs 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 hrs of site study personnel learning of the event.
  - Follow-up information must be sent to Rockwell Medical within 48 hrs of receipt of the information by the investigational site.

7.4.2. Serious Adverse Event 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, the initial report will also include the onset date, relationship to study drug, and a brief narrative of the event.

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 Adverse Events

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 or hematology) or other abnormal assessments (e.g., ECGs or 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 AE (Section 7.1, Definition of an Adverse Event), and also 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 Adverse Events

Adverse events, including SAEs, will be recorded on the AE CRF from the start of the first dose of Triferic through the end of study participation or 7 days after the last dose of 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 Triferic, 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 AE and/or SAE.

7.7. Follow-up of Adverse Events

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 Triferic, a copy of any post-mortem findings, including histopathology, should be obtained, if available, and forwarded to Rockwell Medical.

7.8. Post-study Adverse Events

Investigators are not obligated to actively seek new AEs or SAEs that begin more than 7 days after the last dose of Triferic. 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 24 patients is planned. The total sample of 24 patients should provide enough information for an analysis of the PK and dose proportionality of Triferic iron administered via PD and IV.

8.2. Determination of Sample Size

A total of up to 24 adult patients with CKD-5HD will be enrolled in this study. The sample size was determined empirically. One half (12 patients) will be CAPD and one half will be CCPD patients.

8.3. Analysis Populations

Two analysis populations will be defined as follows:

- **PK Population** will include all enrolled patients who receive at least 1 dose of study drug and have sufficient PK samples (a sample at end of administration and at least 3 samples during the elimination phase) to include in the PK assessments.
- **Safety Population** will include all enrolled patients who received at least 1 dose of study drug.

The analyses of disposition, baseline characteristics, and exposure will be performed for the Safety Population. The PK analyses will be performed for the PK population. All safety analyses will be performed for the Safety Population.

8.4. Patient Disposition

Patient disposition will be summarized for the Safety Population.

8.5. Baseline Characteristics

Baseline characteristics will be summarized for the Safety Population.

8.6. Concomitant Medications

Concomitant medications will be categorized by World Health Organization (WHO) classification (Anatomical Therapeutic Chemical classification system [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.

8.8. Safety Assessments

8.8.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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.

Withdrawals from the study due to AEs will be summarized.

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

8.8.2. Clinical Laboratory Assessments

With the exception of the PK analyses for total serum iron, all hematology and chemistry results (including serum iron profiles and hepcidin) will be summarized for the Safety Population and follow-up values will be summarized separately where applicable.

8.8.3. Vital Signs

Changes from baseline at each time point will be summarized for the Safety Population.

8.9. Pharmacokinetic Analyses

The primary PK analysis will be performed on the total serum iron values.

PK parameters will be derived using non-compartmental methods employing WinNonlin® Phoenix version 6.3 or later (Pharsight Corp, Mountain View, CA). The following PK parameters will be estimated for serum iron as data permit and as appropriate:

C_{max}	The maximum drug concentration in serum determined directly from individual concentration-time data
T_{max}	The observed time to reach maximum concentration
$AUC_{(0\text{-}t)}$	The area under the serum concentration-time curve from time zero to the time of the last quantified concentration, calculated using the linear-up/log-down trapezoidal rule
$AUC_{(0\text{-}end)}$	The area under the serum concentration-time curve from time zero to the end of each study drug infusion, calculated using the linear-up/log-down trapezoidal rule

λz	The terminal phase rate constant, estimated by linear regression through the terminal phase of the log concentration-time profile
$t_{½}$	The terminal phase half-life, calculated as: $t½ = \frac{\ln(2)}{\lambda z}$
AUC_{inf}	The area under the serum concentration-time curve from time zero extrapolated to infinity; calculated using the linear-up/log-down trapezoidal rule
CL or CL/F	Systemic clearance calculated as: Total Dose/AUC_{last}

Individual PK parameters for total serum iron will be summarized with descriptive statistics. Pharmacokinetic parameters including the maximum observed serum concentration (C_{max}), time to C_{max} (T_{max}), the area under the serum concentration versus time curve from time 0 (pre-dose) to the last quantified time point (AUC_{0-t}), the area under the serum concentration versus time curve from time 0 (pre-dose) to the end of each study drug infusion (AUC_{0-end}), AUC from time 0 (pre-dose) to time infinity (AUC_{inf}), the elimination rate constant (λ_z), the total systemic clearance (CL or CL/F), and elimination half-life ($t_{½}$) will be calculated as data permit and as appropriate using non-compartmental analyses.

8.10. Quantitation of Iron Administered

An estimate of the amount of iron transferred from the PD solution to the circulation will be obtained in two different analyses.

a) The C_{max} and AUC_{0-t} for sFe at each dose level compared to the C_{max} and AUC_{0-t} for the Triferic IV administration will be used to calculate the relative bioavailability of Triferic iron during the PD period.

b) A sample of the initial dosing solution and the final PD drainage will be analyzed for iron content using ICP-MS. The difference between the dosing solution and the final drainage (corrected for volume effects) is a direct measure of Triferic iron absorbed during the PD dwell.

8.11. Planned Modeling

Pharmacokinetic results from this study for total serum iron may be used to develop a model to provide a method to estimate PK parameters for Triferic.

A population PK model may be used to combine all data for a PK estimate for the full population.

8.12. Pharmacogenomics Analyses

None are planned.

8.13. Statistical and Analytical Issues

8.13.1. Statistical Analysis Plan

A 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.

8.13.2. Handling of Missing Data

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

8.13.3. Interim Analyses and Data Monitoring

No interim analysis is planned.

8.13.4. 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 possible hypersensitivity during infusion of study drug as evidenced by any of the following, that is not consistent with the patient's ongoing medical history:
  - Hypotension, respiratory difficulty, angioedema, generalized pruritis and flushing;
- Signs of potential iron toxicity as evidenced by any of the following, that is not consistent with the patient's 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/mL 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, a safety review committee will review the entire study's safety data before a decision is made to 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 according to the applicable IRB/EC policy.

The Investigator must notify the IRB 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), the ICF will be revised accordingly and submitted to the IRB/EC for review and approval. The approved ICF will be used to obtain informed consent from new patients prior to enrollment and must be used to re-obtain informed consent from patients 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 to ensure accurate and timely information is provided at all times 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 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 the sponsor or its designee and should be handled in accordance with instructions from Rockwell Medical.

In accordance with the US 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, ECG 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.

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 the 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 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 new drug application, 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, which will include, but not be limited to, notification that the study has concluded, the number of patients enrolled/ treated, and the number of AEs and SAEs that occurred during the study. The report to the IRB will be consistent with the applicable IRB 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 GCP for the conduct and monitoring of clinical investigations must be followed.

9.5. Informed Consent

A copy of the proposed ICF should be submitted to Rockwell Medical for review and comment prior to submission to the reviewing IRB. The ICF must be approved by the IRB 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 or in a separate document to be signed by the patient.

The Investigator will be responsible for obtaining written informed consent from the potential subjects prior to any study-specific screening and entry into the study. The research study will be completely explained to each prospective study subject. The Investigator or designee must explain that the subject 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 Independent Ethics Committee Approval

In accordance with 21 CFR Parts 50 and 56, the Investigator agrees to provide the appropriate IRB 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 approval of the protocol and ICF 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 members to demonstrate compliance with membership requirements. If the Investigator or a sub-investigator is a routine voting member of the IRB, Rockwell Medical will be provided with a statement from the IRB that the Investigator/sub-investigator did not and will not vote on any IRB decisions pertaining to this clinical investigation.

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

It is the Investigator's obligation to maintain an IRB 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.

11. REFERENCES

Reference List

(1) III. Clinical practice recommendations for anemia in chronic kidney disease in children. *Am J Kidney Dis* 2006;47:S86-108.

(2) Wetmore JB, Peng Y, Monda KL et al. Trends in anemia management practices in patients receiving hemodialysis and peritoneal dialysis: a retrospective cohort analysis. *Am J Nephrol* 2015;41:354-361.

APPENDIX 1. TIME AND EVENTS SCHEDULE

Table 3: Time and Events Schedule

Assessments	Screening	Enrollment	Triferic PD	Triferic 6.6 mg Fe IV	Follow-up*
Visit #	**1**	**2**	**3/4**	**3/4**	**5**
Target study day	-28 to -1	-3 to -1	1/3	1/3	5 to 8
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics	X				
Medical history	X	X			
Height and weight[a]	X		X	X	X
Vital signs[f]	X		X	X	X
Physical examination	X				X
ECG	X				
Serum pregnancy test (if applicable)	X				
Hematology[b]	X				X
Chem-14, CRP[b]	X				X
Serum iron profile[b,c]	X		X	X	X
Hepcidin			X	X	
Enrollment in study		X			
Triferic administration PD[d]			X		
Triferic administration IV[d]				X	
PK samples[e] (total serum iron profile)			X	X	
50 mL PD fluid for cell count/differential			X	X	
50 mL PD fluid for iron content			X	X	
6 15-mL PD fluid for future analysis			X	X	
Weight of PD fluid			X	X	
Discharge from study					X
Adverse events			X	X	X
Medications	X	X	X	X	X

* A visit window of ±5 days will be permitted for the follow-up visit.
[a] Height is measured at Visit 1 (Screening) only.
[b] Hematology, Chem-14, CRP (Visit 1/Screening only), the serum iron profile (total serum iron, ferritin, TIBC, and TSAT), and pregnancy test samples will be analyzed by a central clinical laboratory.
[c] If an SAE occurs during or within 30 min after any Triferic infusion, a serum iron profile will be obtained as soon as the SAE is recognized.
[d] See Appendix 4 for instructions on the preparation and dosing of Triferic.
[e] See Appendix 2 for the schedule for obtaining PK, serum iron profile, and hepcidin samples. See Appendix 3 for instructions on the handling of the PK, serum iron profile, and hepcidin samples.
[f] Vitals include blood pressure and pulse. Temperature is to be recorded at Screening and Follow-up only.

APPENDIX 2. PHARMACOKINETIC, SERUM IRON PROFILE, AND HEPCIDIN SAMPLE COLLECTION SCHEDULE

At each time point marked with an "X" in Table 3 below, collect one (1) 7.5 mL sample using serum separator tubes; to be used for the PK, serum iron profile, and hepcidin analyses (see Appendix 3)

Table 4: PK, Serum Iron Profile, and Hepcidin Sample Collection Schedule

Nominal Time Hrs.	Triferic IP	Triferic 6.6 mg Fe IV/4 Hrs.
0	X[a,b,c]	X[a,b,c]
0.5	X[a,b]	X[a,b]
1	X[a,b]	X[a,b]
1.5	X[a,b]	X[a,b]
2	X[a,b]	X[a,b]
3	X[a,b]	X[a,b]
4	X[a,b]	X[a,b]
6	X[a,b]	X[a,b]
8	X[a,b]	X[a,b]
10	X[a,b]	X[a,b]
12	X[a,b]	X[a,b]

[a] PK sample

[b] Serum iron profile sample

[c] Hepcidin sample

See Appendix 3 for PK, serum iron profile, and hepcidin sample processing, storage, and shipping instructions.

APPENDIX 3. PHARMACOKINETIC, SERUM IRON PROFILE, AND HEPCIDIN SAMPLE HANDLING

Supplies for the Study

7.5-mL clot activator serum separator vacutainer tubes

1.0 -2.0-mL screw top plastic sample transport tubes

PK, Serum iron Profile, and Hepcidin Sample Collection and Processing Instructions

a) Collect the 1 X 7.5 mL tubes and allow toclot for at least 10 minutes at room temperature.
b) Spin the tubes at 4,000 X g for 15 minutes
c) Separate the serum from the 7.5 mL tube and transfer 1000 µL aliquots into 2 labeled screw top plastic sample transport tubes (aliquots #1 and #2).
    a. For the t = 0 (Baseline) sample only, transfer an additional 1000 µL aliquot into a labeled screw top plastic sample transport tube (Aliquot #3) for the hepcidin analysis, and store Aliquot #3 at -70 to -80°C until shipment. For all other time points, skip this step and proceed with step (d) below.
d) Transfer any remaining serum into another transport tube. Keep tubes on ice until they are placed in the freezer. Store all aliquots frozen at -20°C until they are shipped (with the exception of the hepcidin aliquot, which should be stored at -70 to -80°C until shipment).
e) On completion of sample collections, ship aliquot #1 to the central bioanalytical lab frozen on dry ice for assessment of the total serum iron PK profile.
f) On completion of sample collections, ship aliquot #2 to the central clinical lab for analysis of the serum iron profile (total serum iron, ferritin, TIBC and TSAT).
g) On completion of sample collections, ship aliquot #3 to hepcidinanalysis.com frozen on dry ice for analysis of the baseline hepcidin.
h) Store any remaining aliquots frozen until completion of the study or until directed by the Sponsor or designee to ship to the laboratories or destroy.

PK Sample Shipping Instructions

Included in site instructions.

APPENDIX 4. TRIFERIC DOSING SOLUTION PREPARATION

Triferic dosing solutions may be prepared up to 24 hrs prior to planned infusion start times. All pre-prepared solutions should be stored at controlled room temperature and protected from light until use.

PD fluids containing Dextrose or Icodextrin may be used for this study. For dextrose containing PD fluid any dextrose concentration is permissible according to the patient's usual PD prescription.

Triferic PD Dosing Solution Preparation for Cohorts 1 - 3

- For each patient, prepare the Triferic PD dosing solution by adding the appropriate amount of Triferic solution to each 2L bag of PD fluid.
- Draw up the required amount under aseptic conditions and add to 2 L PD solution using a syringe and aseptic technique. Mix the bag to disperse.
- Retain one (1) 50-mL aliquot of each PD fluid (containing Triferic) in polypropylene screw-cap tubes and store at approximately 4°C for dosing solution analysis.
- Weigh each PD bag after removal of the dosing solution aliquot to the nearest gram (gm.)
- Keep all Triferic solutions protected from light until use.

Table 5: Preparation of Triferic PD Dosing Solution

Dose	Volume Triferic* (5.44 mg/mL)	Final Concentration Mg Fe/L
10 mg Fe/2L	1.85 mL	5 mg/L
25 mg Fe/2L	4.60 mL	12.5 mg/L
40 mg Fe/2L	7.35 mL	20 mg/L

*use the COA for Triferic batch for exact iron concentration to determine the volume required.

Triferic 6.6 mg IV Dosing Solution Preparation for IV Infusion

- Withdraw 1.52 mL Triferic solution under aseptic conditions
- Add to 250 mL D5/W and mix
- Administer via peripheral IV at 50 mL/hr via calibrated pump for 4 hours
- Keep all Triferic solutions protected from light