Clinical Trial Protocol

A RANDOMIZED 3 PERIOD CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF TRIFERIC PLUS HEPARIN INFUSION COMPARED TO HEPARIN ALONE ON COAGULATION PARAMETERS IN HEMODIALYSIS PATIENTS.

Protocol Identifying Number: RMFPC-24

Principal Investigator:	Thomas C Marbury, MD Orlando Clinical Research Center 5055 S. Orange Ave. Orlando FL 32809, USA
Sponsor:	Rockwell Medical Inc. 30142 S Wixom Rd Wixom MI 48393, USA
Funded by:	Rockwell Medical Inc.
USA IND #	051,290
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PROTOCOL APPROVAL PAGE

Protocol Title:	**A Randomized 3 period crossover study to investigate the effect of Triferic plus heparin infusion compared to heparin alone on coagulation parameters in hemodialysis patients.**
Protocol Number:	RMFPC-24
Version:	1.1
Date of Issue:	July 12 2019
Sponsor Name and Address:	Rockwell Medical, Inc. 30142 S. Wixom Rd Wixom, MI 48393 USA

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

Sponsor Signatory:

Raymond D Pratt, MD FACP
Chief Medical Officer

(Date)

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title:	**A Randomized 3 period crossover study to investigate the effect of Triferic plus heparin infusion compared to heparin alone on coagulation parameters in hemodialysis patients.**
Protocol Number:	RMFPC-24 Version: 1.1

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 EMA guidelines, China Food and Drug Administration (CFDA) regulations, the International Conference on Harmonisation (ICH) GCP guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human Patients.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Ethics Committee (EC), except when necessary to eliminate an immediate hazard to the Patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of the case report forms (CRFs) and source documents by Rockwell Medical or designee and to onsite inspection of CRFs and source documents by appropriate regulatory authorities, including but not limited to the EMA, CFDA, local governing regulatory bodies, and IRB/EC inspectors.

Investigator's Signature Date

Thomas C Marbury, MD

Print Name

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LIST OF ABBREVIATIONS

Abbreviations	Term
ACT	activated clotting time
AE	adverse event
ALT	alanine transaminase (SGPT)
ANCOVA	analysis of covariance
Anti-Xa	heparin anti Xa activity
aPTT	activated partial thromboplastin time
AST	aspartate transaminase (SGOT)
BP	blood pressure
C	Celsius
CAP	College of American Pathologists
CBC	complete blood count
CFDA	China Food and Drug Administration
CFR	Code of Federal Regulations
Chem-20	comprehensive metabolic panel including 20 analytes
CHr	reticulocyte hemoglobin
CI	confidence interval
CKD	chronic kidney disease
CKD-5HD	chronic kidney disease stage 5 undergoing chronic hemodialysis
CLIA	Clinical Laboratory Improvement Amendments
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
EC	ethics committee
EoT	end-of-treatment
ESA	erythropoiesis-stimulating agent
FPC	ferric pyrophosphate citrate; Triferic
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HD	hemodialysis
HDF	hemodiafiltration
Hgb	hemoglobin
hr	hour
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	institutional review board
IV	intravenous
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water
LS	least squares
MI	Michigan
MITT	modified intent-to-treat
NIH	National Institutes of Health
NKF	National Kidney Foundation

PMAM	protocol-mandated change in anemia management
PT	prothrombin time
QB	blood flow rate during dialysis
RBC	red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SFP	soluble ferric pyrophosphate, a previous name for FPC
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvate transaminase (ALT)
Tf	transferrin
TIBC	total iron-binding capacity
TSAT	transferrin saturation
TSATTf	transferrin saturation based on transferrin value
TSATUIBC	transferrin saturation based on UIBC value
TT	thrombin time
UFH	Unfractionated heparin
UIBC	unsaturated iron-binding capacity, calculated as TIBC – total serum iron
URR	urea reduction ratio
US	United States
WBC	white blood cell

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following applicable regulations depending on study location and sponsor requirements.

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

ICH E6

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

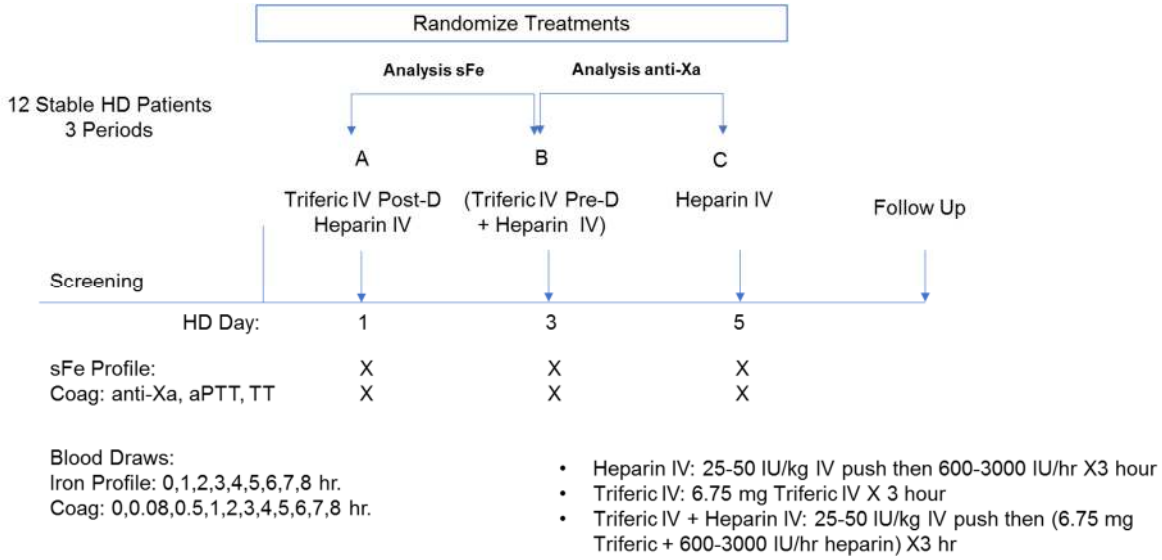
PROTOCOL SUMMARY

Title:	**A Randomized 3 period crossover study to investigate the effect of Triferic plus heparin infusion compared to heparin alone on coagulation parameters in hemodialysis patients.**
Precis:	This study will investigate the administration of Triferic intravenously into the pre-dialyzer blood line with and without concomitant administration of continuous infusion heparin for anticoagulation of the dialyzer circuit.
Study Design	Prospective, randomized, three period crossover open label single site study.
Objectives:	To investigate the effect of co-administration of Triferic and heparin on the ability to maintain circuit anti-coagulation and iron delivery when compared to control conditions when each treatment is administered via separate routes..
Primary Objectives:	Investigate if there is a drug-drug interaction between Triferic and concomitant administration of continuous dose heparin to anticoagulate the dialyzer blood circuit for plasma by measuring Anti-Xa activity
Secondary Objectives	Investigate if there is a drug-drug interaction between Triferic and continuous heparin on the ability to deliver Triferic iron as measured by the serum iron profile pharmacokinetics. Investigate the effect of the administration of Triferic and concomitant continuous dose heparin on aPTT and TT activity. Investigate the effect on dialyzer circuit clotting as measured by a visual scale Investigate the overall safety profile of Triferic and heparin as measured by, targeted adverse events, serious adverse events, number and quantity of equired extra heparin bolus doses and standard laboratory analyses
Study Design:	Prospective, randomized three period crossover, open-label single site study. Enrolled patients will be randomized to receive 3 sequential HD treatments as shown in the Study Design. Each treatment will examine a unique combination of Triferic and heparin administration. **Treatment A:** Patients will receive Triferic 6.75 mg IV over 3 hours into the post-dialyzer blood line (or drip chamber) administered by an infusion pump. Anti-coagulation will be provided by a bolus of heparin administered into the venous return line immediately prior to the initiation of hemodialysis followed by a continuous infusion of heparin using the on-machine infusion pump. The infusion of heparin to be stopped at hour 3 of hemodialysis.

	Treatment B: Patients will receive Triferic 6.75 mg IV plus the appropriate volume of unfractionated heparin for continuous infusion over 3 hours into the pre-dialyzer "heparin line". This mixture will be administered by the on-machine syringe infusion pump for continuous infusion. Anti-coagulation will be provided by a bolus of heparin administererd into the venous return line immediately prior to the initiation of hemodialysis followed by a continuous infusion of Triferic + heparin. The infusion of Triferic + heparin will be stopped at hour 3 of hemodialysis. **Treatment C:** Patients will receive no Triferic. Anti-coagulation will be provided by a bolus of heparin administered into the venous return line immediately prior to the initiation of hemodialysis followed by a continuous infusion of heparin via the on-machine syringe pump. The infusion of heparin to be stopped at hour 3 of hemodialysis. The heparin dose to be utilized will be what the patient normally receives during their regular outpatient hemodialysis within the ranges specified below: the heparin dose will be the same at each treatment. Heparin IV: 25-50 IU/kg IV push then 600-3000 IU/hr X 3 hour Triferic IV: 6.75 mg Triferic IV X 3 hour Triferic IV + Heparin IV: 25-50 IU/kg UFH IV push, followed by a continuous infusion of Triferic 6.75 mg + sufficient volume of heparin to meet the patients anti-coagulation requirements. The entire contents of the syringe are programmed to be delivered over the first 3 hours of dialysis. Safety parameters to be assessed are adverse events, evidence of clotting in the dialyzer circuit by visual inspection at intervals, abnormal vital signs, and abnormal laboratory analyses (complete blood counts and blood chemistries) for this patient population.
Primary Endpoint	Anti-Xa activity between Triferic IV + heparin IV infusion mixture compared to Heparin IV infusion (Treatment B vs Treatment C) as measured by the AUC_{0-t} for the Anti-Xa concentration vs time.
Secondary Endpoints	• anti-Xa as measured by the AUC_{0-4} hours between Treatment B vs C. and Treatment A vs B • aPTT as measured by the AUC_{0-4} hours between Treatment B vs C and Treatent A vs B • TT as measured by the AUC_{0-4} hours between Treatment B vs C and Treatent A vs B . • Iron profile as measured by the sFe C_{max} and AUC_{0-t} of Treatment B (Triferic +Heparin) versus Treatment A (Triferic IV pre—dialyzer, separate heparin infusion).
Safety Endpoints	• The incidence and amount of clotting in the dialyzer circuit by visual inspection: Visual Clotting Scale (VCS)

	• The incidence of treatment-emergent adverse events (TEAEs), including the seriousness, severity, and assessed relatedness to anemia management protocol. • The number and quantity of additional heparin bolus doses by treatment • The change from baseline to end-of-treatment (EoT) in laboratory assessments.
Population:	Patients ≥18 years of age with end stage kidney disease receiving chronic hemodialysis (CKD-5HD).
Phase:	I/II
Number of Sites:	1 site
Countries	US
Description of Study Agent(s) :	**Triferic IV:** Triferic (ferric pyrophosphate citrate, FPC), an iron-replacement product, is an iron complex in which iron(III) is bound to pyrophosphate and citrate. Triferic will be supplied as liquid luer-lock ampules containing 6.75 mg of Fe/4.5 ml and will be administered directly into the post-dialyzer blood line via a separate infusion pump at a rate to deliver the entire contents over 3 hours. **Triferic IV + Heparin:** Triferic can be mixed with heparin to provide a mixture containing both agents. The heparin dose to be administered by continuous infusion should be drawn up in a syringe. The syringe should then be connected to the LDPE luer-lock ampule containing Triferic and the contents withdrawn. The total volume to be administered is noted and the on-machine syringe pump is programmed to deliver the entire contents over 3 hours. **Heparin IV Standard Dose Protocol:** Unfractionated heparin 25 – 50 IU/kg administered as an IV bolus into the venous blood line immediately prior to the start of hemodialysis followed by a continuous infusion of 600-3000 IU/hr X 3 hours (per referring hemodialysis unit protocol).
Study Duration:	4 week
Participant Duration:	1 week

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

Sponsor Medical Monitor	Raymond D Pratt, MD Chief Medical Officer Rockwell Medical Inc.
Principal Investigator	Thomas C Marbury , MD Orlando Clinical Research Center 5055 S Orange Ave. Orlando FL 32809, USA
Clinical Laboratory	Orlando Regional Medical Center Clinical Lab 1414 Kuhl Ave Orlando, FL 32806
Contract Research Organization Data Management Statistical analysis Mdical Writing-clinical study report	Innovative Analytics, Inc. 161 E. Michigan Ave Kalamazoo, MI 49007, USA
Pharmacokinetic analysis Pharmacokinetic analysis report	Nuventra, Inc. 2525 Meridian Parkway Suite 280 Durham NC 27713, USA

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND ON IRON DEFICIENCY IN HEMODIALYSIS AND TREATMENT WITH IV IRON

Chronic kidney disease (CKD) is a worldwide public health concern with an increasing incidence and prevalence, and is accompanied by poor outcomes and high healthcare costs. (National Kidney Foundation [NKF] Kidney Disease Outcomes Quality Initiative [KDOQI] 2002) Patients with CKD develop anemia primarily due to deficient production of erythropoietin by the diseased kidneys, as well as iron deficiency[1]. Anemia commonly contributes to poor quality of life in patients with CKD[2]. The appropriate

treatment of anemia is important; in addition to reduced quality of life, anemia is associated with fatigue, left ventricular hypertrophy and other deleterious consequences, and correction of anemia has been associated with improved quality of life, morbidity, and survival in uremic patients[3].

Treatment with erythropoiesis stimulating agents (ESAs) can lead to rapid depletion of iron stores and functional iron deficiency due to stimulated erythropoiesis. Iron deficiency is further exacerbated by iron losses that are particularly high in hemodialysis patients: up to 15 to 25 mL of whole blood are lost with each dialysis treatment (approximately 60 mL per week) as a result of retention of blood in the dialyzer and tubing, frequent phlebotomy for blood testing and excessive gastrointestinal blood loss[4].

Oral iron supplements are often either not sufficiently effective or not tolerated in a significant proportion of patients due to associated gastrointestinal adverse events. Thus, oral iron frequently fails to maintain adequate iron stores in hemodialysis patients, particularly those on ESA[5;6]. The anemia working group of the NKF KDOQI concluded that oral iron is unlikely to maintain iron stores, and most hemodialysis patients will require intravenous (IV) iron on a regular basis to achieve and maintain target hemoglobin levels[7].

IV iron is associated with acute toxicity, thought to be related at least in part to the carbohydrate moiety and/or release of labile iron. IV iron administration is well recognized to be associated with anaphylactoid reactions, other hypersensitivity reactions, and profound hypotension[8]. The other recognized acute adverse reactions from IV iron administration such as nausea, vomiting, cramps, back pain, and chest pain, are likely attributable to free or labile iron liberated from the iron complex[9]. Labile iron effects may also be associated with increased oxidative stress and inflammation[10].

Theoretically, IV iron may also increase the risk of infections via two potential mechanisms. The uptake of iron carbohydrate complexes from the circulation is by the same phagocytic cells (macrophages) in the reticuloendothelial system (liver, spleen and lymph nodes) that act as scavengers to pick up bacteria or foreign substances in the circulation; their function can be theoretically overwhelmed by the handling of the iron complexes, thereby predisposing to infections. In addition, while in the circulation, iron can potentially serve as a nutrient for the microorganisms.

Repeated administration of IV iron over prolonged periods of time can result in the accumulation of iron in storage sites, as reflected by persistently elevated ferritin levels[11]. Over prolonged periods of time, this has the potential to cause toxic effects associated with iron overload, including liver damage, atherosclerosis, and heart disease. All IV iron compounds are known to increase ferritin levels.

2.2 RATIONALE

Triferic (ferric pyrophosphate citrate, or FPC), an iron-replacement product, is an iron complex in which iron(III) is bound to pyrophosphate and citrate[12]. Triferic does not require processing by macrophages, and it donates iron directly to transferrin for optimal utilization in erythropoiesis, avoiding sequestration within reticuloendothelial system macrophages[13]. Additional information regarding Triferic may be found in the Investigator's Brochure[14] (IB) v10.0 (2018).

- The amount of iron Triferic delivered via HD at the approved dose of 2 μM (110 μg Fe/L) was determined by PK parameters to be 6.75 mg Fe/HD.
- The amount of iron delivered IV into the pre-dialyzer blood line is 6.75 mg.

Rationale for the Current Study

Hemodialysis requires some form of anticoagulation to prevent clotting in the dialyzer circuit. Unfractionated heparin (UFH) has been the long time standard to provide anticoagulation[15]. UFH is typically administered as a bolus dose of 25 to 50 IU/kg at the initiation of hemodialysis followed by a continuous infusion via the on-machine syringe (heparin) pump of 600-3000 IU/hour[16]. Alternately UFH or low molecular weight heparins (LMWH) can be administered as a single IV bolus predialysis followed by an additional bolus if needed. This mode of administration does not require use of the on-machine syringe (heparin) pump. Anticoagulation within the dialysis circuit is monitored by visual observation of the dialyzer and drip chambers. The UFH dose needs to be individually determined and may be variable depending on the underlying comorbidities[17-19].

Triferic can be administered to HD patients via the dialysate or intravenously into the pre- or post-dialyzer blood lines. This can be accomplished by using an accessory infusion pump, or in the case where the patient is receiving intermittent bolus heparin using the on-machine infusion pump.

The current study will investigate the administration of the admixture of Triferic + heparin during hemodialysis in those patients who are receiving heparin as a continuous infusion during HD. Triferic has no effect on the anti-coagulant effects of UFH and LMWH when mixed together (data on file: Rockwell Medical Inc). Macromolecular iron has been previously administered to patients with continuous infusion heparin[20].

The test administration will be Treatment B to assess the impact of the Triferic + heparin mixture on the ability to maintain adequate anticoagulation of the dialyzer circuit and administration of Triferic iron. The Control arms will compare heparin continuous infusion alone (Treatment C) and Heparin administered via constant infusion with Triferic administered into the post-dialyzer blood line by a separate infusion pump (without heparin admixture -Treatment A).

Justification for Dose

Triferic at 2 µM iron (110 µg Fe/L) final concentration in hemodialysate was shown to provide 6.75 mg iron per dialysis and is the approved dialysate concentration in the United States[21].

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Triferic is generally well-tolerated. In controlled clinical studies, the safety profile is similar to patients receiving placebo treatment. The most common adverse reactions leading to treatment discontinuation included headache, asthenia, dizziness, constipation, nausea, hypersensitivity reactions, intradialytic hypotension, pruritus, and pyrexia. Adverse reactions reported in the treatment extension periods were similar to those observed in the randomized clinical studies.

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving parenteral iron products. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Patients receiving IV iron should be monitored for signs and symptoms of hypersensitivity during and after hemodialysis until clinically stable.

Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions.

Adverse events in controlled clinical trials of Triferic were mild to moderate in severity. The pattern of AE was similar between Triferic and placebo treated patients. There were no events of anaphylaxis in controlled trials. Since product launch, over 600,000 individual doses of Triferic have been administered via HD and IV with no reported hypersensitivity or anaphylaxis.

Anticoagulation is required to prevent clotting of the dialyzer circuit. The use of continuous dose heparin administered via the on-machine infusion pump has been demonstrated to be safe and effective in preventing clots from forming in the dialyzer circuit.

Triferic has been demonstarated to be compatible with unfractionated heparin in an *in-vitro* study. This study will examine the effect of administering an admixture of Triferic and heparin on the coagulation parameters and iron delivery during infusion of the mixture.

2.3.2 KNOWN POTENTIAL BENEFITS

Triferic administered at each dialysis treatment can maintain hemoglobin concentrations without increasing body iron stores as measured by serum ferritin concentrations[22]. In one clinical study, patients receiving Triferic over 9 months required 35% less erythropoiesis stimulating agents (ESA) than patients receiving placebo[23].

3 OBJECTIVES AND PURPOSE

To investigate the co-administration of Triferic and heparin on the ability to maintain circuit anti-coagulation and iron delivery when compared to control conditions when each treatment is administered via separate routes.

3.1 PRIMARY OBJECTIVE

Investigate if there is a drug-drug interaction between Triferic and concomitant administration of continuous dose heparin to anticoagulate the dialyzer blood circuit for plasma by measuring Anti-Xa activity.

3.2 SECONDARY OBJECTIVES

Investigate if there is a drug-drug interaction between Triferic and continuous heparin on the ability to deliver Triferic iron as measured by the serum iron profile pharmacokinetics.

Investigate the effect of the administration of Triferic and concomitant continuous dose heparin on aPTT and TT activity.

Investigate the overall safety profile of Triferic and heparin as measured by, targeted adverse events, serious adverse events, number and quantity of equired extra heparin bolus doses and standard laboratory analyses.

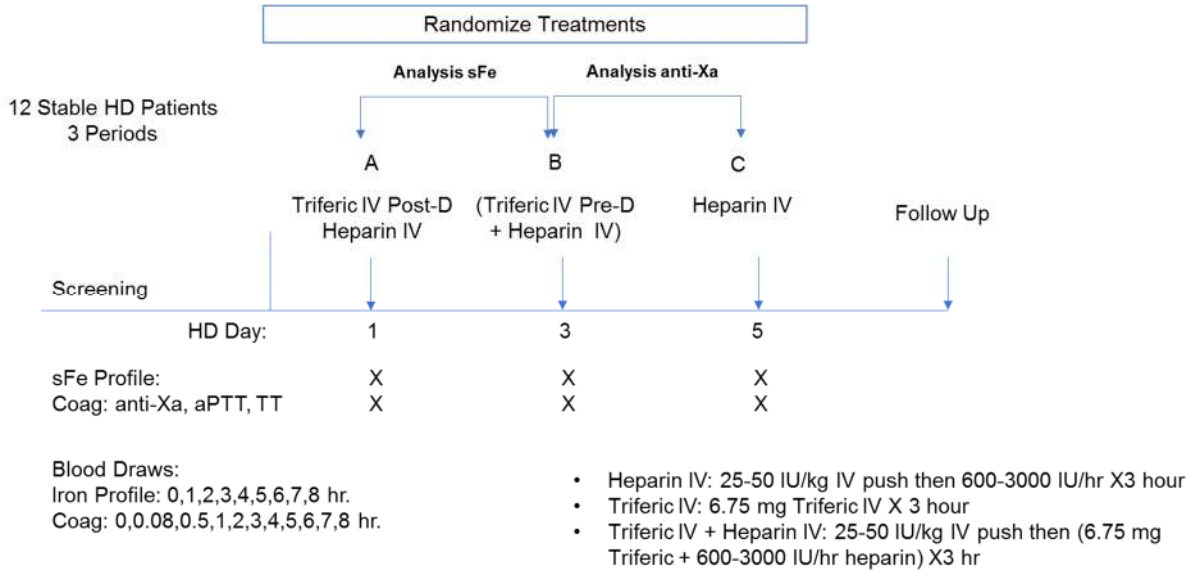
4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a prospective, single-center, open-label, three period crossover clinical trial investigating the delivery of Triferic IV with continuous heparin infusion compared to control delivery of heparin and Triferic by different routes. (Figure 1).

A total of 12 chronic hemodialysis patients will be enrolled. Patients will be randomized to one of three treatment periods and will cross over to the other two periods according to a pre-defined randomization sequence. There is one day between crossover periods which is sufficient to prevent carryover effects of heparin and Triferic due to their short half-lives.

Figure 1: RMFPC-24 Study Design Schematic



Coagulation parameters (anti-Xa activity, aPTT and TT) will be measured at specified intervals for 8 hours to include the 4 hours hemodialysis and 4 hours post HD.

Serum iron profile will be obtained at specified times for 8 hours to assess delivery of Triferic iron.

Safety parameters to be assessed are the visual evaluation of clotting in the dialyzer circuit, targeted adverse events, abnormal vital signs, and abnormal laboratory analyses (complete blood counts and blood chemistries including liver function tests) for this patient population.

4.2.1 PRIMARY ENDPOINT

- Anti-Xa activity between Triferic IV + heparin IV infusion mixture compared to Heperin IV infusion (Treatment B vs Treatment C) as measured by the $AUC_{0\text{-}t}$ for the Anti-Xa concentration vs time.

4.2.2 SECONDARY ENDPOINTS

- anti-Xa as measured by the $AUC_{0\text{-}4}$ hours between Treatment B vs C. and Treatment A vs B
- aPTT as measured by the $AUC_{0\text{-}4}$ hours between Treatment B vs C and Treatent A vs B
- TT as measured by the $AUC_{0\text{-}4}$ hours between Treatment B vs C. and Trreatment A vs B

- Iron profile as measured by the sFe C_{max} and AUC_{0-t} of Treatment B (Triferic + Heparin) versus Treatment A (Triferic IV post-dialyzer, separate heparin bolus + infusion).

4.2.3 SAFETY ENDPOINTS

- The incidence and amount of clotting in the dialyzer circuit by visual inspection: Visual Clotting Scale (VCS)
- The incidence of treatment-emergent adverse events (TEAEs), including the seriousness, severity, and assessed relatedness to anemia management protocol.
- The number and quantity of additional heparin bolus doses by treatment
- The change from baseline to end-of-treatment (EoT) in laboratory assessments.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

1. Adult hemodialysis patients ≥18 years of age.
2. Signed informed consent to participate in the study.
3. Stable on hemodialysis prescription for ≥3 months.
4. Hemoglobin concentration >9.5 g/dL.
5. Serum TSAT ≥20%.
6. Able to receive continuous heparin infusion as their anticoagulation protocol.
7. Receiving hemodialysis via AV fistula or graft.
8. Able to receive hemodialysis for 4 hours at each session over the duration of the treatment periods.

5.2 EXCLUSION CRITERIA

1. Active bleeding disorder (GI, skin, nasal…)
2. Receiving hemodialysis via catheter.
3. Receiving heparin free dialysis.
4. Receiving low molecular weight heparin as sole anti-coagulation for dialysis.
5. Receiving IV iron within 2 weeks of the first on-study hemodialysis treatment.
6. Receiving oral anti-coagulants or anti-platelet agents.
7. Any other condition, that in the opinion of the investigator would not allow completion of the 3 hemodialysis treatments in the study.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be recruited from hemodialysis centers in the local area.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

Patients may withdraw from the study at any time for any reason. Patients who withdraw prior to completion of the three study periods will be replaced to ensure a balanced sequence design is completed.

5.4.1 REASONS FOR STUDY DRUG WITHOLDING, WITHDRAWAL OR TERMINATION

Safety monitoring of enrolled patients will be ongoing during the study. The Investigator is responsible for guarding the patient's welfare and can discontinue study drug administration at any time that this action appears to be in the patient's best interest.

The rationale for all decisions to permanently discontinue test drugs and/or discontinue a patient from the study must be documented. A patient may choose to have study drug withheld or discontinue from the study at any time and for any reason.

There is no provision for study drug withholding. Patients who cannot continue in the study for any reason must be withdrawn and will be replaced.

Study drug ***must*** be permanently withdrawn (patient must be discontinued from the study) if:

- Patient has a serious adverse event that is due to study drug.

1. Systemic and/or serious infection such as bacteremia or fungemia.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Possible reasons for discontinuing a patient from the study include the following:

- Death
- Adverse event
- Withdrawal of consent
- Permanent discontinuation of study drug
- Lost to follow-up
- Investigator's discretion
- Sponsor's discretion
- Other (kidney transplant, patient changed dialysis clinics, patient moved, pregnancy, etc.)

Discontinued patients will be replaced.

If the reason for withdrawal is an adverse event, the patient will be followed until the event resolves or stabilizes, as defined in the adverse event reporting section of this protocol.

In accordance with legal requirements and International Conference on Harmonization-Good Clinical Practice (ICH-E6) guidelines, all patients are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice. In addition, Rockwell Medical retains the right to end the study at any time if the study cannot be carried out as agreed upon in the protocol. In the case of premature termination or suspension of the study, Rockwell Medical or its

representative will promptly inform the investigator/institutions and regulatory authorities of the termination or suspension and the reason for the termination. It is the responsibility of the Investigator, however, to notify the IRB or local Ethics Committee in the case of premature termination/suspension.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

Should the study be terminated or suspended, all administration of study drug will stop and patients will return to the direction of their nephrologist.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Triferic for administration IV will be provided in 5 mL LDPE luer-lock ampules containing 6.75 mg Triferic iron in 4.5 mL water for injection.

Unfractionated heparin will be provided by the investigative site for administration as IV bolus and continuous infusion.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Triferic is a pale yellow-green liquid.

Triferic for IV adminsitrateion will be labeled as an investigative drug.

Unfractionated heparin will retain its FDA-approved labeling and will not include study-specific labeling.

6.1.3 PRODUCT STORAGE AND STABILITY

All drugs will be kept in a secured area with limited access.

Triferic ampules for IV use will be stored protected from light at controlled room temperature (20° to 25°C [68° to 77°F] in the provided packages until use; excursions will be permitted to 15° to 30°C [59° to 86°F].

Heparin products must be stored according to their product labeling.

6.1.4 TRIFERIC PREPARATION

For Treatment A, the Triferic for IV administration should be drawn up into a syringe of appropriate volume by connecting the syringe tip to the luer connector and withdrawing the contents of the ampule. The syringe containing Triferic will be mounted on a separate infusion pump and programmed to deliver the 4.5 mL contents over 3 hours into the post-dialyzer blood line (or drip chamber). The UFH will be infused during the first 3 hours of hemdialysis via the on-machine syringe pump into the pre-dialyzer blood line.

For Treatment B, the UFH dose to be administered by continuous infusion should be drawn up in a syringe. The syringe should then be connected to the LDPE luer-lock ampule containing Triferic and the contents withdrawn. The syringe containing Triferic + heparin will be mounted on the on-machine syringe pump and programmed to deliver the entire contents over 3 hours via the pre-dialyzer blood line.

For Treatment C, the UFH dose to be administered by continuous infusion should be drawn up in a syringe and infused over the first 3 hours of hemodialysis via the heparin pump into the pre-dialyzer blood line.

A detailed description of dosing solution preparation is included in APPENDIX 4.

6.1.5 DOSING AND ADMINISTRATION

Doses of Triferic and heparin will be delivered according to the sequence to which patients have been assigned.

6.1.6 ROUTE OF ADMINISTRATION

See section 6.1.4.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

All heparin doses are fixed at the patients standard dose of heparin to maintain circuit anticoagulation.

Triferic doses are fixed at 6.75 mg Triferic iron via IV infusion.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

No Triferic dose adjustments are allowed.

Heparin may be adjusted if visible clots are observed in the arterial drip chamber at any time. Extra heparin can be administered in boluses of 200 to 400 U if required.

6.1.9 DURATION OF THERAPY

The study will encompass three sequential hemodialysis treatments.

6.1.10 TRACKING OF DOSE

This is a parenteral dosing study. The investigative site will be responsible for tracking all study drugs and dosing.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

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, time, quantity, and subject number);
- Return or destruction of study drug (date, quantity, and subject number);

- Initials of individual dispensing study drug; and
- Compliance assessment as outlined in Section 6.1.10.

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

6.2.1 STUDY DRUG DOSING

Triferic will be dosed as described in Section 6.1.4.

Heparin will be administered according to the study periods described in Section 6.1.4.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

All procedures for the study are described in Section 7.3.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

All other patient requirements for medication administration will be administered according to the patients standard hemodialysis prescription as determined by their referring nephrologist.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

A schedule of laboratory assessments is presented in **Section 7.3.7**.

7.2.2 OTHER ASSAYS OR PROCEDURES

None

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Hematology: All specimens should be collected in 2.0 mL K2EDTA tubes (BD# 367841 or equivalent).

Coagulation: All specimens should be collected in 2.7 mL BD # 363083 tubes or equivalent.

Chemistry (including iron profile): All specimens should be collected in 3.5-mL clot activator, serum separator vacutainer tubes (BD# 367983 or equivalent).

7.2.4 SPECIMEN SHIPMENT

All laboratory specimens for the hematology, coagulation and iron profile assessments are to be shipped to the local laboratory within 24 hours after collection.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Patients will be recruited from local hemodialysis centers and will sign an informed consent document and will undergo the following procedures:

- Eligibility evaluation
- Demographics and medical history (including current heparin prescription)
- Height and pre-/post-dialysis weight
- Vital signs (blood pressure, pulse, and temperature)
- Physical exam
- ECG
- Pregnancy test (if applicable)
- Serum chemistry (Chem-14)
- Hematology and coagulation profile
- C-reactive protein
- Serum iron profile (total serum iron, ferritin, TIBC, TSAT, transferrin)

7.3.2 ENROLLMENT AND TREATMENT PERIODS

Prior to the first Treatment Period (HD Day 1):

- Ascertain the patient meets all inclusion criteria and none of the exclusion criteria.
- Determine the UFH loading dose and infusion dose for each patient depending on their previous UFH history ascertained at Screening.
- Determine the randomization allocation to a specific sequence from the randomization schedule prepared by Innovative Analytics.

For each of the Treatment Periods (HD Days 1, 3, 5), the following study procedures will be performed:

- Prepare the UFH and Triferic according to the treatment assignments:

Treatment A: Triferic infusion post-dialyzer; UFH via continuous infusion pre-dialyzer

- UFH: Prepare the syringe containing UFH for continuous infusion via the pre-dialyzer heparin line.
- Administer the priming bolus of heparin into the post-dialyzer blood line port.
- Mount the syringe containing heparin on the on-machine syringe pump and program the pump to deliver the UFH over 3 hours of the 4 hour dialysis period.
- Triferic: The volume of Triferic to be administered is 4.5 mL via a separate infusion pump into the post-dialyzer blood line (or drip chamber). The administration rate is 1.5 mL/hour for 3 hours.
- Prepare the solution by withdrawing 4.5 mL Triferic IV solution in a 10 mL syringe.
- Inject 0.25 mL of the solution into the connecting tubing in order to displace the air present in the line prior to initiating blood flow.

- Mount the syringe on the infusion pump.
- Start infusion and administer over 3 hours of the 4 hour HD session.
- Keep all Triferic solutions protected from light until use.

Treatment B: UFH + Triferic admixture

- UFH + Triferic: Prepare the syringe containing UFH for continuous infusion via the pre-dialyzer heparin line by removing the required volume of UFH into a 10 mL syringe. In the same syringe, attach the Triferic luer lock ampule to the syringe and remove the contents (4.5 mL). Mix the contents by inverting and rotating the syringe until the solution has a uniform appearance.
- Note the final volume of the Triferic + heparin.
- Attach the syringe containing Triferic and heparin to the pre-dialyzer heparin line and mount the syringe on the on-machine “heparin pump”.
- Administer the priming bous of heparin into the post-dialyzer blood line port.
- Program the syringe pump to deliver the entire contents of the syringe over 3 hours of the 4 hour HD session.
- Keep all Triferic solutions protected from light until use.

Treatment C: UFH via continuous infusion pre-dialyzer

- UFH: Prepare the syringe containing UFH for continuous infusion via the pre-dialyzer heparin line.
- Administer the priming bous of heparin into the post-dialyzer blood line port.
- Mount the syringe containing heparin on the machine syringe pump and program the pump to deliver the UFH over 3 hours of the 4 hour dialysis period.

In addition to the study drug administration noted above, the following procedures will be performed at each treatment visit (HD Days 1, 3, and 5):

- Blood sampling for pharmacokinetic analysis (serum total iron, ferritin, TIBC, TSAT, transferrin): t = 0, 1, 2, 3, 4, 5, 6, 7, 8 hr
- Blood sample for coagulation studies (Anti-Xa, aPTT, TT): t = 0, 0.08, 0.5, 1, 2, 3, 4, 5, 6, 7, 8 hr
- Dialyzer visual scale
- Adverse events
- Concomitant medications

Visual Dialysis Circuit Clottiing Scale: Assessment of visible clotting to be assessed at 1 hour intervals during dialysis (Appendix 3).

7.3.3 FOLLOW-UP VISIT

Patients who complete the study or withdraw prior to completion will undergo a follow up evaluation within 1 week. The evaluation may be done by phone contact to assess any adverse events that may have occurred or medications that were administered after completion of the final hemodialysis treatment.

7.3.4 FINAL STUDY VISIT OR EARLY TERMINATION VISIT

See Section 7.3.3.

7.3.7 SCHEDULE OF EVENTS TABLE

Assessments	Screening	Treatment A	Treatment B	Treatment C	Follow Up[f]
Visit #	**1**	**2**	**3**	**4**	**5**
Target study day	*-28 to -1*	*1*	*3*	*5*	*8*
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical history	X				
Height and pre- and post-HD weight[a]	X				
Vital signs	X				
Physical examination	X				
ECG	X				
Serum pregnancy test (if applicable)	X				
Hematology[b]	X				
Chem-14, CRP[b]	X				
Serum iron profile[b,c]	X				
Heparin HD Rx	X				
Enrollment in study		X			
Randomized Triferic Administration[d]		FPC 6.75 mg IV Post-dialyzer	FPC 6.75 mg IV Pre-dialyzer +heparin		
Heparin Administration		Heparin Bolus + Heparin IV infusion	Heparin Bolus + Heparin IV infusion	Heparin Bolus + Heparin IV infusion	
PK samples[e]		X	X	X	
aPTT anti-Xa, TT collection[e]	X	X	X	X	
Dialyzer circuit clotting visual scale[g]		X	X	X	
Discharge from study					X
Adverse events		X	X	X	X
Medications	X				X

[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, TSAT and transferrin), and pregnancy test samples will be analyzed by the local clinical laboratory. Hematology and Chem-14 required only if not performed within 1 month prior to screening
[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 Section 7.3.2 for instructions on the preparation and dosing of Triferic.
[e] See Appendix 2 for the schedule for obtaining PK samples. PK samples will be sent to and analyzed by the local clinical laboratory. See Appendix 3 for instructions on the handling of the PK samples.
[f] 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.
[g] See Appendix 4 for the Dialyzer circuit clotting visual scale

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

All procedures in this study are standard of care.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All prescription and non-prescription medications (including multivitamins and oral and IV iron products) taken during the study are standard care.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

None.

7.6 PROHIBITED OR RESTRICTED MEDICATIONS, TREATMENTS, AND PROCEDURES

Patients may not receive IV or oral iron from the first day of screening until after completion of the final Treatment Period.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

None.

7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

None.

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Triferic will be available for commercial use by dialysis units at the conclusion of this study.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

The safety endpoints are:

- The visual scale for dialyzer circuit clotting at t=0, 1, 2, 3 and 4 hours.
- The incidence of all treatment-emergent adverse events (TEAEs) attributed to anemia management protocol, including the seriousness, severity, and assessed relatedness to Triferic or standard anemia management.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse events attributed to Triferic or standard anemia management will be collected starting with the first study drug administration during the treatment period as described in the protocol section on the collection and reporting of adverse events.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any SAE that occurs from the first day of site participation to the end of study participation 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.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An unanticipated problem is any event not listed in the Research Investigators Brochure that does not meet the definition of an AE or SAE. Examples include HD machine malfunctions or other events that may occur during the study but are not related to study drug.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The Investigator must categorize the severity of each AE related to anemia management according to the following guidelines.

Mild:

The patient is aware of signs or symptoms but is able to perform activities of daily living.

Moderate:

The event is sufficiently discomforting to the patient that it interferes with the patient's performance of activities of daily living.

Severe:

Due to the event, the patient is unable to perform activities of daily living.

8.2.2 RELATIONSHIP TO STUDY AGENT

The relationship of each AE to the anemia management treatment administration will be assessed by the Investigator after careful consideration, and according to the following guidelines.

No, Not Related:

This category is applicable to those AEs that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and do not meet the criteria for drug relationship listed under UNLIKELY, POSSIBLY, PROBABLY, AND DEFINITELY RELATED.

Unlikely Related:

This category applies to those AEs that are judged to be unlikely to be related to the study drug administration. An AE may be considered to be UNLIKELY RELATED when it meets at least two (2) of the following criteria:

a) It does not follow a reasonable temporal sequence from administration of the study drug.

b) It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

c) It does not follow a known or expected response pattern to the study drug.

d) It does not reappear or worsen when the study drug is re-administered.

Possibly Related:

This category applies to those AEs that are judged to be perhaps related to the study drug administration. An AE may be considered POSSIBLY RELATED when it meets at least one (1) of the following criteria:

a) It follows a reasonable temporal sequence from administration of the study drug.

b) It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

c) It follows a known or expected response pattern to the study drug.

Probably Related:

This category applies to those AEs that are felt with a high degree of certainty to be related to the study drug administration. An AE may be considered PROBABLY RELATED if it meets at least two (2) of the following criteria:

a) It follows a reasonable temporal sequence from administration of the study drug.

b) It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

c) It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.).

d) It follows a known or expected response pattern to the study drug.

Definitely Related:

This category applies to those AEs that are incontrovertibly related to study drug administration. An AE may be assigned to this category if it meets at least the first three (3) of the following criteria:

a) It follows a reasonable temporal sequence from administration of the study drug.

b) It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

c) It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.).

d) It follows a known or expected response pattern to the study drug.

e) It reappears or worsens when the study drug is re-administered.

8.2.3 EXPECTEDNESS

Adverse events listed in any ESA or Iron product labeling are considered expected. All other SAEs considered by the investigator to be associated or related to the anemia management drugs are considered unexpected and should be reported as such.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

At appropriate intervals, patients should be assessed for AEs and SAEs.
All SAEs (related and unrelated) will be recorded from the first day of site participation until the end of study participation. AEs will be recorded from the first day of site participation to end of study participation.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

Adverse events, including SAEs, will be recorded on the adverse events CRF through the end of study participation.

Any SAE that occurs from the first day of site participation to the end of study participation will be reported on an SAE report form.

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

8.4.2 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 or its designee 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 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 or its designee.

8.4.3 POST STUDY ADVERSE EVENTS

Investigators are not obligated to actively seek new AEs or SAEs that begin after the end of study participation. The investigator should notify Rockwell Medical of any SAEs that begin following study completion only if the event is considered related to study drug

8.4.4 SERIOUS ADVERSE EVENT REPORTING

REPORT ALL SAEs WITHIN THE TIMEFRAMES SPECIFIED TO NOTIFY ROCKWELL MEDICAL OF ANY SAEs.

All SAEs (related and unrelated) will be recorded from the first day of site participation until the end of study participation. 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 or its designee 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 to Rockwell Medical or its designee at the specified facsimile number or email address (TBD).

At a minimum, the event name, a reporter's name and contact information, the name of the suspected investigational product and subject 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 or its designee 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 the Medical Monitor (TBD) any AEs for which the issue of seriousness is unclear or questioned.

The designated CRO and Rockwell Medical are responsible for notifying the relevant regulatory authorities of certain events. Multiple inquiries with the study site may be necessary for report preparation.

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

Timeframes for Reporting SAEs

Prompt notification 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 or its designee **within 24 hr** 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 or its designee **within 48 hr.**
  - Follow-up information must be sent to Rockwell Medical or its designee within 48 hr 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 or its designee within 48 hr of site study personnel learning of the event.
  - Follow-up information must be sent to Rockwell Medical or its designee within 48 hr of receipt of the information by the investigational site.

SAE Information to Report

All information available regarding an SAE must be submitted in the timeframes indicated above. 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 or its designee. Please note that **relationship to study drug/causality is very important** and optimally should be included in the initial report as it may impact expedited regulatory reporting requirements for 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 or its designee, 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.

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.

8.4.5 UNANTICIPATED PROBLEM REPORTING

All unanticipated problems occurring during the study should be discussed with the Medical Monitor to determine the need for reporting events.

8.4.6 EVENTS OF SPECIAL INTEREST

8.4.6.1 DEFINITION OF HYPERSENSITIVITY/ANAPHYLAXIS

For the purposes of this study, hypersensitivity reactions, including anaphylaxis/ anaphylactoid reactions, are defined as the acute onset (within minutes to one hour after exposure to study drug) of an illness characterized by either or both of the following:

(1) Involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus, or flushing; or swollen lips-tongue-uvula), or

(2) Thoraco-lumbar back pain not known to be caused by any factor other than possible hypersensitivity reaction,

AND either or both of the following:

(A) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia), or

(B) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).

Possible events of anaphylaxis/anaphylactoid reaction will be reviewed and assessed by the Sponsor and Investigator as to whether or not the event was indeed a hypersensitivity reaction and related to study drug using the above proposed definition.

8.4.7 REPORTING OF PREGNANCY

If any patient is found to be pregnant, they will not be permitted to participate in the study. Any verified pregnancy after initial exposure to study drug in a patient on study must be immediately reported to the Investigator and in turn to Rockwell Medical or its designee per study reporting procedures, and the patient must discontinue study drug administration. Pregnancy during the study period will be reported and followed until final resolution (i.e., delivery or early termination). Any treatment-emergent birth defect or congenital anomaly will be reported to Rockwell Medical or its designee per study reporting procedures immediately as an SAE.

8.5 CLINICAL LABORATORY ABNORMALITIES

If not known to be associated with a diagnosis, abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., vital signs) that are judged by the investigator as clinically significant must be recorded as AEs or SAEs if they meet the definition of an adverse event (**Section 8.1.1**, Definition of an Adverse Event), and reported as SAEs if they meet the criteria for seriousness (**Section 8.1.2**, 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.

8.6 SAFETY OVERSIGHT

There is no Data Safety Monitoring Board required for this study. The oversight of safety reporting and assessment is the responsibility of the Sponsor and the Medical Monitor.

9 CLINICAL MONITORING

Representatives of Rockwell Medical, in conjunction with Study Monitor(s) representing Rockwell, will perform a number of on-site visits to the study center. Prior to commencement of the study, representatives of Rockwell will visit the study center to assure adequacy of facilities to conduct the protocol, and to discuss with the Investigator the general obligations regarding studies with investigational new drugs. This visit will be documented in a report. In some cases, for example when the study center has recently participated in a clinical trial in conjunction with Rockwell Medical, the Pre-Study Qualification visit may be waived according to applicable standard operating procedures.

Upon satisfactory receipt of all necessary documentation (including, but not limited to, an allowed IND, an executed Clinical Trials Agreement, and IRB/EC approval of the protocol and informed consent form), Rockwell or its designated monitor(s) will arrange for all study material to be delivered to the study center and for the scheduling of a mutually convenient appointment for a Study Initiation visit. Patient entry must not begin until this initiation visit has been completed. At this meeting, all personnel expected to be involved in the conduct of the study should undergo an orientation to include review of the study protocol, instruction for CRF completion, and overall responsibilities including those for drug accountability and study file maintenance. This visit will be documented in a report.

Throughout the course of the study, Rockwell Medical's and/or its designated monitor(s) will make frequent contacts with the Investigator. Study Monitors representing Rockwell will visit study centers periodically throughout the trial for routine monitoring visits. The Study Monitor will review CRFs to verify that they are accurate, complete and verifiable from source documents. They will also verify the rights and well-being of the study patients are protected and that the study conduct is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements. 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 or its designee monitor(s). The study and its monitors may also be similarly evaluated by auditors representing Rockwell. For these purposes, the Investigator will make CRFs, source documents and study files available when requested. A report will be generated for each monitoring visit.

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. In accordance with applicable standard operating procedures (Rockwell or contracted vendor), a closeout visit may be scheduled, during which Rockwell or its representative will review all informed consents, CRFs, drug accountability records, and other study-related documents. Rockwell or its representative will hold a final meeting with the Investigator and study staff to explain procedures for record retention, publication policy, site audit notification, and financial disclosure. A final letter to the site will record the events of this closeout visit. Study-closure activities will be documented in a report. 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 or its designee monitoring personnel, or for administrative reasons, at any time. In that event, Rockwell or its designee will notify each Investigator in writing that the study is to be discontinued. The Investigator will comply with Rockwell'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 or its designees, the study may be audited by representatives of the US FDA, EMA, CFDA or other applicable regulatory agencies, who will also be allowed access to study documents. The Investigator should immediately notify the Clinical Research Department at Rockwell or its designee of any proposed or scheduled audits with any regulatory authorities.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

A formal statistical analysis plan for the analysis of primary and secondary endpoints will be prepared and completed prior to database lock.

10.2 STATISTICAL HYPOTHESES

The primary endpoint in this study is the difference between Period B and Period C for anti-Xa activity.

- H_o: The AUC_{0-t} anti-Xa is not different between the Heparin infusion period (Period C) and the Triferic +heparin infusion (Period B);
- H_a: The AUC_{0-t} anti-Xa is different between the Heparin infusion period (Period C) and the Triferic + heparin infusion (Period B).

10.3 ANALYSIS DATASETS

The primary analysis dataset for this study will be based on patients who complete all 3 study periods.

The Safety population dataset will include all randomized patients. The primary safety analysis of interest is the comparison of safety parameters during the randomized treatment period.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

A pharmacokinetic analysis plan (PKAP) describing the analytical methodology will be completed prior to commencing analysis of the data.

Summary descriptive statistics will be calculated for all parameters by treatment group; natural logarithmic transformations will be performed prior to the statistical analysis of the parameters. For categorical variables, the frequency and percentage in each category will be reported. Percentages will be based on the number of patients in the analysis population for whom there are non-missing data, unless otherwise specified. For continuous variables, number of available observations (n), arithmetic mean, 95% confidence interval about the arithmetic mean, standard deviation [sd], minimum, median and maximum will be reported.

Unless otherwise stated, all summaries will be presented by treatment group. Unless otherwise specified, baseline data presentations will be based on the primary analysis dataset and safety analyses will be based on the Safety population.

The statistical test to be used to determine equivalence of test to reference will be a two one-sided t-test (TOST) that requires a 90% confidence interval of the ratio of the geometric means obtained from a mixed effects model with sequence, period and treatment as fixed effects and patient (sequence) as a random effect, to be within the boundaries of 0.8 to 1.25.

Test of significance will be based on 5%, one-sided (α=0.05)

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary analysis will compare anti-Xa activity between the Triferic + heparin (Treatment B) and Control heparin (Treatments A andC) as measured by the $AUC_{0\text{-}t}$.

To investigate the drug-drug interaction between Triferic and concomitant administration of heparin, a mixed effects linear analysis of variance (ANOVA) model will be fit to the log-transformed parameters ($AUC_{0\text{-}t}$ for anti-Xa). Effects associated with treatment sequence, period, and treatment will be considered fixed; effects associated with patient (within each treatment sequence) will be considered random.

Point estimates corresponding 90% confidence intervals (CI) will be derived from the differences in model least-squares means for the pairwise treatment comparisons of interest (B-A and B-C) using the residual error from the ANOVA mean square error (MSE). The log-transformed point and interval estimates will be exponentiated (back transformed) to obtain estimates for the geometric mean (GLSM) ratio along with the 90% CI for the GLSM ratios (B:A and B:C). Confidence intervals that fall entirely with the range of 0.8 to 1.25 will indicate no interaction between Triferic and concomitant administration of heparin.

An estimate of the within-subject coefficient of variation ($CV_w\%$) for each log-transformed parameter will be calculated based on the log-normal distribution as follows:

$$CV_w\% = \sqrt{exp(MSE) - 1} \times 100$$

where MSE if the residual error from the ANOVA model described above.

In addition to descriptive summary statistics, the GM, 95% confidence interval about the geometric mean and between-patient coefficients of variation ($CV_b\%$) will be calculated for the log-transformed parameters. The $CV_b\%$ will be calculated as follows:

$$CV_b\% = \sqrt{exp(sd^2) - 1} \times 100$$

where sd is the standard deviation of the log-transformed data.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary efficacy endpoints are:

- The aPTT and TT time comparisons between the Triferic + heparin (Treatment B) and Control heparin (Treatment C) as measured by the $AUC_{0\text{-}t}$.
- The sFe comparison between treatment periods (Treatment B vs Treatment A) as measured by C_{max} and $AUC_{0\text{-}t}$.
- The aPTT and TT time comparisons between the Triferic + heparin (Treatment B) and Control heparin (Treatment C) as measured by the $AUC_{0\text{-}4}$.
- The aPTT and TT time comparisons between the Triferic + heparin (Treatment A) and Control heparin (Treatment C) as measured by the $AUC_{0\text{-}4}$.

10.4.3.1 SECONDARY EFFICACY ENDPOINT

Similar analyses will be conducted that will mirror the approach used for the primary analysis described in section 10.4.2. For these analyses, the mixed effects linear ANOVA model will be the same as the primary analysis to fit the log-transformed parameters ($AUC_{0\text{-}t}$ for anti-Xa; $AUC_{0\text{-}t}$ for aPTT; $AUC_{0\text{-}t}$ for TT; $AUC_{0\text{-}t}$ and C_{max} for sFe;). Point estimates corresponding 90% CI will be reported from the differences in model for the pairwise treatment comparisons. The GM ratio along with the 90% CI for the GM ratios will be reported.

10.4.3.2 SECONDARY EFFICACY ENDPOINTS

- anti-Xa as measured by the $AUC_{0\text{-}4}$ hours between Treatment B vs C.
- aPTT as measured by the $AUC_{0\text{-}4}$ hours between Treatment B vs C
- Number of aPTT measurements between 0.08 hr and 4 hours that are <1.5 X baseline (t=0) or >2.5 X baseline (t=0)

10.4.3.3 SAFETY ANALYSES

Demographics and safety analyses will be presented using descriptive statistics.

The following safety endpoints will be summarized and compared among the three treatment groups:

- The visual dialyzer circuit clotting scale score from start of dialysis to the end of dialysis at 1 hour intervals.
- The number and quantity of additional heparin bolus administered by treatment.
- The incidence of all treatment-related, treatment-emergent adverse events (AEs), including the seriousness, severity, and assessed relatedness to study drug.

- The number and percentage of patients permanently discontinued from study drug treatment due to treatment-emergent AEs.

10.4.3.4 PHARMACOKINETIC ANALYSES

- Noncompartmental pharmacokinetic analysis of serum iron concentrations will be conducted
- Iron profile as measured by the sFe C_{max} and AUC_{0-t} Treatment B (Triferic + Heparin) vs Treatment A (Triferic IV post-dialyzer) will be analyzed as described in Section 10.4.2.

10.4.4 ADHERENCE AND RETENTION ANALYSES

A summary of any dropouts and reasons will be provided in the clinical study report.

10.4.5 PLANNED INTERIM ANALYSES

No interim analyses are planned.

10.4.5.1 SAFETY REVIEW

Safety reviews are the responsibility of the Sponsor and will occur at the time of annual reporting to regulatory agencies unless otherwise required.

10.4.5.2 EFFICACY REVIEW

There will be no interim efficacy review.

10.4.6 ADDITIONAL SUB-GROUP ANALYSES

Sub-groups of age and sex, will be analyzed where indicated by the data.

10.4.7 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable.

10.4.8 TABULATION OF INDIVIDUAL RESPONSE DATA

All tabulations of individual responses will be included in the data listings.

10.4.9 EXPLORATORY ANALYSES

Additional post-hoc analyses may be conducted after analysis of the primary, secondary and safety results.

10.5 SAMPLE SIZE

The samples size has been estimated empirically..

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

This is an open-label randomized, 3 period crossover study. All treatment arms utilize heparin in various permutations of administration; two of the treatment arms utilize Triferic.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

N/A

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

This is an open label study. All patients and study personnel have knowledge of the treatments administered.

If the protocol is revised, protocol amendments will be prepared and approved by Rockwell. All protocol amendments must be submitted to the IRB/EC for review and approval must be obtained prior to implementation. However, as discussed in **Section 14.3**, 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 Medical or its designee.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

In accordance with the applicable regulations a case report form (CRF), whether paper or electronic, must be completed for eachpatient enrolled in the study. CRFs are an integral part of the trial and subsequent reports. All data collected for each study patient will be recorded on CRFs provided or approved by Rockwell.

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. CRF completion may be formally delegated to other study personnel. However, Rockwell Medical or its designee must be informed in writing of the name of such persons and the scope of their authority. 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. It is the obligation of the Investigator to review each page of the CRFs and to sign the designated and appropriate CRFs as the study's authority. The Investigator is also responsible for maintaining any source documentation related to the study, including, but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs, files or tapes.

If using paper source documents, they must be completed legibly, preferably with **black ballpoint pen**. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be initialed and dated by the person making the correction. Erasure or the use of correction fluid or film is unacceptable.

For each study subject, the completed CRFs must be promptly reviewed, and required pages signed and dated by the Investigator. The Investigator must retain a copy of all CRFs.

12 QUALITY ASSURANCE AND QUALITY CONTROL

All CRF entries will be monitored and subject to verification against source documents during routine monitoring visits by Rockwell Medical personnel or their designees.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

This study is a Phase I/II study involving both investigational products (Triferic IV) and approved therapeutic agents (UFH). All applicable regulations governing human patient protection for the study location must be followed. All ethical and regulatory requirements necessary to comply with the principles of Good Clinical Practice (GCP) for the conduct and monitoring of clinical investigations must be followed.

To ensure ethical conduct of this clinical study, Investigators will be expected to adhere to basic principles provided from generally recognized guidelines such the Belmont Report and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. Participants must have provided written informed consent to document their voluntary participation in this study. Updated safety information will be provided to the Investigators, Institutional Review Boards (IRBs)/Ethics Committees (ECs) and patients as necessary in order that they may consider relevant and emerging information that could affect their willingness to continue participation in this study.

13.2 INSTITUTIONAL REVIEW BOARD

In accordance with the Food and Drug Law in each locality the Investigator agrees to provide the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) with all appropriate material, including a copy of the protocol, informed consent form (ICF), and any proposed advertisement for the study prior to the start of the study.

The proposed informed consent form (ICF) and any proposed advertisement must also be agreed to by Rockwell Medical. A copy of the IRB/EC approval letter of the protocol and the ICF must be supplied to Rockwell Medical or its designee prior to consenting any patients for the study. A copy of the IRB/EC approval letter of any protocol amendments and any advertisements must be supplied to Rockwell Medical or its designee prior to implementing these documents. The study may not begin screening or enrolling patients until the Investigator has obtained IRB/EC approval of the protocol and ICF and Rockwell Medical or its designee has received a hardcopy documentation of each.

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

During the course of the study, the Investigator shall make timely and accurate reports to the IRB/EC on the progress of the trial, at intervals not exceeding one year, as well as satisfying any other local IRB/EC regulations regarding reporting. Copies of all reports to and correspondence with and from the IRB/EC must be provided to Rockwell or its designee. Furthermore, at the completion or early termination of the study, a final report should be made to the IRB/EC by the Investigator within the applicable IRB/EC time frames. A copy of this report will be provided to Rockwell or its designee.

Any significant changes or revisions in the study protocol or any changes that may alter patient risk must be approved by Rockwell (and may require CFDA/other regulatory agency review and/or approval) and must be approved in writing by the IRB/EC prior to implementation (see **Section 13.2** for protocol amendments). The Investigator must also receive a written notice of approval from Rockwell 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 is immediately notified and an amendment is subsequently provided by Rockwell and approved by the IRB/EC.

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

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

A copy of the proposed patient information document should be submitted to Rockwell Medical or its designee for review and comment prior to submission to the reviewing IRB/EC. The patient information document must be approved by the IRB/EC and contain all elements required by all applicable federal, state, local, and institutional regulations or requirements prior to study initiation.

The proposed patient information document must contain a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages, risks, and a statement of confidentiality of patient study records,an explanation of whom to contact about the research, the patient's rights, compensation, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits. These requirements are in accordance with the US Code of Federal Regulations (CFR) as detailed in the 21CFR50.25 and the Declaration of Helsinki. The patient information document should also indicate that access to relevant medical records by Rockwell Medical and/or its duly appointed agent and by representatives of the Food and Drug Administration (FDA) or other applicable regulatory agency may be required and informs patients that their data may to be used in publications.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

See Section 13.3.1.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

All investigational sites and laboratories or entities providing support for this study, must, where applicable, comply with all applicable data protection and patient confiendtiality regulations in force at the time of study initiation.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES,SPECIMENS OR DATA

Data collected for this study will be analyzed and stored by the Sponsor. No blood or serum sample retention is part of this study.

All data collected is anonomized and may be provided to investigators for additional analysis upon acceptance of a protocol for data analysis.

13.5 FUTURE USE OF STORED SPECIMENS

N/A

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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,
- 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 patient,
- Any advertisements for this study,
- The Investigator's final report to the IRB/EC,
- 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 Investigator must advise Rockwell 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 or its designee.

In the event of accidental loss or destruction of any study records, the Investigator will immediately notify Rockwell Medical or its designee 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.

The laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation. Reference values and/or normal ranges for the test results must be provided. Rockwell or its designee must be notified immediately in writing of any changes occurring in reference values during the course of the study.

Local and central laboratories used in the study may be asked to provide the following or its local equivalent:

- College of American Pathologist (CAP) accreditation, and/or
- Clinical Laboratory Improvement Amendments (CLIA) accreditation,
- Listing of laboratory normal reference values (for all protocol required tests),
- Laboratory license,

- Curriculum vita of laboratory director may also be requested.

14.2 STUDY RECORDS RETENTION

The period of time these documents must be maintained is governed by US law and, when applicable, non-US regulations. Some countries require these documents to be maintained for 15 years or longer. All records are to be retained by the Investigator for a minimum of two (2) years after the approval of a 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 may request retention for a longer period of time. Therefore, Rockwell or its designee will inform the Investigator when these documents may be destroyed. The Investigator must obtain written approval from Rockwell prior to destruction of any records.

14.2.1 INVESTIGATORS 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.

14.3 PROTOCOL DEVIATIONS

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

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 the Sponsor 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 the Sponsor. Examples of possible protocol deviations include, but are not limited to:

- Failure to provide required patient information,
- 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.

14.4 PUBLICATION AND DATA SHARING POLICY

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 or its designee 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.

Data from the study will be made available under the regulations in force at each country participating in the study. Final study data wil be posted to the Clinicaltrials.gov website according to requirements in force at the time of completion of the CSR.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

This study in under the leadership of Rockwell Medical Inc. Rockwell Medical is responsible for coordination of study design, execution, monitoring, data mangagement, analysis and reporting. Rockwell Medical may designate certain activities to contract research organizations (CRO) as needed.

16 CONFLICT OF INTEREST POLICY

Each Investigator is required to provide financial disclosure statements or certifications to Rockwell Medical or its designee prior to study initiation. In accordance with the US 21CFR54 and other non-US regulations, Investigators and all sub-investigators are required to disclose all financial interests in Rockwell Medical in order to permit complete and accurate certification statements in an application for marketing authorization. This includes compensation affected by the outcome of a clinical study, significant equity interest in Rockwell Medical, and proprietary interest in the tested product. The Investigators must promptly update this information if any relevant changes occur during the course of the investigation and over the period of one year following completion of the investigation.

17 LITERATURE REFERENCES

Reference List

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Appendix 1: Protocol Revisions

Version	Date	Significant Revisions
1.1	07/12/2019	Corrected Clinical Laboratory Harmonized the figures with text

Appendix 2: Schedule of PK Assessments

HEPARIN INFUSION PROTOCOL:

Nominal T=0: Draw baseline coagulation and serum iron profiles

T=0 Administer UFH IV push at the patients usual bolus dose and start continuous infusion heparin at the usual rate to be administered over 3 hours of dialysis

Triferic + heparin: mix together and administer at a rate to infuse the entire volume over 3 hours.

Draw bloods from the arterial blood line port during HD; Post HD draw from peripheral vein or indwelling needle.

Nom Time (Min)	NomTime (hr.)	Coag. Profile	Serum Fe Profile	Syringe Volume	Calc Hep Inf Rate IU/hr
0	**0**	X	X	X	
5	**0.08**	X		X	
30	**0.5**	X		X	X
60	**1**	X	X	X	X
120	**2**	X	X	X	X
180	**3**	X	X	X	X
240	**4**	X	X		
300	**5**	X	X		
360	**6**	X	X		
420	**7**	X	X		
480	**8**	X	X		

BLOOD DRAWS:

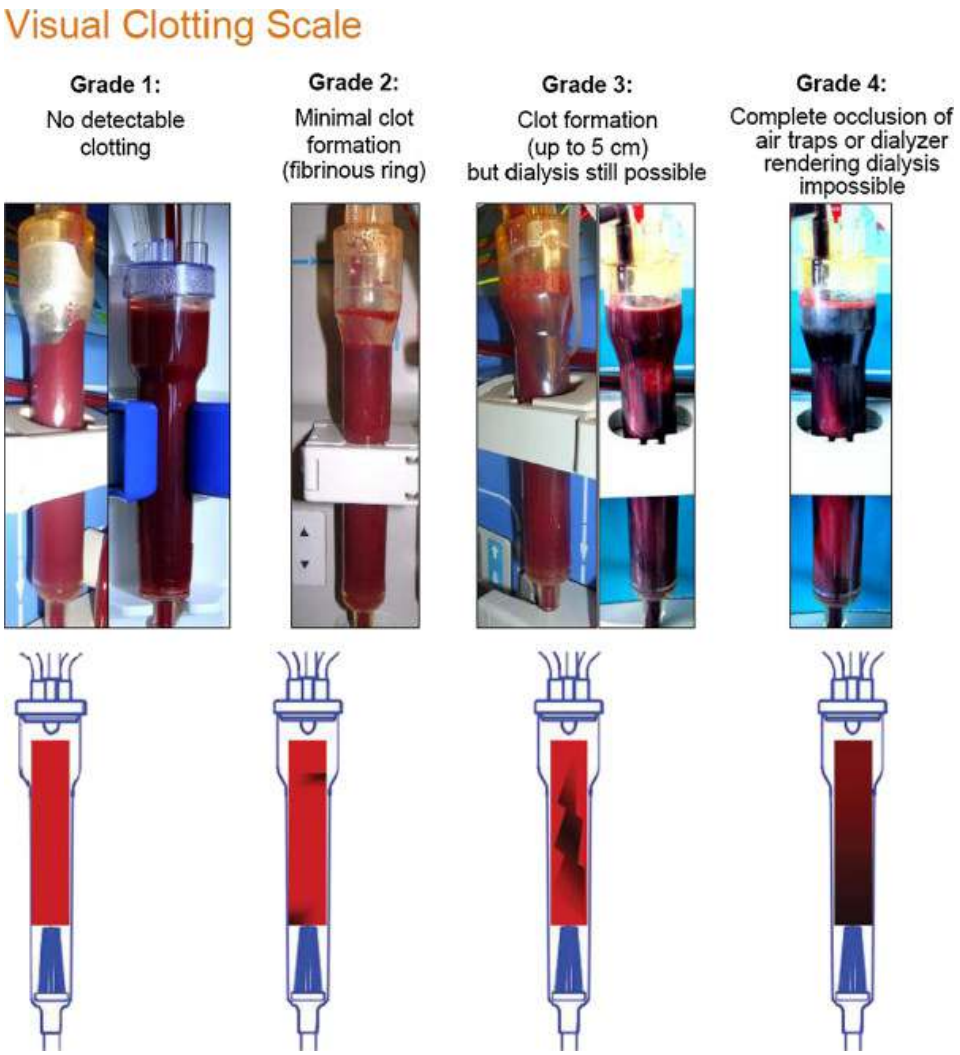
Coag: BD 363083 2.7 mL blue top citrate tube: 12 X 2.7 X 3=108 mL

aPTT, anti-Xa and PT

sFe Profile: BD 367983 3.5 mL SST tube: 10 X 3.5 X3 = 105 mL

sFe, TIBC, TSAT, Ferritin

Appendix 3: Visual Scale for Dialyzer Circuit Clotting



Appendix 4: Instructions for administration of heparin + Triferic and Triferic alone.

PROTOCOL FOR TRIFERIC INFUSION WITH HEPARIN

1. Heparin: Aseptically draw total treatment amount of heparin into the 10 mL syringe
2. Remove needle
3. Obtain plastic ampule of Triferic: wipe the tip with alcohol, open by twisting the top, hold the ampule vertically, screw the tip of the inverted syringe into the neck of the ampule, raise the ampule so that it is upside down. Draw Triferic solution into the syringe and invert to mix.
2. *CAUTION: Air should not be injected into the plastic ampule prior to drawing out the Triferic solution. Doing so may result in leakage of solution through the luer lock.*

3. Unscrew the tip of the syringe from the luer lock in the neck of the ampule
4. Inject ~0.25 to 0.4 mL of the solution into the heparin line in order to displace the saline present in the line.
5. Mount the syringe on the heparin pump
6. Start the heparin + Triferic infusion and program the pump to administer the entire volume.
7. Set heparin infusion pump to end 1 hour before end of dialysis treatment, or as per unit policy for heparin infusion.

(Note: for a 4 hour hemodialysis treatment, heparin infusion is usually given over the first 3 hours and Triferic would be infused concurrently with heparin over the first 3 hours of treatment)

PROTOCOL FOR TRIFERIC INFUSION WITHOUT HEPARIN

1. Obtain plastic ampule of Triferic: wipe the tip with alcohol, open by twisting the top, hold the ampule vertically, screw the tip of the inverted syringe into the neck of the ampule, raise the ampule so that it is upside down. Draw Triferic solution into the syringe.
8. *CAUTION: Air should not be injected into the plastic ampule prior to drawing out the Triferic solution. Doing so may result in leakage of solution through the luer lock.*
9. Unscrew the tip of the syringe from the luer lock in the neck of the ampule
10. Inject an amount of the Triferic equal to the priming volume of the administration line (~0.25 to 0.4 mL) in order to displace the saline present in the line
11. Mount the syringe on the infusion pump
12. Start infusion and administer over 3 hours of the dialysis session into the post dialyzer blood line (or drip chamber).

PROTOCOL FOR HEPARIN INFUSION WITHOUT TRIFERIC

1. Heparin: Aseptically draw total treatment amount of heparin into the 10 mL syringe
2. Inject the priming bolus of heparin into the venous blood line
3. Remove the needle and mount the syringe on the heparin pump
4. Start the heparin and program the pump to administer the entire volume.
5. Set heparin infusion pump to end 1 hour before end of dialysis treatment, or as per unit policy for heparin infusion.
6. (Note: for a 4 hour hemodialysis treatment, heparin infusion is usually given over the first 3 hours and Triferic would be infused concurrently with heparin over the first 3 hours of treatment)