CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206317 (S-0000)
Priority or Standard	Standard
Submit Date(s)	March 24, 2014
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Division / Office	DHP/OHOP
Reviewer Name(s)	Min Lu, M.D., M.P.H.
Review Completion Date	December 19, 2014
Established Name	Soluble Ferric Pyrophosphate
(Proposed) Trade Name	Triferic
Therapeutic Class	Iron via Hemodialysate
Applicant	Rockwell Medical, Inc.
Formulation(s)	(b) (4) mg of elemental iron/mL vials
Dosing Regimen	2 mcM iron (110 mcg iron per L of dialysate)
Indication(s)	Treatment of iron loss or iron deficiency to maintain hemoglobin and to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels
Intended Population(s)	Adult patients with hemodialysis-dependent chronic kidney disease

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Abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
AV	Arteriovenous
BP	Blood pressure
CAD	Coronary Artery Disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CERA	Continuous erythropoietin receptor activator
CFR	Code of Federal Regulations
CHF	Congestive Heart Disease
CHr	Reticulocyte hemoglobin content
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRF	Case Report Form
CRP	C-reactive protein
CRUISE	Continuous replacement using iron soluble equivalents
CTCAE	Common Terminology Criteria for Adverse Event
dL	Deciliter
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EoT	End-of-treatment
ERI	ESA Resistance Index
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GFR	Glomerular Filtration rate
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
Hgb	Hemoglobin
HD	Hemodialysis
HDD-CKD	Hemodialysis Dependent Chronic Kidney Disease
HIV	Human immunodeficiency virus
IBC	Iron Binding Capacity
ICH	International Corrference on Harmonization
IDA	Iron Deficiency Anemia
IDH	intradialytic hypotension
IND	Investigational Drug Application
IRB	Institutional Review Board

ITT	Intent-to-Treat
IV	Intravenous
kg	Kilogram
Kt/V	dialyzer clearance of urea multiplied by dialysis time, divided by
LOCF	last observation carried forward
LS	Least Square
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
mcg	microgram
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MITT	Modified Intent-to-Treat
mg	Milligram
mL	Milliliter
mmHg	Millimeters Mercury
NDA	New Drug Application
ng	Nanogram
OL	open-label
PAES	polyarylethersulfone
PCS	potentially clinically significant
PD	Pharmacodynamics
PK	Phamacokinetics
PMR	Postmarket Requirement
PREA	Pediatric Research Equity Act
PT	Preferred term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard Deviation
SFP	Soluble ferric pyrophosphate
SOC	System Organ Class
SPA	Special protocol assessment
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-emergent serious adverse event
TIBC	Total iron binding capacity
$TIBC_{Tf}$ (µmol/L)	(transferrin [mg/dL] x 1.4) x 0.179
$TIBC_{UIBC}$ (µmol/L)	(serum iron [µg/dL] + UIBC [µg/dL]) x 0.179
TSAT	Transferrin Saturation
$TSAT_{Tf}$(%)	(serum iron [µmol/L])/(TIBCTf [µmol/L]) x 100
$TSAT_{UIBC}$ (%)	(serum iron [µmol/L]/TIBCUIBC [µmol/L]) x 100
UIBC	unsaturated iron binding capacity
ULN	Upper Limit of Normal
URR	Urea reduction ratio
WBC	White Blood Cell

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, Triferic should be approved for the indication for the treatment of iron loss to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

From a clinical perspective, Triferic should not be approved for the indication to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

1.2 Risk Benefit Assessment

The overall benefit/risk assessment was favorable for Triferic in clinical trials for the treatment of iron loss to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD). Triferic is delivered by dialysate during hemodialysis and provides a new option for parenteral iron administration, with a low iron dose as iron maintenance, to patients with HDD-CKD who require iron supplement due to iron loss during the hemodialysis procedure. The summary of efficacy and safety results for Triferic in clinical trials is included below.

Efficacy Summary:

The efficacy of Triferic was evaluated in two randomized controlled phase 3 clinical trials of identical design in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD) (305 patients in SFP-4 and 294 patients in SFP-5) for the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin. Each study was a multicenter, randomized, single-blind, placebo-controlled study in iron-replete patients with HDD-CKD. Study patients received SFP in dialysate at the concentration of 110 mcg iron/L or standard dialysate without SFP as placebo during each hemodialysis for 3 or 4 times per week. Randomized treatment duration was planned for up to 48 weeks. The mean treatment duration in the randomized phase was 157.7 days in the SFP group and 164.6 days in the placebo group in study SFP-4 and 161.2 days in the SFP group and 157.9 days in the placebo group in study SFP-5. About 50% of study patients received study treatment for ≥20 weeks and 20% of study patients received study treatment for 44-47 weeks in the randomized phase.

The primary efficacy endpoint was the change in mean hemoglobin (Hgb) from baseline to the end of treatment period (last one-sixth of the randomized treatment period). In Study SFP-4, the mean hemoglobin decreased 0.03 g/dL in the SFP group as compared to 0.38 g/dL in the placebo group in the Intention-to-Treat (ITT) population. In Study SFP-5, the mean hemoglobin decreased 0.08 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group in the ITT

population. The primary efficacy analysis used an ANCOVA analysis with baseline hemoglobin as the covariate. The treatment difference in hemoglobin calculated as least square (LS) mean difference was 0.35 g/dL in each study between the SFP (0.06 g/dL in SFP-4 and -0.04 g/dL in SFP-5) and the placebo groups (-0.30 g/dL in SFP-4 and -0.39 g/dL in SFP-5) and was statistically significant (p=0.01) in both studies after adjusting for baseline hemoglobin and ESA stratum. The results of additional analyses in Modified ITT (MITT) population and secondary endpoints in changes in TSAT and serum ferritin level from baseline to the end of treatment were consistent with the results from the primary efficacy analysis in both studies. The results from the two phase 3 clinical studies demonstrated that Triferic was effective to maintain hemoglobin during the treatment period in patients with HDD-CKD.

Although treatment duration was planned for up to 48 weeks, it is notable that only a minority of patients completed full 48 weeks treatment, due in large part to protocol-mandated change in anemia management (involving changes in ESA and/or iron dosing). In Study SFP-4 these included 45.4% of patients in the SFP group and 53.6% in the placebo group; in Study SFP-5 these included 46.3% of patients in the SFP-group and 61.2% in the placebo group. Of those, the majority of study patients were due to required ESA dose change for hemoglobin in Study SFP-4 (42.8% in the SFP group and 45.1% in the placebo group) and in Study SFP-5 (44.2% in the SFP group and 46.9% in the placebo group) and a few patients were due to requirement of intravenous iron administration for serum ferritin level <100 mcg/L in Study SFP-4 (2.6% in the SFP group and 9.2% in the placebo group) and in Study SFP-5 (2.0% in the SFP group and 14.3% in the placebo group). A greater percentage of patients in the SFP group (27%) as compared to the placebo group (20.9%) had hemoglobin >12 g/dL prior to withdrawal and more subjects in the placebo group as compared to the SFP group (17.6% vs. 11.2%, respectively) had hemoglobin <9 g/dL in Study SFP-4. Similarly, in Study SFP-5, there were more subjects with hemoglobin < 9 g/dL prior to withdrawal in the placebo group as compared to the SFP group (23.1% vs. 15%, respectively) and more subjects had hemoglobin >12 g/dL in the SFP group as compared to the placebo group (21.8% vs. 14.3%, respectively) prior to withdrawal. There were also more subjects who had serum ferritin level <100 mcg/L in the placebo group as compared to the SFP group in Study SFP-4 (11.1% vs. 3.3%, respectively) and in Study SFP-5 (15.6% vs. 2.7%, respectively). Although there was unexpected large proportion of patients didn't completed 48 weeks of study treatment mainly due to significant ESA dose changes during the study the final hemoglobin and serum ferritin level between the SFP and placebo groups prior to withdrawal were consistent with the primary efficacy results.

The submission also includes a Phase 2 study (NIH-FP-01) to support a labeling statement for reduction of ESA dose in these patients. In this multicenter, randomized, double-blind, placebo-controlled study in 108 patients with HDD-CKD patients received either SFP or placebo during dialysis. The mean treatment duration was 212 days in the SFP group and 222 days in the placebo groups. The primary efficacy endpoint was the percent change from baseline in ESA dose at the end of treatment. The results in ITT population showed that the subjects receiving SFP had a mean increase of 5.0% in prescribed ESA dose at end-of-treatment as compared to a mean increase of 37.3% in the placebo group (p=0.052). It also showed that the subjects receiving SFP had a mean 11.1% increase in actual ESA dose as compared to a mean 40.7%

increase in the placebo group in ITT population and the differences between the two treatment groups was again not statistically significant (p=0.111). The secondary efficacy endpoint analysis showed a similar distribution of changes in the prescribed ESA dose between the SFP and the placebo groups (p=0.915). The NIH-FP-01 study protocol stated that this study was exploratory in nature and statistical tests were considered to be descriptive rather than conclusive. No formal sample size determination was provided in the protocol. Because of the exploratory nature of the study, the submitted data is insufficient to support the proposed second indication to reduce the prescribed dose of ESA required to maintain desired hemoglobin levels. Large Phase 3 trials should be conducted to further evaluate the efficacy of Triferic for this indication.

Safety Summary:

The safety of Triferic was evaluated primarily in two randomized placebo-controlled phase 3 clinical trials (SFP-4 and SFP-5) in patients with HDD-CKD (total of 292 patients received SFP). Overall treatment-emergent adverse events (TEAEs) were reported at similar rates for the SFP-treated patients and the placebo-treated patients (78.4% and 75.3%, respectively) during the studies. Non-fatal treatment-emergent serious adverse events (SAEs) were reported at similar rates for the two groups (24.0% in SFP-treated patients and 25.3 % in the placebo-treated patients). Thirteen (4.5%) patients had at least one TEAE that led to treatment discontinuation permanently in the SFP group as compared to 7 (2.4%) the placebo group in the clinical trials.

A total of 17 deaths were reported in the two phase 3 clinical trials including 12 (4.1%) among the SFP-treated patients and 5 (1.7%) among the placebo-treated patients. Among the death cases, the duration of on study treatment ranged from 8 to 328 days in the SFP-treated patients and 27 to 227 days in the placebo-treated patients. Time to event leading to death since the last hemodialysis with study drug ranged from 1 to 15 days in the SFP-treated patients and 1 to 3 days in the placebo-treated patients. Almost all patients had significant underlying cardiac conditions in addition to end-stage renal disease. Six patients in the SFP group and one patient in the placebo group died at home or nursing home without detailed information provided. The events leading to death were cardiac arrest in 8 cases (6 in SFP-treated patients and 2 in placebo-treated patients), sudden death or unknown cause in 5 cases (4 in SFP-treated patients and 1 in placebo-treated patients), acute myocardial infarction in 3 cases (1 in SFP-treated patients and 2 in placebo-treated patients), and one case of bronchopneumonia in the SFP group. No deaths were considered to be related to the study treatment by investigator and cases could be most likely attributed to co-morbid disease and/or disease progression.

In the two phase 3 clinical trials, suspected hypersensitivity reaction was reported in one (0.3%) patient in the SFP group as compared to none in the placebo group (0%). The event was considered as moderate and related to study drug. Five additional cases of suspected hypersensitivity reaction were reported in phase 2 and the phase 3 open-label extension treatment studies. Overall, six (0.4%) cases of suspected hypersensitivity reactions were reported in 1411 SFP-treated patients in clinical trials in the SFP development program. In 2 of the 6 cases events occurred at the first dose, were considered to be study drug related and study treatment was

discontinued permanently. The remaining 4 patients continued the SFP treatment without recurrent events and the events were not considered to be related to the study drug. Occurrence of other adverse events of special interest, including intradialytic hypotension, composite cardiovascular events, hemodialysis vascular access thrombotic event, and systemic or serious infection, were similar for the SFP group and the placebo group.

The most common TEAEs (≥3% in the SFP-treated patients) that were reported more frequently in the SFP-treated patients than in the placebo-treated patients were procedural hypotension, muscle spasms, headache, dizziness, peripheral edema, pain in extremity, dyspnea, pyrexia, urinary tract infection, hyperkalemia, back pain, asthenia, fatigue, arteriovenous fistula site hemorrhage, arteriovenous fistula thrombosis, and hypertension. The nonfatal SAEs that were reported more frequently in the SFP group as compared to the placebo group included: diabetic foot infection (1% vs. 0%), arteriovenous fistula thrombosis (1.7% vs. 0.7%), and pulmonary edema (1.4% vs. 0.3%). The most common TEAEs (occurred in at least 2 subjects) leading to study discontinuation in the SFP group were asthenia, dizziness and headache.

A total of 1411 patients were exposed to Triferic in all clinical trials including open-label extension studies. The safety profile of Triferic in those patients was similar to that observed in the Phase 3 clinical trials.

Overall, SFP was reasonably tolerated in patients with HDD-CKD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Two Postmarketing Requirements (PMRs) should be issued under the requirements of Pediatric Research Equity Act (PREA). The applicant requested a deferral of two pediatric studies to meet the requirements of PREA. The proposed studies included one pharmacokinetics/ pharmacodynamics (PK/PD) study and one efficacy and safety study in pediatric patients aged from birth to (b) (4) years with hemodialysis-dependent chronic kidney disease.

2 Introduction and Regulatory Background

2.1 Product Information

Based on the sponsor's submission and labeling discussions with the review team, the following is a summary of product information:

Triferic is ferric pyrophosphate citrate solution, a mixed-ligand iron complex in which iron (III) is complexed to pyrophosphate and citrate. It has a molecular formula of $Fe_4(C_6H_5O_7)_3(P_2O_7)_3$

and a relative molecular weight of approximately 1312.5 Daltons. Triferic does not contain any carbohydrate moiety.

Triferic is a clear solution with a slightly yellow-green color. Triferic is available in 5 mL ampules for a single use by adding to bicarbonate concentrate for hemodialysis and diluting further as described below. Each mL of Triferic contains 5.44 mg of elemental iron.

Triferic is administered at each hemodialysis session by adding to bicarbonate concentrate dialysate and dilution. Once in the dialysate, SFP crosses the dialyzer membrane during the hemodialysis and enters the blood.

A 5 mL vial of Triferic (27.2 mg elemental iron) is designed for addition to 2.5 gallons (9.46 liters) of bicarbonate concentrate. (b) (4) The final concentration of Triferic in dialysate is at 110 mcg/L (27.2 mg iron/247.5 L dialysate).

(b) (4)

Drug established name: ferric pyrophosphate citrate
Proposed trade name: Triferic
Chemical class: iron products
Pharmaceutical class: Anti-anemic products

Proposed indication:

- "treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD)."
- "to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels."

2.2 Tables of Currently Available Treatments for Proposed Indications

Current available treatment for iron deficiency anemia includes oral iron products and intravenous iron products in the U.S. The approved intravenous (IV) iron products include iron dextran (INFeD and Dexferrum), Ferrlecit, Venofer, Feraheme, and Injectafer. All these IV iron products are approved for treatment of iron deficiency anemia in patients with hemodialysis-dependent CKD (HDD-CKD) except for Injectafer (approved for non-dialysis-dependent CKD only). Oral iron administration has not been considered to be effective in patients with HDD-CKD. The approved indications, dose regimens and main safety concerns for these intravenous iron products are shown in the table below.

Table 1. Currently Approved Intravenous Iron Products in US

Chemical name	Iron Dextran (INFeD, Dexferrum)	Ferrlecit (Sodium Ferric gluconate complex)	Venofer (Iron Sucrose)	Feraheme (ferumoxytol)	Injectafer (ferric carboxymaltose)
Year of first U.S. approval	1974	1999 (marketed in Europe since 1950's)	2000 (marketed in Europe since 1950's)	2009	2013
Indication	IDA in broad patients	IDA in patients with HDD-CKD	IDA in patients with CKD	IDA in patients with CKD	IDA in broad patients IDA in patients with NDD-CKD
Safety	Box warning for anaphylactic-type reactions	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions
Population	Adults and Pediatrics	Adults and Pediatrics	Adults and Pediatrics	Adults	Adults
Elemental Iron per dose	100 mg daily	125 mg at HD	HDD-CKD: 100 mg NDD-CKD: 200 mg Peritoneal dialysis: 300 mg, 400 mg	510 mg	750 mg
Total iron dose per treatment course	Calculated using desired Hgb	1000 mg over 2-3 weeks	1000 mg over 2-3 weeks	1020 mg over 3-8 days	1500 mg over at least 7 days
Injection rate per dose	≤ 50 mg/ min	12.5 mg/min	20-50 mg/min	≤ 30 mg/sec	100 mg/min
Infusion duration per dose		Over 1 hr	100-200 mg over at least 15 min 300 mg over 1.5 hrs 400 mg over 2.5 hrs	Over at least 15 min	Over at least 15 min

Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

This drug has not been approved in the U.S. However, there are five other intravenous iron products available in the U.S. as shown in Table 1 above. Iron has been considered as an active ingredient for all IV iron products.

2.4 Important Safety Issues with Consideration to Related Drugs

Intravenous iron products have been associated with anaphylactic-type reactions. Iron dextran products (INFeD and Dexferrum) have a boxed warning for anaphylactic-type reactions. Ferrlecit, Venofer, Feraheme and Injectafer have bolded warnings for hypersensitivity reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Ferric pyrophosphate (FePPi) was initially submitted in August 1996 under an investigator-sponsored Investigational New Drug (IND) application (b) (4) The product was

transferred to the current applicant, Rockwell Medical, in 2002 and the product name was subsequently changed to Soluble Ferric Pyrophosphate (SFP). (b) (4) [redacted] n End-of-Phase 2 meeting was held on June 30, 2010 between the Agency and the applicant regarding the phase 3 development program (see Meeting Minutes dated July 21, 2010). The applicant submitted a Special Protocol Assessment (SPA) on October 29, 2010, for which FDA issued a No-Agreement letter on December 1, 2010 because the design and planned analysis of the study did not adequately address the objectives necessary to support regulatory submission. A Type A meeting was subsequently held between the FDA and the applicant on January 14, 2011 to discuss the SPA submission. A pre-New Drug Application (NDA) meeting was held in September 9, 2013.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission is an electronic submission in eCTD format. Two U.S. clinical sites (Sites 406 and 424) with most patients enrolled in RMTI-SFP-4 and two Canada sites (Sites 508 and 529) with most patients enrolled in RMTI-SFP-5 were requested for inspection to the Office of Scientific Investigations (OSI). The inspection of these sites concluded that the study data collected from these clinical sites appeared reliable (Clinical inspection summary, Dr. Anthony Orencia, M.D. dated 11/24/14).

3.2 Compliance with Good Clinical Practices

Informed consent was required from patients in all clinical trials. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

3.3 Financial Disclosures

The sponsor certified that there was no financial arrangement with clinical investigators in clinical trials except the following:

- Financial Disclosure Forms for fourteen sub-investigators were not available at initial but were confirmed not to have received compensation beyond the value of which could be affected by the outcome of the study.

- [redacted] At that time, he completed Form FDA 3455 disclosing his financial interests in the study. However, financial disclosures of the eight sub-investigators were not completed. [redacted]. Rockwell Medical has been unable to track the subinvestigators to get financial disclosure information. [redacted] No financial arrangements with Rockwell Medical were made with any sub-investigator [redacted]
- One sub-investigator [redacted] for [redacted] of Study [redacted] was also compensated as a consultant for additional work at the site. The applicant indicated that consultancy was such that the compensation (not provided) could not be affected by the outcome of the study.
- [redacted] was principal investigator for the [redacted] funded by a grant from [redacted]

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Review is pending.

4.2 Clinical Microbiology

Review is pending.

4.3 Preclinical Pharmacology/Toxicology

Review is pending.

Based on the sponsor's reports and labeling discussions with the review team, the following is a summary of preclinical information:

In a fertility and early embryonic development study in female rats, the maternally toxic dose of 40 mg/kg administered three times per week by intravenous (IV) infusion was not toxic to the developing embryo.

In embryo-fetal developmental toxicity studies, ferric pyrophosphate was administered during the period of organogenesis as a one-hour IV infusion to pregnant rats and rabbits. No maternal

or developmental toxicity was observed at doses up to 30 mg/kg/day in rats and 20 mg/kg/day in rabbits. Maternally toxic doses affected embryo-fetal development, resulting in post-implantation loss due to early resorptions, abnormal placentae, decreased fetal body weight and fetal head and vertebral malformations at 90 mg/kg/day in rats and vertebral malformations at 40 mg/kg/day in rabbits.

A pre-and post-natal development study was conducted in pregnant rats with intravenous doses of ferric pyrophosphate up to 90 mg/kg/day. The maternally toxic dose of 90 mg/kg/day resulted in reductions in the number of live offspring and lower offspring body weights. There were no adverse effects on survival of offspring at doses up to 30 mg/kg/day, or on behavior, sexual maturation or reproductive parameters of offspring at any dose level.

The sponsor reported that studies examining the carcinogenic potential of ferric pyrophosphate have not been conducted. Ferric pyrophosphate citrate was clastogenic in the *in vitro* chromosomal aberration assay in CHO cells in the presence of metabolic activation. Ferric pyrophosphate was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test, or clastogenic in the *in vitro* chromosomal aberration assay in CHO cells in the absence of metabolic activation or in the *in vivo* mouse micronucleus assay.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Triferic® contains iron in the form of ferric pyrophosphate citrate and is administered to patients via transfer from hemodialysis solution, across the dialyzer membrane to the blood. It is designed for slow continuous administration throughout the course of hemodialysis.

4.4.2 Pharmacokinetics/Pharmacodynamics

The sponsor conducted a dose-ranging study in patients with HDD-CKD, a PK study in healthy subjects, and a cross-over study evaluating the effect of different dialysis conditions on the delivery of iron.

The following are summary results from FDA clinical pharmacology review (Olanrewaju Okusanya, Pharm.D., dated 12/11/14)

Using data from the dose-escalation trial SFP-2, there was a dose-related change in serum iron after dialysis with different doses of SFP. SFP 100 mcg Fe/L or greater did not result in a markedly higher increase in serum iron. This supports the adequacy of the 110 mcg Fe/L dose of SFP.

Concentration-response analyses could not be performed because pharmacokinetic sampling was not performed in efficacy and safety studies.

In patients with HDD-CKD, the impact of varying hemodialysis (HD) conditions such as re-used dialyzers, low bicarbonate, low blood flow rate to dialysis flow rate (Qb/Qd) and polyarylyethersufone (PAES) membrane on the delivery of iron was evaluated. The median

cumulative net iron delivered, under standard conditions, was estimated to be 0.348 mg (range = -0.296 to 3.32 mg). The median cumulative net iron delivered with low blood flow rate to dialysis flow rate (Qb/Qd) in the same patients (Qb/Qd of ≥ 350/≥600 mL/min vs. 250/400mL/min) in the aforementioned study was estimated to be 0.130 mg (range= -0.101 to 1.28 mg). The other factors did not appear to remarkably impact the net iron delivered.

The applicant did not conduct a human ADME study or a metabolism study, given that absorbed iron is not metabolized and is highly conserved within the body.

The Interdisciplinary Review Team (IRT) for QT Studies evaluated the QTc data from SFP-2 and concluded that SFP did not show large effects on QTc. IRT concluded that no further investigation on the effect of SFP on ECG intervals were required (IND 51,290, Monica Fiszman, dated 11/10/10).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The following table lists the clinical studies submitted for this NDA.

Table 2. Clinical Studies

Study	Study Period	Study Design/Population	Treatment/Regimen	No. Subjects Randomized
Pivotal Clinical Studies				
RMTI-SFP-4 (SFP-4) 43 U.S. sites	23 Mar 2011 – 24 Mar 2013	Randomized, single-blind. placebo controlled study in patients with hemodialysis-dependent chronic kidney disease	SFP: SFP added in bicarbonate concentrate dialysate at 2 µM (11 µg iron/dL of dialysate), 3-4 hemodialysis sessions per week Placebo: standard bicarbonate concentrate dialysate, 3-4 hemodialysis sessions per week	SFP: 152 Placebo: 153
RMTI-SFP-5 (SFP-5) 41 U.S. sites 2 Canada sites	27 Apr 2011 – 19 Jul 2013	Randomized, single-blind. placebo controlled study in patients with hemodialysis-dependent chronic kidney disease (HDD-CKD)	SFP: SFP added in bicarbonate concentrate dialysate at 2 µM (11 µg iron/dL of dialysate), 3-4 hemodialysis sessions per week Placebo: standard bicarbonate concentrate dialysate, 3-4 hemodialysis sessions per week	SFP: 147 Placebo: 147

Supportive Clinical Studies				
NIH-FP-01	31 Jan 2011 – 10 Jan 2013	Randomized, placebo-controlled, double blinded, phase 2 study in patients with HDD-CKD	SFP: SFP added in bicarbonate concentrate dialysate at 2 µM (11 µg iron/dL of dialysate), 3-4 hemodialysis sessions per week Placebo: standard bicarbonate concentrate dialysate, 3-4 hemodialysis sessions per week	SFP: 54 Placebo: 54
SFP-4-OL	01 Mar 2010-19 Jul 2011	Open-label extension safety study of RMTI-SFP-4	SFP: 2 µM (11 µg iron/dL of dialysate), 3-4 hemodialysis sessions per week	SFP: 206
SFP-5-OL	01 Mar 2010-19 Jul 2011	Open-label extension safety study of RMTI-SFP-5	SFP: 2 µM (11 µg iron/dL of dialysate), 3-4 hemodialysis sessions per week	SFP: 214
SFP-6-RC	Dec 2012-Feb 2013	randomized, double-blind, placebo-controlled, cross-over study	SFP: 2 µM (11 µg iron/dL of dialysate)	SFP/Placebo: 360 Placebo/SFP: 358
SFP-6-OL	May 2012-ongoing	Open-label extension safety study of SFP-6-RC	SFP: 2 µM (11 µg iron/dL of dialysate), 3-4 hemodialysis sessions per week	SFP: 308
SFP-1		randomized, open-label, placebo-controlled, dose escalation study	SFP: 20, 40, 80, and 120 µg iron/L dialysate, monthly dose escalation	SFP: 12 Placebo: 11
SFP-2	Aug 2007-Oct 2009	randomized, double-blind, placebo-controlled, dose ranging study	SFP: 0, 50, 100, 120 and 150 µg iron/L dialysate fixed dose for 26 weeks	SFP 0 µg/L: 27 SFP 50 µg/L: 28 SFP 100 µg/L: 29 SFP 120 µg/L: 23 SFP 150 µg/L: 29
SFP-3	May 2010-Sep 2010	randomized, double-blind, crossover, single-dose SFPFG (food grade formulation of SFP), SFPGMP (Good Manufacturing Practice formulation of SFP) in patients with HDD-CKD.	SFPGMP 2.3 µM (13 µg of iron per deciliter of dialysate) SFP_{FG} 2.3 µM (13 µg of iron per deciliter of dialysate)	SFPGMP/SFPFG: 17 SFPFG/SFPGMP: 16
SFP-8 Phase 1	June 2013 – September 2013	randomized, open-label, sequential treatment to assess the quantitative mass transfer from SFP containing dialysate under varying conditions of blood and dialysate flow rates, dialyzer membrane types and dialysate bicarbonate concentrations in patients with HDD-CKD	SFP: 110 µg iron /L dialysate	SFP: 12

SFP-9 Phase 1	June 2013 – September 2013	randomized, double-blind, placebo-controlled, single ascending dose study of intravenously (IV) administered SFP in healthy volunteers to assess the safety, PK, and PD of IV SFP	SFP: 2.5, 5.0, 7.5, and 10.0 mg iron via IV infusion over 4 hours SFP: 15 and 20 mg iron via IV infusion over 12 hours	SFP 2.5 mg: 6 SFP 5.0 mg: 6 SFP 7.5 mg: 6 SFP 10 mg: 6 SFP 15 mg: 6 SFP 20 mg: 6 placebo: 12

Reviewer's table

5.2 Review Strategy

Two phase 3 trials (SFP-4 and SFP-5) and one phase 2 trial (NIH-FP-01) were reviewed for efficacy for the proposed indications. All clinical data were reviewed for safety.

5.3 Discussion of Individual Studies/Clinical Trials

Two phase 3 studies (SFP-4 and SFP-5) were submitted to support the efficacy and safety of Triferic for the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

One Phase 2 trial (NIH-FP-01) was submitted to support the proposed indication to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

5.3.1 Two Phase 3 Study Protocols SFP-4 and SFP-5

SFP-4 and SFP-5 had identical study protocols and the following is a summary of the study protocols.

Study title

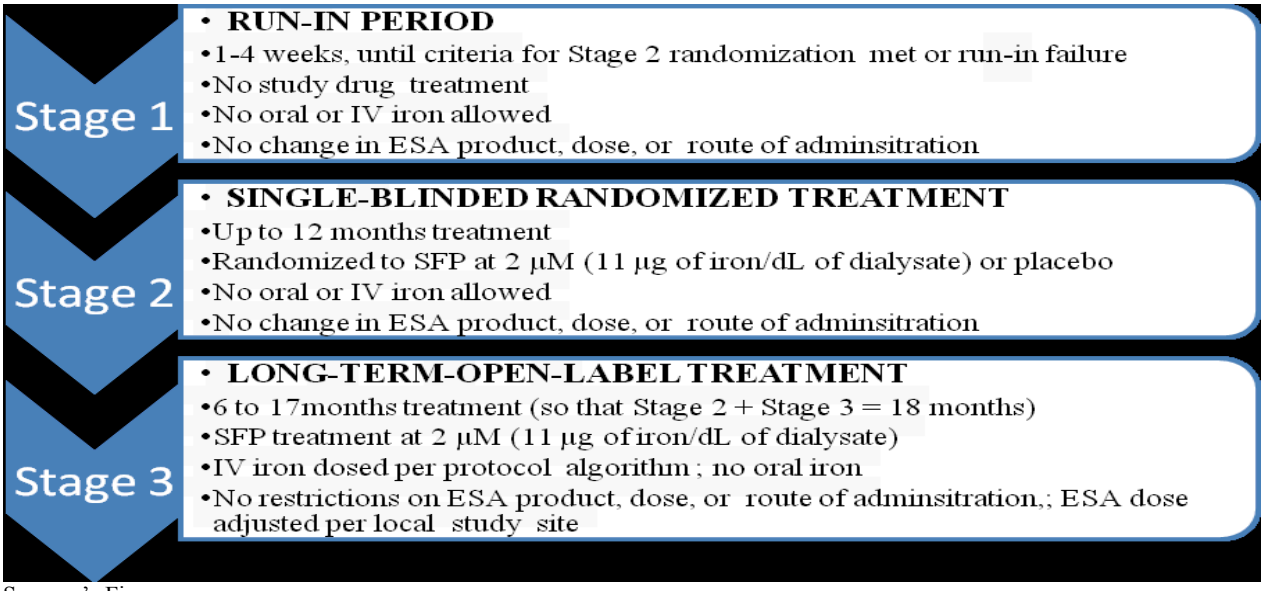
A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 1 or CRUISE 2) Study

Study design

The two studies each were a multicenter, randomized (1:1), single-blinded (only the study patients were blinded to treatment assignment), placebo-controlled, Phase 3 studies to evaluate the efficacy and safety of SFP in adult patients with hemodialysis-dependent CKD (HDD-CKD).

Each study had three sequential stages following the screening period (see Study Flow Diagram below):

Figure 1. Study Flow Diagram



Sponsor's Figure

The protocols provided the following restrictions for iron and ESA treatment during the studies in order to minimize the potential confounding effect of concomitant iron therapy and ESA on hemoglobin and iron parameters:

- Oral iron therapy was prohibited throughout the entire study duration, including the screening period
- Intravenous (IV) iron was prohibited during the screening period and the run-in and randomized treatment stages of the study, but was permitted during the long-term open-label treatment extension stage of the study, during which time IV iron could be administered according to the protocol-specified IV Iron Administration Algorithm.
- During the run-in stage, and the randomized treatment stage the product, route of administration and dose of the erythropoiesis stimulating agent (ESA) were not to be changed. There were no restrictions on the ESA product, route of administration, and dose in the open-label treatment extension stage.

Patients were expected to undergo hemodialysis three or four times each week throughout the study. The duration of each dialysis session and the dialysate flow rate were determined by the Investigator and could be changed at any time based on individual patient needs.

Hematology and iron parameter laboratory evaluations included weekly hemoglobin (Hgb), every-other-week pre-dialysis serum ferritin, reticulocyte hemoglobin content (CHr), and serum iron panel (serum iron, UIBC, transferrin, and calculated TIBC and TSAT), and every-four-week post-dialysis serum iron panel.

Patients were to be withdrawn from the study for the following reasons:

For Stage 1 (Run-in phase):

- RBC or whole blood transfusion.
- Medical necessity for IV iron, defined as serum ferritin < 100 μg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements.

For Stage 2 (Randomized phase):

- RBC or whole blood transfusion.
- Study drug administration was suspended for ≥ 12 consecutive weeks for any reason.
- Signs or symptoms of unacceptable toxicity attributed to study drug administration occurred.
- ESA dose changed that was NOT required per Protocol-Mandated Change in Anemia Management for either ESA dose (i.e., for Hgb < 9.0 g/dL or > 12.0 g/dL confirmed by a consecutive repeat value obtained between ≥ 1 day and ≤ 2 weeks after the first value), unless each of the following conditions were met:
  - ESA dose change was ≤35% from the average prescribed weekly dose,
  - ESA dose change occurred ≥12 weeks after prior ESA dose change,
  - Baseline ESA dose was resumed within 11 calendar days of the change.
- One time IV iron dose >125 mg or multiple IV iron administrations of any dose, that were NOT required Protocol-Mandated Change in Anemia Management (i.e., for ferritin <100 μg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements)

For Stage 3 (Open-label extension phase):

- Study drug administration was suspended for ≥ 12 consecutive weeks for any reason.
- Signs or symptoms of unacceptable toxicity attributed to study drug administration occurred.

Criteria for transition from Stage 2 to Stage 3:
Patients who were withdrawn from Stage 2 were eligible to transition to Stage 3 if they met one of the following criteria, AND less than four weeks had elapsed since withdrawal from Stage 2:

- completed the full duration of Stage 2 and less than four weeks had elapsed since completion of Stage 2, OR
- required protocol-defined Protocol-Mandated Change in Anemia Management for ESA dose (i.e., Hgb < 9.0 g/dL or > 12.0 g/dL confirmed by a consecutive repeat value obtained between ≥ 1 day and ≤ 2 weeks after the first value), OR
- required protocol-defined Protocol-Mandated Change in Anemia Management for IV iron (i.e., serum ferritin < 100 μg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements), OR
- Hgb >11.5 g/dL over ≥ 1 week confirmed by ≥ 2 consecutive weekly measurements AND an associated increase in Hgb by ≥ 1 g/dL over 4 weeks.

Study population

Inclusion criteria:

Stage 1 selection:

1. Adult subject ≥ 18 years of age undergoing chronic hemodialysis three or four times per week for chronic kidney disease (CKD) for at least 4 months, and expected to remain on hemodialysis three to four times weekly and be able to complete the duration of the study.
2. Received IV iron therapy between 6 months and 2 weeks prior to enrollment in order to replace iron losses resulting from hemodialysis procedure.
3. Mean Screening Hgb ≥ 9.5 to ≤ 11.5 g/dL.
4. Mean Screening TSAT ≥ 15% to ≤ 40%. Excursion of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
5. Mean Screening serum ferritin ≥ 200 to ≤ 800 µg/L. Excursion of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
6. If being administered epoetin, darbepoetin, or CERA, epoetin dose ≤ 45,000 U/week, darbepoetin dose ≤ 200 µg/week, or CERA dose ≤ 400 µg/month during the four weeks prior to enrollment.
7. Minimally adequate *measured* dialysis dose defined as:
    a. For three times weekly dialysis, URR (urea reduction ratio) ≥ 65%, or single-pool Kt/V (dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water) ≥ 1.2, or KIDt/V (online dialyzer clearance measured using ionic dialysance multiplied by dialysis time, divided by patients total body water) ≥ 1.2, or
    b. For four times weekly dialysis, single-pool Kt/V ≥ 0.9.
8. Stable dialyzer blood flow rate that is generally ≥ 250 mL/min and acceptable to the Investigator.
9. Vascular access for dialysis that will be used upon enrollment with stable function in the judgment of the Investigator without requiring medical or surgical thrombectomy for restoring patency or antibiotics for confirmed infection over the 3 months prior to enrollment, and consisting of either a tunneled catheter (internal jugular or subclavian) or an arteriovenous (AV) fistula or graft. The percent of patients enrolling in Stage 1 with a catheter will be limited to 20% of the enrolled population within each individual country.
10. Female subjects must be either amenorrheic for ≥ 1 year or agree to not become pregnant by continuous use, during sexual activity, of an effective birth control method acceptable to the Investigator from enrollment in Stage 1 through the duration of their participation on study.
11. Must be willing and able to provide written informed consent directly or through their authorized representative.

Stage 2 patient selection:

1. Patient currently enrolled in the Stage 1 run-in period of study
2. Undergoing chronic hemodialysis three or four times per week for chronic kidney disease (CKD), and expected to remain on hemodialysis three to four times weekly and be able to complete duration of the study.
3. Mean Hgb ≥ 9.5 to ≤ 11.5 g/dL over the three most recent consecutive every-week measurements prior to randomization.
4. Stable Hgb defined as ≤ 1.0 g/dL difference between the maximum and minimum Hgb values over the 3 weeks immediately prior to randomization.
5. Mean TSAT ≥ 15% to ≤ 40% over the two most recent consecutive every-other-week measurements prior to randomization of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
6. Mean serum ferritin ≥ 200 to ≤ 800 µg/L over the two most recent consecutive every other week measurements prior to randomization of either TSAT or ferritin by ≤10% outside these ranges permitted only if all other inclusion/exclusion criteria are met.
7. If being administered epoetin, darbepoetin, or CERA, epoetin dose ≤ 45,000 U/week, darbepoetin dose ≤ 200 µg/week, or CERA dose ≤ 400 µg/month during the four weeks prior to randomization.
8. Minimally adequate measured dialysis dose defined as:
    - For three times weekly dialysis, URR (urea reduction ratio) ≥ 65%, or single-pool Kt/V (dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water) ≥ 1.2, or $K_{ID}t/V$ (online dialyzer clearance measured using ionic dialysance multiplied by dialysis time, divided by patients total body water) ≥ 1.2, or
    - For four times weekly dialysis, single-pool Kt/V ≥ 0.9.
9. Dialyzer blood flow rate (QB) at the mid-point of dialysis sessions averaged over the 3 to 4 weeks prior to randomization ≥ 250 mL/min.
10. Vascular access for dialysis that will be used upon enrollment with stable function in the judgment of the Investigator without requiring medical or surgical thrombectomy for restoring patency or antibiotics for confirmed infection over the 3 months prior to randomization, and consisting of either a tunneled catheter (internal jugular or subclavian) or an arteriovenous (AV) fistula or graft.
11. Female subjects must be either amenorrheic for ≥ 1 year or agree to not become pregnant by continuous use, during sexual activity, of an effective birth control method acceptable to the Investigator throughout the duration of their participation on study.
12. Patient must be competent and have voluntarily signed the informed consent form.

Exclusion criteria:

1. Patient has living kidney donor identified or living-donor kidney transplant scheduled. (Note: Patients awaiting deceased-donor transplant need not be excluded.)
2. Vascular access for dialysis with femoral catheter or non-tunneled catheter.
3. Received any amount of IV iron during the 4 weeks prior to randomization.

4. If being administered an ESA, change in prescribed dose over the 6 weeks immediately prior to randomization.
5. Serum albumin < 3.0 g/dL any time over the 8 weeks prior to randomization.
6. Known cause of anemia other than anemia attributable to renal disease (e.g., sickle celldisease, thalassemia, pure red cell aplasia, hemolytic anemia, myelodysplastic syndrome, etc.).
7. Known active bleeding from any site other than AV fistula or graft (e.g., gastrointestinal, hemorrhoidal, nasal, pulmonary bleeding).
8. Scheduled surgery during the study that may be expected to lead to significant blood loss.
9. RBC or whole blood transfusion during Stage 1.
10. Hospitalization in the previous three months (except for vascular access surgery) that, in the opinion of the Investigator, confers a significant risk of hospitalization during the course of this study.
11. Noncompliance with the protocol during Stage 1 defined as missing ≥ 3 dialysis sessions during the 3 to 4 weeks immediately prior to Stage 2.
12. Evidence of current malignancy involving a site other than skin (except any melanoma, which renders the patient non-eligible).
13. History of drug or alcohol abuse within the last 6 months.
14. Regularly requiring hemodialysis more than four times per week during Stage 1.
15. Pregnancy or intention to become pregnant before completing all study drug treatment.
16. Known ongoing inflammatory disorder (other than CKD), such as systemic lupus erythematosus, rheumatoid arthritis, or other collagen-vascular disease.
17. Any current febrile illness (e.g., oral temperature > 100.4°F, 38°C).
18. Known active bacterial, tuberculosis, fungal, viral, or parasitic infection requiring antimicrobial therapy or anticipated to require anti-microbial therapy during the patient's participation in this study.
19. Occult tuberculosis requiring prophylactic treatment with anti-tubercular drug(s) that overlaps with the patient's participation in this study.
20. Known positive status for hepatitis B surface antigen (hepatitis B testing is not required as part of this protocol).
21. Known human immunodeficiency virus (HIV) infection (HIV testing is not required as part of this protocol).
22. Cirrhosis of the liver based on histological criteria or clinical criteria (i.e., presence of ascites, esophageal varices, spider nevi, or history of hepatic encephalopathy).
23. Hepatitis C infection with ALT and/or AST levels consistently greater than two times the upper limit of normal during the two months prior to randomization.

Study treatment

Stage 1:
During Stage 1 there was no study treatment administered.

Stage 2:
Patients who meet the Stage 2 eligibility criteria were to be randomized in a 1:1 ratio to:

- SFP in dialysate at 2 μM (11 μg iron/dL of dialysate) or
- Placebo (standard dialysate without SFP).

Patients were stratified at randomization by the following factors:

- Baseline Hgb value (Hgb > 11 g/dL vs. Hgb ≤ 11 g/dL, using the average of the three most recent Hgb values preceding randomization), and
- Baseline ESA dose (the weekly dose as of the time of randomization), with patients receiving > 13,000 units/week epoetin (or > 40 μg/week darbepoetin, or > 220 μg/month CERA) randomized separately from patients receiving ≤ 13,000 Units/week epoetin (or ≤ 40 μg/week darbepoetin, or ≤ 220 μg/month CERA).

Stage 3:
During Stage 3, all patients received open-label SFP at 2 μM (11 μg/dL).

The study duration for Stages 2 and Stage 3 combined was intended to be 18 months, regardless of whether the patient was randomized to SFP or placebo in Stage 2.

Study Drug Withholding:
Study drug administration was to be withheld for a minimum of four weeks if any one of the following hematological or iron parameter criteria is met. All laboratory criteria for study drug withholding including Hgb, TSAT, and serum ferritin required confirmation by 2 consecutive values measured at any time within a 2-week period.

- During both Stages 2 and 3:
  - Pre-dialysis TSAT > 50%, OR
  - Serum ferritin > 1,200 μg/L.
- During Stage 3 only:
  - Hgb ≥ 12.5 and< 13.0 g/dL in conjunction with serum ferritin > 500 μg/L, OR
  - Hgb ≥ 13.0 and< 13.5 g/dL in conjunction with serum ferritin > 100 μg/L, OR
  - Hgb ≥ 13.5 g/dL regardless of serum ferritin.

Efficacy evaluation

Primary Endpoint:

- Mean change from baseline in Hgb assessments during the last 8 weeks of the 12-month randomized treatment period, or last one-sixth of the randomized treatment period for patients who prematurely withdraw from study treatment, but will include a minimum of at least the last two Hgb values.

Secondary Endpoints:

- The incidence of "treatment failures," defined as decrease in Hgb to < 9 g/dL sustained for ≥ 2 consecutive weeks.

- The incidence of a decrease in Hgb of ≥ 1.0 g/dL from baseline sustained for ≥ 2 consecutive weeks.
- The incidence of decrease in ferritin to < 100 µg/L sustained for ≥ 2 consecutive weeks.
- The percent of patient maintaining Hgb concentration in the range of ≥ 9.5 to ≤ 11.5 g/dL for ≥80% of time on study.
- The percent of patients maintaining TSAT in the range of TSAT 20-50% for ≥80% of time on study.
- The percent of patients maintaining ferritin in the range of ferritin 200-800 µg/dL for ≥80% of time on study.
- Variability in Hgb.
- The incidence of requiring red blood cell or whole blood transfusion, and IV iron administration (in aggregate and separately).

Exploratory Endpoints:

- The incidence of increase in Hgb to >12 g/dL sustained for ≥ 2 consecutive weeks.
- The incidence of increase in Hgb of ≥ 1.0 g/dL from baseline sustained for ≥ 2 consecutive weeks.
- Time to decrease in Hgb < 9 g/dL or ferritin to < 100 µg/L; to decrease in Hgb of ≥ 1.0 g/dL from baseline; increase in Hgb to >12 g/dL; to increase in Hgb of ≥ 1.0 g/dL from baseline.
- Change in ferritin, TSAT, serum iron and CHr, from baseline to the last 8 weeks (or one sixth) of the randomized treatment period.
- The incidence sustained increase in ESA dose by ≥ 25%
- The change in prescribed ESA dose, and ESA Resistance Index (ERI) and weight adjusted ERI, from baseline to the last 8 weeks (or one-sixth) of the randomized treatment period.
  ERI is defined as (based on prescribed ESA dose):
  ERI = ESA dose (U/wk)/Hgb (g/dL) = U/wk/g/dL and
  The body weight-adjusted ERI is calculated as:
  ERI/kg = ESA dose (U/kg/wk)/Hgb (g/dL) = U/kg/wk/g/dL.

Safety assessment

The studies included the following safety endpoints:

- The incidence of all adverse events (AEs) reported during the study, including the seriousness, severity, and assessed relatedness to study drug.
- Number and percent of patients temporarily or permanently discontinued from study drug treatment due to AEs.
- The number and percent of patients with of AEs of special interest, including:
  - Cardiovascular events (e.g., cerebrovascular accident, nonfatal myocardial infarction, cardiac death),

  - Other venous or arterial thrombotic events including vascular access thrombosis,
  - Systemic/serious infections (e.g., bacteremia, fungemia, pneumonia, vascular access infection),
  - Intradialytic hypotension,
  - Anaphylactic/anaphylactoid reactions and other hypersensitivity reactions
- Change from baseline in physical examination findings, vital signs, laboratory data, and electrocardiograms (ECGs).
- The change in serum iron, unbound iron binding capacity (UIBC) and TSAT from pre to post dialysis, overall and in subjects with serious adverse events (SAEs).

Definition of Intradialytic Hypotension (IDH) as Adverse Events:

IDH were to be reported as an AE in this study only if the IDH met both of the following definitions:

- Definition of IDH: a systolic blood pressure (SBP) decreased from pre-dialysis baseline by ≥ 20 mm Hg that results in a value < 90 mm Hg during dialysis, OR any procedural hypotension that results in premature termination or interruption of dialysis irrespective of the magnitude of decrease in SBP.
- Definition of AE: an untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. IDH observed in a patient on study would not be reported as an AE unless the severity [e.g., magnitude of decrease in blood pressure (BP)] or frequency [e.g., number of IDH events per dialysis session] of the IDH exceeded that patient's established pattern of IDH prior to entering the study.

Each report of an AE of IDH (meeting both above criteria) was to be characterized by the Investigator as (1) symptomatic vs. asymptomatic and (2) requiring intervention vs. not requiring intervention, according to the criteria below.

- Symptomatic IDH if the BP changes were associated with any one or more of the following: abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; or anxiety.
- IDH requiring intervention if the BP changes were associated with any one or more of the following interventions: IV saline or other isotonic solution, IV mannitol, low temperature dialysate, terminating or reducing ultrafiltration, or stopping dialysis altogether.

Definition of Anaphylaxis/Anaphylactoid Reactions:

Hypersensitivity reactions, including anaphylaxis/anaphylactoid reactions, were 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 were to be reviewed and assessed by an independent Data Safety Monitoring Board (DSMB) as to whether or not the event was indeed a hypersensitivity reaction and related to study drug using the above proposed definition but subject to modification by the DSMB.

Statistical methods

Sample Size Estimation:

Sample size estimation was based on a comparison of means using a 2-sample t-test with an alpha level of 5% (2-sided). Assuming a common standard deviation of 1.25 g/dL for the change from baseline Hgb, a sample size of 133 patients per treatment group would provide 90% power to detect a treatment difference ≥ 0.5 g/dL in the Hgb change from baseline between SFP and placebo.

A blinded interim analysis was to be performed after approximately 50% of the targeted 300 patients have been randomized to Stage 2 for the purpose of verifying assumptions underlying the sample size calculation to assure adequate power for the primary efficacy endpoint. (This was done and did not result in a sample size change).

Analyzed population:

Efficacy Data Sets
The primary analysis of the primary, secondary and exploratory endpoints were to be based on the intent-to-treat (ITT) population, defined as all patients who are randomized to treatment group in the randomized, controlled treatment period (Stage 2).

A supportive efficacy analysis of the primary efficacy endpoint was to be based on the "efficacy-evaluable" patient population, which is defined as all randomized patients who received study drug and either (1) complete ≥ 36 study drug exposures (expected to be approximately 12 weeks), or (2) are withdrawn from study prior to 36 study drug exposures for a reason of suspected study drug toxicity or Protocol-Mandated Change in Anemia Management and did not have an ESA dose change or receive any IV iron, both of which are prohibited during Stage 2.

Safety Data Set
The safety analysis data set included all patients exposed to any amount of study drug, in either Stage 2 or Stage 3; with the primary analysis of interest being the comparison of safety parameters during the parallel-group Stage 2 period of the study.

Efficacy Analyses:

Primary Efficacy Endpoint:
Formal hypothesis testing of the primary efficacy endpoint (the mean change from baseline in Hgb assessments during the last 8 weeks of the 12-month randomized treatment period, or last one-sixth of the randomized treatment period for patients who prematurely withdraw from study treatment, but will include a minimum of at least the last two Hgb values) was to be based on the comparison of SFP 2 μM (11 μg/dL) vs. placebo, tested with a two-sided 5% significance level.

The change from baseline in Hgb (average value during evaluation period at end of study minus baseline value) during Stage 2 was to be compared between the treatment groups using an analysis of covariance (ANCOVA) model. The ANCOVA model should include treatment as the main effect, with adjustment for stratification factors used for randomization: baseline Hgb (> 11 g/dL vs. ≤ 11 g/dL) and baseline ESA dose ([> 13,000 units/week epoetin or > 40 μg/week darbepoetin, or > 220 μg/month CERA] vs. [≤ 13,000 units/week epoetin or ≤ 40 μg/week darbepoetin, or ≤ 220 μg/month CERA]). Least-squares means were to be presented for each treatment group.

For the primary analysis, missing Hgb values were not to be imputed or carried forward from previous visits in the derivation of mean values over designated time periods. All observed Hgb values in a given time interval were to be used to calculate the mean value. Further details for handling missing and incomplete data for were to be addressed in the statistical analysis plan.

Secondary and Exploratory Endpoints:
Secondary efficacy endpoints were to be analyzed in a sequential manner with fixed sequences using hierarchical ordering to control alpha at an overall 0.05 level. Once a secondary efficacy endpoint was assessed to be not statistically significant, the remaining efficacy endpoint analyses were to be considered descriptive. Any statistical testing of exploratory endpoints was to be considered for descriptive purposes only. ANCOVA should be used as the primary method of analysis for all continuous outcome variables. The Cochran-Mantel-Haenszel chi-square test should be used to evaluate differences between treatment groups in categorical variables. These analyses should control for the randomization stratification variables, as appropriate.

Safety Analyses:
Descriptive analysis was to be performed.

Protocol Amendments:

Protocol amendment 1 (April 20, 2011):
Major changes included:

- The design of Stage 2 of the study was changed from double-blinded to single-blinded (only the study patients are blinded to treatment assignment).
- For entry criteria, the maximal allowable mean ferritin for Stage 2 was increase from 700 to 800 μg/L
- Added a secondary efficacy endpoint: "The percent of patients maintaining Hgb concentration ≥ 10.0 g/dL analyzed at 4-week intervals (e.g., Weeks 1 through 4, 5 through 8, etc.)."
- Expanded the definition of intra-dialytic hypotension (IDH) to also include "any procedural hypotension that results in premature termination or interruption of dialysis irrespective of the magnitude of decrease in systolic blood pressure."
- Transferred responsibility for review of intra-dialytic hypotension (IDH) and anaphylaxis/anaphylactoid reactions events from an adjudication panel to the DSMB.

Protocol amendment 1 (November 8, 2011):
Major changes included:

- Recent changes in ESA dosing guidelines related to safety concerns with higher Hgb levels introduced ESA dose withholding at lower Hgb levels than previously, which has been widely adopted in clinical practice. As a result, several key changes were made to the protocol to enable continued participation in the study:
    - The duration of Stage 1 of the study was changed from 4 to 16 weeks to 1 to 4 weeks. The several-months long run-in Stage 1 was aimed at achieving a stable ESA dose, and it allowed only two ESA dose changes by ≤30% no more frequently than every 4 weeks. Per the new ESA dose labeling, ESA dose adjustments are made more frequently, and ESA dose reduction or withholding is now recommended when Hgb reaches or exceeds 11 g/dL. Therefore, investigators were unable to abide by the original protocol's ESA dosing requirements during Stage 1 given concerns of patient safety, leading to many protocol deviations and discontinuations from the study. Given these changing practices, the prolonged Stage 1 could not achieve its intended objective of a stable ESA dose. As a result of shortening Stage 1 the maximum possible duration of the study changed from 22 ½ months to approximately 20 months.
    - The Hgb threshold levels were changed, in entry criteria as well as in the "Protocol Mandated Changes in Anemia Management":
        - For Stage 1, the Hgb entry criterion was changed from 10.0-12.5 g/dL to 9.5 to 11.5 g/dL.
        - For Stage 2, the Hgb entry criterion was changed from 10.0-12.0 g/dL to 9.5 to 11.5 g/dL.

        - The "Protocol-Mandated Change in Anemia Management" threshold was changed from Hgb < 9.0 g/dL or > 12.5 g/dL to Hgb < 9.0 g/dL or > 12.0 g/dL.
    - The confirmation of high/low Hgb threshold in "Protocol Mandated Changes in Anemia Management" was changed from "over ≥ 1 week confirmed by ≥ 2 consecutive measurements" to "confirmed by a consecutive repeat value obtained between ≥ 1 day and ≤ 2 weeks after the first value," to allow for clinical judgment regarding urgency of making change in ESA.
- Clarification of criteria for patient withdrawal from study, with addition of a separate section to clarify criteria for transition to Stage 3, and addition of clarifications of protocol deviations that would require patients to be withdrawn from study.
- The study endpoints and statistical analysis section were significantly updated to:
    - simplify the analysis populations and the analyses being performed on the primary efficacy endpoint;
    - simplify and reorganize the list of additional endpoints, creating secondary and exploratory endpoints that can be more readily compared across treatment groups, and moving items to safety endpoints or to statistical section, as appropriate;
    - add intent to perform formal statistical testing on secondary endpoints.
- Following initial 8 weeks of exposure to study drug, vital signs were to continue to be monitored per dialysis clinic routine and clinically significant episodes of hypotension will be as noted as AEs, but vital signs were to be recorded only once per week instead of at every dialysis session to identify intradialytic hypotension programmatically.

5.3.2 **Phase 2 Study Protocol NIH-FP-01**

Study title

Physiological Iron Maintenance in ESRD Subjects by Delivery of Soluble Ferric Pyrophosphate (SFP) via Hemodialysate: The PRIME Study

Study Design

This was a multicenter, randomized, placebo-controlled, double-blinded, phase 2 trial to evaluate the safety and efficacy of SFP via hemodialysate in patients with HDD-CKD.

Study population

Inclusion Criteria:

1. Male and female subjects ≥ 18 years of age.
2. End-stage renal disease undergoing maintenance hemodialysis 3 to 4 times a week for at least 4 months and expected to remain on this schedule and be able to complete the study. Subjects on a cadaveric transplant list need not be excluded for this reason unless there is an identified donor.
3. Mean Hgb in the range of ≥ 9.5 to ≤ 12.0 g/dL during screening

4. The difference between the maximum and minimum Hgb values during screening does not exceed 1.0 g/dL.
5. Mean ferritin ≥ 200 to ≤ 1000 mcg/L during screening.
6. Mean TSAT ≥ 15% to ≤ 40% during screening (Excursion of TSAT by ≤10% outside this range permitted only if all other inclusion/exclusion criteria are met).
7. Any and all serum albumin measured during the 2 months preceding randomization must be ≥ 3.0 g/dL.
8. Prescribed ESA dosing remaining in the range of ≥ 4,000 to ≤ 45,000 U/week epoetin or ≥ 12.5 to ≤ 200 mcg/week darbepoetin during the 6 weeks preceding randomization.
9. Required IV iron at any time in the 6 months preceding randomization.
10. Female subjects must be either amenorrheic for a minimum of 1 year or agree to not become pregnant by continuous use, during sexual activity, of an effective birth control method acceptable to the Investigator throughout the duration of their participation on study.
11. Minimally adequate measured dialysis dose defined as:
    i. For 3 times weekly dialysis, URR (urea reduction ratio) > 65% or single-pool Kt/V (dialyzer clearance of urea multiplied by dialysis time, divided by patient's total body water) > 1.2, or
    ii. For 4 times weekly dialysis, single-pool Kt/V > 0.9.
12. Dialyzer blood flow rate (QB) at the mid-point of dialysis sessions averaged over the
13. 4 weeks prior to randomization ≥ 225 mL/min.
14. Undergoing dialysis only using an arteriovenous (AV) fistula or graft.
15. Must be willing and able to provide written informed consent directly or through their authorized representative.

Exclusion Criteria:

1. Vascular access for dialysis is a catheter.
2. During the 6 months prior to randomization, infection of the vascular access to be used at the time of randomization.
3. Received a total of > 600 mg IV iron during the 6 weeks prior to randomization.
4. Received any amount of IV or oral iron during the 2 weeks prior to randomization.
5. Change in prescribed ESA dose:
    a. Any change in prescribed ESA dose within 4 weeks prior to randomization.
    b. The prescribed ESA dose at the time of randomization is > 25% higher or lower than the prescribed dose at 6 weeks prior to randomization.
    c. Change in prescribed type of ESA (e.g., epoetin vs. darbepoetin) or route of administration within 6 weeks prior to randomization.
6. Actual ESA dosing missed or withheld for a cumulative total of ≥ 1 week for any reason during the 6 weeks prior to randomization.
7. Known cause of anemia other than anemia attributable to renal disease (e.g., sickle cell disease, thalassemia, pure red cell aplasia, hemolytic anemia, myelodysplastic syndrome, etc.).
8. Known active bleeding from any site other than AV fistula or graft (e.g., gastrointestinal, hemorrhoidal, nasal, pulmonary bleeding).
9. Known coagulation disorder.

10. Scheduled surgery during the study that may be expected to lead to significant blood loss.
11. RBC or whole blood transfusion within 12 weeks prior to randomization.
12. Scheduled kidney transplant or a donor has been identified but the transplant has not been scheduled.
13. Known ongoing inflammatory disorder (other than CKD), such as systemic lupus erythematosus, rheumatoid arthritis, other collagen-vascular diseases, etc.
14. Hospitalization in the previous 3 months (except for vascular access surgery) that, in the opinion of the Investigator, confers a significant risk of hospitalization during the course of this study.
15. Evidence of current malignancy involving sites other than skin (except any melanoma, which renders the patient non-eligible).
16. History of drug or alcohol abuse within the last 6 months.
17. Regularly requiring hemodialysis more than 4 times per week.
18. Known to be pregnant or breast-feeding at screening.
19. Any febrile illness (e.g., oral temperature > 100.4°F, 38°C) during screening.
20. Known active tuberculosis, fungal, viral, or parasitic infection requiring anti- microbial therapy or anticipated to require anti-microbial therapy during the patient's participation in this study. Subjects with hepatitis C, in the absence of cirrhosis, are not excluded from participation in the study if ALT and AST levels are below 2 times the upper limit of normal on a consistent basis during the 2 months preceding randomization.
21. Occult tuberculosis requiring prophylactic treatment with anti-tubercular drug(s) that overlaps with the patient's participation in this study.
22. Known positive status for hepatitis B surface antigen (hepatitis B testing is not required as part of this protocol).
23. Known human immunodeficiency virus (HIV) infection (HIV testing is not required as part of this protocol).
24. Cirrhosis of the liver based on histological criteria or clinical criteria (e.g., presence of ascites, esophageal varices, spider nevi, or history of hepatic encephalopathy).
25. Hepatitis C infection if ALT and/or AST levels are consistently greater than twice the upper limit of normal at any time during the 2 months prior to randomization.
26. Participated in another clinical trial of an investigational drug or device within 30 days prior to randomization in this trial.
27. Subjects who are anticipated to be unable to complete the entire study (e.g., due to a concurrent disease).

Study Treatment

Subjects were randomized in a 1:1 ratio to receive SFP-containing dialysate or control iron free dialysate (placebo) at every dialysis session.

SFP dose: approximately 2 mcM (11 mcg /dL) of iron in final dialysate solution.
Placebo control solution: iron-free liquid bicarbonate concentrate.

The total treatment duration of the study was 36 weeks plus a 1-week follow-up after the last study drug treatment.

Oral or IV iron and ESA use:
Oral iron treatment was prohibited for a total of 2 weeks prior to anticipated randomization and for the entire duration of the study.

During Week 1 through Week 4, IV iron was prohibited; and changes in ESA dose, type of ESA (e.g., epoetin vs. darbepoetin), and route of administration were prohibited except where ESA dose reduction was needed to manage high Hgb levels.

Beginning at Week 5, IV iron could be administered and the ESA dose could be adjusted. The administration of IV iron and adjustment of ESA dose were based on a pre-specified algorithms, with the goal of maintaining Hgb in the target range of 9.5 to 11.5 g/dL.

Study drug administration was to be withheld in 2-week blocks of time for any one of the following:

- Pre-dialysis TSAT >50% confirmed by a consecutive repeat value any time ≥1 day and ≤2 weeks after the first value, OR
- Serum ferritin >1,200 mcg/L confirmed by a consecutive repeat value any time ≥1 day and
  ≤2 weeks after the first value, provided that high-sensitivity C-reactive protein (hs-CRP) had not simultaneously increased by ≥100% from the subject's baseline hs-CRP level, OR
- Hgb ≥13.0 g/dL confirmed by a consecutive repeat value any time ≥ 1 day and ≤2 weeks after the first value, provided that the subject had been off all ESA for ≥ 4 weeks at the time of the confirming Hgb value.

Efficacy Endpoints

Primary Endpoints

1. Efficacy Endpoint: The percent change from baseline in ESA dose required to maintain Hgb in the target range, adjusted for Hgb.
2. Safety Endpoints: Safety and tolerability will be determined by clinically significant changes in physical examinations and vital signs, clinical laboratory measures, and incidence and severity of adverse events.

Secondary Efficacy Endpoints

1. The incidence of "patient responders," defined as ≥ 25% decrease from baseline in ESA dose sustained continuously for ≥ 8 weeks and the incidence of "patient failures," defined as ≥ 25% increase from baseline in ESA dose sustained continuously for ≥ 8 weeks
2. The amount of supplemental IV iron needed.
3. Maintenance of hemoglobin in the range of 9.5 to 11.5 g/dL.
4. Variability in hemoglobin [Hgb-var].
5. Iron delivery to the erythron as estimated by hemoglobin generation in response to

erythropoietin (ESA response index, or ERI, calculated as ESA dose/Hgb). The ERI was to be divided by body weight in kilograms to obtain a modified ERI (ERI/kg).

6. Markers of inflammation and oxidative stress.

Safety Assessment

Safety and tolerability of the drug were determined by the incidence and severity of AEs, clinical laboratory measures, and clinically significant changes in physical examinations and vital signs.

Statistical Methods

The protocol stated that this clinical trial was exploratory in nature. Statistical tests were considered to be descriptive rather than conclusive and were not adjusted for multiple comparisons. All tests were to be two-sided. The sample size of approximately 50 patients per treatment group (100 patients combined for the two groups, not including the 11 patients enrolled prior to protocol version 34) was considered adequate for the intended purposes of this trial.

6 Review of Efficacy

Efficacy Summary

The efficacy of Triferic was evaluated in two randomized controlled phase 3 clinical trials of identical design in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD) (305 patients in SFP-4 and 294 patients in SFP-5) for the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin. Each study was a multicenter, randomized, single-blind, placebo-controlled study in iron-replete patients with HDD-CKD. Study patients received SFP in dialysate at the concentration of 110 mcg iron/L or standard dialysate without SFP as placebo during each hemodialysis for 3 or 4 times per week. Randomized treatment duration was planned for up to 48 weeks. The mean treatment duration in the randomized phase was 157.7 days in the SFP group and 164.6 days in the placebo group in study SFP-4 and 161.2 days in the SFP group and 157.9 days in the placebo group in study SFP-5. About 50% of study patients received study treatment for ≥20 weeks and 20% of study patients received study treatment for 44-47 weeks in the randomized phase.

The primary efficacy endpoint was the change in mean hemoglobin (Hgb) from baseline to the end of treatment period (last one-sixth of the randomized treatment period). In Study SFP-4, the mean hemoglobin decreased 0.03 g/dL in the SFP group as compared to 0.38 g/dL in the placebo group in the Intention-to-Treat (ITT) population. In Study SFP-5, the mean hemoglobin decreased 0.08 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group in the ITT population. The primary efficacy analysis used an ANCOVA analysis with baseline hemoglobin as the covariate. The treatment difference in hemoglobin calculated as least square (LS) mean difference was 0.35 g/dL in each study between the SFP (0.06 g/dL in SFP-4 and -0.04 g/dL in SFP-5) and the placebo groups (-0.30 g/dL in SFP-4 and -0.39 g/dL in SFP-5) and was

statistically significant (p=0.01) in both studies after adjusting for baseline hemoglobin and ESA stratum. The results of additional analyses in Modified ITT (MITT) population and secondary endpoints in changes in TSAT and serum ferritin level from baseline to the end of treatment were consistent with the results from the primary efficacy analysis in both studies. The results from the two phase 3 clinical studies demonstrated that Triferic was effective to maintain hemoglobin during the treatment period in patients with HDD-CKD.

Although treatment duration was planned for up to 48 weeks, it is notable that only a minority of patients completed full 48 weeks treatment, due in large part to protocol-mandated change in anemia management (involving changes in ESA and/or iron dosing). In Study SFP-4 these included 45.4% of patients in the SFP group and 53.6% in the placebo group; in Study SFP-5 these included 46.3% of patients in the SFP-group and 61.2% in the placebo group. Of those, the majority of study patients were due to required ESA dose change for hemoglobin in Study SFP-4 (42.8% in the SFP group and 45.1% in the placebo group) and in Study SFP-5 (44.2% in the SFP group and 46.9% in the placebo group) and a few patients were due to requirement of intravenous iron administration for serum ferritin level <100 mcg/L in Study SFP-4 (2.6% in the SFP group and 9.2% in the placebo group) and in Study SFP-5 (2.0% in the SFP group and 14.3% in the placebo group). A greater percentage of patients in the SFP group (27%) as compared to the placebo group (20.9%) had hemoglobin >12 g/dL prior to withdrawal and more subjects in the placebo group as compared to the SFP group (17.6% vs. 11.2%, respectively) had hemoglobin <9 g/dL in Study SFP-4. Similarly, in Study SFP-5, there were more subjects with hemoglobin < 9 g/dL prior to withdrawal in the placebo group as compared to the SFP group (23.1% vs. 15%, respectively) and more subjects had hemoglobin >12 g/dL in the SFP group as compared to the placebo group (21.8% vs. 14.3%, respectively) prior to withdrawal. There were also more subjects who had serum ferritin level <100 mcg/L in the placebo group as compared to the SFP group in Study SFP-4 (11.1% vs. 3.3%, respectively) and in Study SFP-5 (15.6% vs. 2.7%, respectively). Although there was unexpected large proportion of patients didn't completed 48 weeks of study treatment mainly due to significant ESA dose changes during the study the final hemoglobin and serum ferritin level between the SFP and placebo groups prior to withdrawal were consistent with the primary efficacy results.

The submission also includes a Phase 2 study (NIH-FP-01) to support a labeling statement for reduction of ESA dose in these patients. In this multicenter, randomized, double-blind, placebo-controlled study in 108 patients with HDD-CKD patients received either SFP or placebo during dialysis. The mean treatment duration was 212 days in the SFP group and 222 days in the placebo groups. The primary efficacy endpoint was the percent change from baseline in ESA dose at the end of treatment. The results in ITT population showed that the subjects receiving SFP had a mean increase of 5.0% in prescribed ESA dose at end-of-treatment as compared to a mean increase of 37.3% in the placebo group (p=0.052). It also showed that the subjects receiving SFP had a mean 11.1% increase in actual ESA dose as compared to a mean 40.7% increase in the placebo group in ITT population and the differences between the two treatment groups was again not statistically significant (p=0.111). The secondary efficacy endpoint analysis showed a similar distribution of changes in the prescribed ESA dose between the SFP and the placebo groups (p=0.915). The NIH-FP-01 study protocol stated that this study was

exploratory in nature and statistical tests were considered to be descriptive rather than conclusive. No formal sample size determination was provided in the protocol. Because of the exploratory nature of the study, the submitted data is insufficient to support the proposed second indication to reduce the prescribed dose of ESA required to maintain desired hemoglobin levels. Large Phase 3 trials should be conducted to further evaluate the efficacy of Triferic for this indication.

6.1 Indication: Treatment of iron loss or iron deficiency to maintain hemoglobin

The proposed first indication was the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

6.1.1 Method

Two phase 3 studies (RMTI-SFP-4 and RMTI-SFP-5) were evaluated for the efficacy and safety of Triferic for the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).

The two studies had identical study protocols. They were multicenter, randomized (1:1), single-blinded (only the study patients were blinded to treatment assignment), placebo-controlled, Phase 3 studies to evaluate the efficacy and safety of SFP in adult patients with hemodialysis-dependent CKD (HDD-CKD).

See Section 5.3.1 for detailed study protocols.

6.1.2 Demographics

Demographics

The Study RMTI-SFP-4 randomized 305 patients at the Stage 2 from 43 sites in the U.S. The Study RMTI-SFP-5 randomized 294 patients from 41 sites in U.S. and 2 sites in Canada. In Study RMTI-SFP-4, the majority of the subjects were male (67.9%) and Caucasian (55.1%). The mean age was 58.3 years (range of 23 to 89 years). Similarly, in Study RMTI-SFP-5, the majority of the subjects was male (59.5%) and Caucasian (53.1%). The mean age was 58.5 years (range of 20 to 89 years).

The demographic characteristics were similar for the SFP and placebo groups except that there were slightly more patients in the younger age group in the SFP group as compared to the placebo group in both studies and slightly more males and more Caucasians in the placebo group than in the SFP group in Study SFP-5 (see Table below).

Table 3. Demographics in ITT Population

Demographics	SFP-4		SFP-5	
	SFP (N=152)	Placebo (N=153)	SFP (N=147)	Placebo (N=147)
Age, years				
Mean (SD)	56.6 (12.6)	59.9 (13.0)	58.1 (12.7)	59.0 (14.4)
<65 years	111 (73.0)	97 (63.4)	102 (69.4)	95 (64.6)
65-74 years	34 (22.4)	35 (22.9)	31 (21.1)	28 (19.0)
≥75 years	7 (4.6)	21 (13.7)	14 (9.5)	24 (16.3)
Median (range)	58 (23, 86)	60 (26, 89)	59 (20, 84)	60 (21, 89)
Gender, n (%)				
Male	102 (67.1)	105 (68.6)	82 (55.8)	93 (63.3)
Female	50 (32.9)	48 (31.4)	65 (44.2)	54 (36.7)
Race, n (%)				
Asian	8 (5.3)	5 (3.3)	8 (5.4)	4 (2.7)
African American	50 (32.9)	48 (31.4)	64 (43.5)	54 (36.7)
Caucasian	84 (55.3)	84 (54.9)	73 (49.7)	83 (56.5)
Other	10 (6.4)	16 (10.4)	2 (1.4)	6 (4.1)

Reviewer's table

Baseline Characteristics

Baseline hemoglobin and iron parameters

The baseline mean pre-dialysis hemoglobin level was comparable between the SFP and placebo groups in both studies (see Table below). The baseline mean TSAT and serum ferritin were also similar between the two groups in both studies.

Table 4. Baseline Hemoglobin and Iron Parameters

Hgb and iron parameters	SFP-4		SFP-5	
	SFP (N = 152) Mean (SD)	Placebo (N = 153) Mean (SD)	SFP (N = 147) Mean (SD)	Placebo (N =147) Mean (SD)
Hemoglobin (g/dL)	10.96 (0.59)	10.91 (0.63)	10.96 (0.61)	10.94 (0.62)
TSAT (%)	28.2 (8.2)	27.1 (7.8)	28.0 (8.2)	28.2 (8.5)
Ferritin (µg/L)	508.2 (193.6)	509.3 (209.1)	519.0 (201.6)	478.4 (200.6)

Reviewer's table

Renal failure and other medical history:

In Study SFP-4, at baseline the mean duration of renal failure in the study population was 5 years and the mean duration of hemodialysis was 4 years with a range of 5 months to 30 years. The most frequent underlying causes of renal failure were hypertension (62.3%) and diabetes mellitus (53.1%). The types of vascular access included fistula (75%), graft (17%), and Tunneled Catheter (8%). The baseline renal history parameters were similar between the SFP and placebo groups. About 98% of patients received 3 hemodialysis sessions per week and 2% of patients received 4 hemodialysis sessions per week in both groups. The dialysis parameters were similar between the two groups with a mean Kt/V (Dialyzer clearance of urea multiplied by dialysis time, divided by subject's total body water) of 1.68 and a mean URR (urea reduction ratio) of 74%. The history of intradialytic signs and symptoms was similar for the SFP and placebo groups. The most frequent intradialytic signs or symptoms in the SFP and placebo groups were hypotension (69.6% and 66.9%, respectively) and muscle cramps (64.9% and 62.8%, respectively). At baseline, the classes of other medical history reported most frequently were vascular disorders (99.0% of subjects), metabolism and nutrition disorders (98.3%), endocrine disorders (93.7%), renal and urinary disorders (91.7%), and blood and lymphatic system disorders (89.0%). The most frequently reported individual diagnoses were hypertension (97.3%), hyperphosphatemia (81.7%), anemia (70.7%), and secondary hyperparathyroidism (52.7%). There were no significant differences between the SFP and the placebo groups regarding medical history.

Similarly, in Study SFP-5, the baseline renal history parameters were similar between the SFP and placebo groups. The mean time since the initial diagnosis of renal failure was 6.1 years and the mean duration of hemodialysis was about 4.1 years with a range of 5 months to 22 years. The most frequent underlying causes of renal failure were diabetes mellitus (46.3%) and hypertension (43.5%). The types of vascular access included fistula (68%), graft (21%), and Tunneled Catheter (11%). The baseline renal history parameters were similar between the SFP and placebo groups. About 99% of patients received 3 hemodialysis sessions per week and 1% of patients received 4 hemodialysis sessions per week in both groups. The dialysis parameters were similar between the two groups with a mean Kt/V of 1.68 and a mean URR of 74%. The history of intradialytic signs and symptoms was similar for the SFP and placebo groups. The most frequent intradialytic signs or symptoms in the SFP and placebo groups were hypotension (82.4% and 85.2%, respectively) and muscle cramps (71.8% and 81.7%, respectively). The classes of medical history reported most frequently were metabolism and nutrition disorders (98.6%) and vascular disorders (98.6%), followed by renal and urinary disorders (94.8%), endocrine disorders (89.6%), and blood and lymphatic system disorders (86.5%). The most frequently reported individual diagnoses were hypertension (96.2%), renal failure chronic (92.0%), hyperphosphatemia (82.6%), hyperparathyroidism secondary (64.2%), anemia (60.4%), and type 2 diabetes mellitus (52.4%). In both populations, the baseline medical history was similar for the SFP and placebo groups.

History of iron use, ESA and transfusion:

In Study SFP-4, the majority (75%) of subjects received IV iron prior to study, with iron sucrose the most frequently administered type of IV iron (58%), followed by sodium iron gluconate complex (14%). The mean time from the last dose of IV iron to randomization into Stage 2 was 9 weeks. The mean total IV iron administered within the 2 months prior to screening phase of the study was 328 mg elemental iron. There were no significant differences in IV iron administration history between the SFP and placebo groups. Relatively few subjects received any oral iron within the 2 months prior to screening in the SFP (4 subjects, 2.7%) and placebo (5 subjects, 3.3%) groups. Epoetin alfa was the most commonly prescribed type of ESA at baseline in both the SFP (95.4%) and placebo (88.9%) groups. The mean baseline prescribed ESA dose per administration was similar between the two groups. The majority of the subjects were in Stratum I (≤13,000 equivalent units/week epoetin) in the SFP (81.6%) and placebo (81.0%) groups. About 25% of patients had history of blood transfusion and the mean time since the last transfusion was about 3 years with minimum of 4 months in those patients. There were no significant differences in history of blood transfusion between the SFP and placebo groups.

In Study SFP-5, the majority of subjects received IV iron within the 2 months prior to screening (83.3%), with iron sucrose the most frequently administered type of IV iron (67.3%) followed by sodium iron gluconate complex (9.9%). The mean time from the last dose of IV iron to randomization into Stage 2 was 9 weeks. The mean total IV iron administered within the 2 months prior to screening was 383 mg elemental iron. There were no significant differences in IV iron administration history between the SFP and placebo groups. Relatively few subjects received any oral iron within the 2 months prior to screening in the SFP (2 subjects, 1.4%) and placebo (1 subjects, 0.7%) groups. Similarly, epoetin alfa was the most commonly prescribed type of ESA at baseline in both the SFP (81.6%) and placebo (80.3%) groups. The mean baseline prescribed ESA dose per administration was similar in both groups. The majority of the randomized subjects were in Stratum I (≤13,000 equivalent units/week Epoetin) in the SFP (81.6%) and placebo (81.0%) groups. About 26% of subjects had history of RBC or whole blood transfusion and the mean time since the last transfusion was about 3 years. There were no significant differences in the history of transfusion between the SFP and placebo groups.

Table 5. History of Iron and ESA Use and Blood Transfusion

	SFP-4		SFP-5	
	SFP (N=152)	**Placebo (N=153)**	**SFP (N=147)**	**Placebo (N=147)**
Any IV Iron Within the 2 Months Prior to Study	114 (75.0)	115 (75.2)	120 (81.6)	125 (85.0)
Total iron administered within 2 months prior to study (mg)	328.4 (241.7)	328.6 (239.7)	381.8 (220.2)	384.1 (294.5)
ESA Weekly Dose				
ESA Stratum I	124 (81.6)	124 (81.0)	113 (76.9)	114 (77.6)
ESA Stratum II	28 (18.4)	29 (19.0)	34 (23.1)	33 (22.4)
History of RBC or whole blood transfusions [n				

(%)]				
Yes	41 (27.0)	35 (22.9)	38 (25.9)	38 (25.9)
No	111 (73.0)	118 (77.1)	109 (74.1)	109 (74.1)

ESA Stratum I: ≤13,000 equivalent units/week epoetin, Stratum II: >13,000 equivalent units/week epoetin)
Reviewer's table

Hemodialysis parameters during the study

A summary of hemodialysis sessions during Stage 2 for the MITT population is presented in the Table below. Hemodialysis session parameters were similar for the SFP and placebo groups. More than 95% of patients received dialysis 3 times weekly in both groups for both studies. The mean duration of dialysis at each dialysis session was about 3 and half hours, which was similar for the SFP group and the placebo group in both studies. The mean mid-point blood flow rate and the mean dialysate flow rate were also similar for the two treatment groups in both studies (see Table below).

Table 6. Hemodialysis Parameters in Randomized Phase of the study

	SFP-4		SFP-5	
Hemodialysis parameters	**SFP**	**Placebo**	**SFP**	**Placebo**
Frequency of dialysis [n (%)]				
3 times weekly	145 (95.4)	149 (97.4)	142 (96.6)	143 (97.3)
4 times weekly	4 (2.6)	2 (1.3)	1 (0.7)	2 (1.4)
Duration of dialysis session (hours)				
n	149	151	143	145
Mean (SD)	3.6 (0.4)	3.5 (0.4)	3.7 (0.4)	3.7 (0.4)
Mid-point blood flow rate (mL/min)				
n	149	151	143	145
Mean (SD)	415.8 (43.0)	414.4 (47.2)	430.3 (54.7)	425.8 (47.5)
Dialysate flow rate (mL/min)				
n	149	151	143	145
Mean (SD)	711.4 (87.3)	702.2 (88.9)	675.8 (101.0)	663.1 (95.9)

Reviewer's table

Concomitant Medications:

In Study SFP-4, almost all subjects in the SFP (99.3%) and placebo (100%) groups received 1 or more concomitant medications during the study. The percentages of subjects receiving each of the concomitant medications were generally similar for the SFP and placebo groups. The most frequently reported concomitant medications were doxercalciferol (53.7%), acetylsalicylic acid (46.7%), sevelamer carbonate (35.7%), calcium acetate (32.7%), and paricalcitol (32.0%). The numbers and percentages of subjects who received one or more antihypertensive medications were similar in the SFP and placebo groups at baseline (85.9% and 92.1%, respectively) and at the end of study treatment (83.9% and 87.4%, respectively). The mean number of unique antihypertensive medications per subject was 2.8 in the SFP and placebo groups at baseline and at the end of study treatment.

Similarly, in Study SFP-5, all subjects in the SFP and placebo groups received 1 or more concomitant medications during the study. The percentages of subjects receiving each of the concomitant medications were generally similar for the SFP and placebo groups. The most frequently reported concomitant medications were acetylsalicylic acid (43.1%), paracetamol (41.7%), doxercalciferol (39.2%) and cinacalcet hydrochloride (28.8%), sevelamer carbonate (28.1%), and clonidine (28.1%). The numbers and percentages of subjects who received 1 or more antihypertensive medications were similar in the SFP and placebo groups at baseline (90.2% and 89.7%, respectively) and at the end of study treatment (86.0% and 84.1%, respectively). The mean number of unique antihypertensive medications per subject was same in the SFP and placebo groups at baseline (2.8) and at the end of study treatment (2.7).

Study Treatment, Duration and Compliance

The number of vials used per patient per session, was not captured in the database but resides in the manual dosing logs in the study sites. The 2.5 gallon bicarbonate container, to which the 5 mL vial of SFP was added, was designed to provide sufficient SFP for a standard 4 hour dialysis treatment. So the vast majority of subjects used only 1 vial/treatment. In the clinical trials, there were 74 subjects who had dialysis times in excess of 4.5 hrs. Of those, only 16 subjects had ≥ 10 hemodialysis sessions lasting 4.5 hours or longer.

A review of the all HD sessions for the above identified subjects with dialysis times greater than 4.5 hours showed that all subjects used only 1 vial of SFP added to the 2.5 gallon bicarbonate concentrate container for all on study treatments. No subjects required more than 1 vial to complete their treatment.

The mean treatment duration was 157.7 days in the SFP group and 164.6 days in the placebo group in study SFP-4 and 161.2 days in the SFP group and 157.9 days in the placebo group in study SFP-5 (see Table below). Slightly fewer than 50% of study patients received study treatment for ≥20 weeks and only about 20% of study patients received study treatment 44-47 weeks in the randomized phase (Stage 2).

Table 7. Treatment Duration in Randomized Phase

	SFP (N=148)	**Placebo (N=151)**	**SFP (N = 142)**	**Placebo (N = 144)**
Treatment Duration (days)				
Mean (SD)	157.7 (115.42)	164.6 (111.80)	161.2 (111.10)	157.9 (109.76)
Median	125	143	132	135
Min, Max	1, 332	1, 333	1, 332	3, 332
Duration of exposure [n (%)]				
≥1 day	148 (100.0)	151 (100.0)	142 (100.0)	144 (100.0)
≥1 week	147 (99.3)	149 (98.7)	141 (99.3)	143 (99.3)
≥2 weeks	140 (94.6)	147 (97.4)	140 (98.6)	140 (97.2)
≥4 weeks	130 (87.8)	137 (90.7)	133 (93.7)	126 (87.5)

≥8 weeks	109 (73.6)	118 (78.1)	117 (82.4)	114 (79.2)
≥12 weeks	90 (60.8)	103 (68.2)	89 (62.7)	96 (66.7)
≥16 weeks	84 (56.8)	87 (57.6)	77 (54.2)	78 (54.2)
≥20 weeks	68 (45.9)	78 (51.7)	67 (47.2)	71 (49.3)
≥24 weeks	62 (41.9)	65 (43.0)	60 (42.3)	63 (43.8)
≥28 weeks	55 (37.2)	57 (37.7)	51 (35.9)	50 (34.7)
≥32 weeks	46 (31.1)	48 (31.8)	42 (29.6)	44 (30.6)
≥36 weeks	41 (27.7)	40 (26.5)	37 (26.1)	36 (25.0)
≥40 weeks	36 (24.3)	35 (23.2)	34 (23.9)	31 (21.5)
44 -47 weeks	30 (20.3)	32 (21.2)	32 (22.5)	24 (16.7)

Reviewer's table

Reviewer's Comments: *Only about 20% of study patients in both the SFP and the placebo groups completed an anticipated 48 weeks of treatment duration, mainly due to early withdrawal for significant ESA dose change, which was mandated by protocol to protect patient's safety. In clinical practice, all patients would continue SFP treatment with ESA dose adjustment and hemoglobin level would be affected by both treatments. However, in these clinical trials to evaluate the efficacy of SFP, a stable ESA dose during the study was required to evaluate the efficacy of SFP to minimize the confounding effect of ESA on hemoglobin level.*

In Study SFP-4, the total number of subjects with at least 1 dose not administered and the total number of study drug doses not administered was slightly higher in the SFP group (55 subjects and 149 doses, respectively) than in the placebo group (24 subjects and 81 doses, respectively). The percentage of the total number of study drug doses not administered of the expected total number of hemodialysis sessions was 1.5% in the SFP group and 0.8% in the placebo group.

In Study SFP-4, the reasons for missing doses included pre-dialysis TSAT >50%, serum ferritin >1200 mcg/L, investigator discretion, or bacteremia or fungemia or anti-microbial treatment for systemic or serious infection. The percentage of doses of study drug not received due to other reasons was higher in the SFP group (1%, 101 of 10014 doses) than in the placebo group (0.3%, 34 of 10527 doses. The most commonly reported other reason was due to site personnel error which was also higher in the SFP group as compared to the placebo group (28 instances in the SFP group and 4 instances in the placebo group). In the placebo group, the most common of the other reasons was hospitalization (9 instances in the placebo group and 7 instances in the SFP group). Additional other reasons included missed dialysis sessions (e.g., due to subject vacation or reasons other than hospitalization), problems with study drug availability, subject refusal of study drug, withdrawal from the study, subject was being transitioned to Stage 3, dialysis machine or vascular access issues, and Sponsor mandate as part of a corrective action plan due to site non-compliance.

In Study SFP-5, the total number of subjects with at least 1 dose not administered and the total number of study drug doses not administered were also slightly higher in the SFP group (58 subjects and 221 doses, respectively) than in the placebo group (35 subjects and 166 doses, respectively). The percentage of the total number of study drug doses not administered was 2.2% (221/ 9827) in the SFP group and 1.7% (166/9795]) in the placebo group.

The reasons for missing doses included pre-dialysis TSAT >50%, serum ferritin >1200 mcg/L, investigator discretion, or bacteremia or fungemia or anti-microbial treatment for systemic or serious infection. The percentage of doses of study drug not received due to other reasons was higher in the SFP group (1.7%, 167 of 9827 doses) than in the placebo group (1.1%, 110 of 9795 doses). The most commonly reported other reason was due to site personnel error (27 in the SFP group and 10 in the placebo group). Additional other reasons included missed doses due to missed dialysis sessions (e.g., due to subject vacation or reasons other than hospitalization), problems with study drug availability, subject refusal of study drug, withdrawal from the study, subject being transitioned to Stage 3, dialysis machine or vascular access issues, and drug held per sponsor request.

The study drug compliance during Stage 2 randomized phase is shown in Table below.

Table 8. Study Treatment Compliance during Randomized Phase

	SFP-4		SFP-5	
	SFP	**Placebo**	**SFP**	**Placebo**
Randomized subjects	152	153	147	147
Subjects who received at least 1 dose	149	151	142	144
Subjects with at least 1 dose of study drug not administered	55	24	58	35
Total number of study drug doses not administered per subject				
Mean (SD)	2.7 (3.1)	3.4 (5.8)	3.8 (4.4)	4.7 (8.4)
Total number of study drug doses not administered	149	81	221	166
Reasons study drug dose not administered (number of doses [%])				
Pre-dialysis TSAT >50%	12 (0.1%)	0 (0.0%)	12 (0.1)	0 (0.0)
Serum ferritin >1200 mcg/L	0 (0.0%)	15 (0.1%)	0 (0.0)	39 (0.4)
Bacteremia or fungemia or anti-microbial treatment for systemic or serious infection	31 (0.3%)	31 (0.3%)	39 (0.4)	14 (0.1)
Investigator discretion	5 (0.1%)	1 (0.01%)	3 (0.03)	3 (0.03)
Other	101 (1.0%)	34 (0.3)	167 (1.7)	110 (1.1)

Note: Denominator is the total number of HD sessions during the treatment period (from Study Day 1 to the date of the last treatment period visit).
Reviewer's table

6.1.3 Subject Disposition

Study SFP-4

A total of 305 patients with HDD-CKD were randomized, 152 patients to the SFP group and 153 patients to the placebo group. Of the 305 subjects randomized, 300 (149 in the SFP group, 151 in the placebo group) received study drug and 5 patients did not receive any study drug. The reasons for not receiving the study drug included IV iron administration, sponsor's request, and randomization error in the 3 subjects in the SFP group and adverse event and blood transfusion in 2 subjects in the placebo group.

Of the 305 subjects randomized, 54 (17.7%) subjects completed 48 week treatment in Stage 2, 8 (2.6%) subjects died, and 151 (49.5%) subjects who required protocol-mandated change in anemia management were withdrawn from Stage 2 prior to 48 weeks. There were slightly more subjects who required protocol-mandated change in anemia management in the placebo group (53.6%) as compared to the SFP group (45.4%). In the majority of subjects, this was due to a requirement of an ESA dose change (42.8% in SFP and 45.1% in placebo). For 4 (2.6%) subjects in the SFP group compared to 14 (9.2%) subjects in the placebo group change was due to a requirement for IV iron administration.

There were 37 subjects who had ESA dose change and/or received IV iron administration that were not required per protocol-mandated change in anemia management leading to withdrawal prior to 48 weeks (17 [11.2%]) in the SFP group and 20 [13.1%] in the placebo group); most of these subjects also had an ESA dose change as well.

Other reasons for withdrawal included withdrew consent (4.3%), adverse events (3.3%), RBC or whole blood transfusion (2.6%), protocol violations (1.3%), principal investigator decision (1.3%), sponsor's request (0.7%), and lost to follow-up (0.3%). Slightly more patients withdrew from Stage 2 in the SFP group as compared to the placebo group due to withdrawn consent (4.6% vs. 2%, respectively). There were more subjects withdrawn due to RBC or blood transfusion in the placebo group as compared to the SFP group (4.6% vs. 0.7%, respectively).

Study SFP-5:

A total of 294 patients with HDD-CKD were randomized into Stage 2 of the study, 147 patients each to the SFP group and to the placebo group. Of the 294 subjects randomized, 288 subjects (143 in the SFP group and 145 in the placebo group) received study drug and 6 patients did not receive any study drug. The reasons for not receiving study treatment were death (1 in the placebo group), physician's decision (1 in the SFP group), withdrawn consent (1 in the SFP group), and randomization errors (2 in the SFP group and 1 in the placebo group).

Of the 294 subjects randomized, 50 (17%) subjects completed 48 weeks treatment in Stage 2, 10 (3.4%) subjects died, and 158 (53.7%) subjects who required protocol-mandated change in anemia management were withdrawn from Stage 2 prior to 48 weeks. There were more subjects who required protocol-mandated change in anemia management in the placebo group (61.2%) as compared to the SFP group (46.3%). In the majority of subjects, withdrawal was due to a requirement of an ESA dose change (44.2% in SFP and 46.9% in placebo). Three (2%) subjects in the SFP group compared to 21 (14.3%) subjects in the placebo group were due to a requirement for IV iron administration.

There were 20 subjects who had ESA dose change and/or received IV iron administration that was not required per protocol-mandated change in anemia management and were withdrawn prior to 48 weeks (14 [9.5%]) in the SFP group and (6 [4.1%]) in the placebo group); most of these subjects also withdrew due to an ESA dose change.

Other reasons included protocol violations (3.7%), RBC or whole blood transfusion (3.4%), adverse events (3.1%), withdrew consent (2.0%), investigator decision (1.4%), sponsor's request (0.7%), Study drug suspended for >12 weeks (0.3%), and other (5.1%).

The following table presents the subject disposition in the SFP-4 and SFP-5 studies.

Table 9. Subject Disposition

	SFP-4		SFP-5	
Subject Disposition	**SFP (N=152)**	**Placebo (N=153)**	**SFP (N=147)**	**Placebo (N=147)**
Randomized	152	153	147	147
Received at least one dose of study drug	149 (98.0)	151 (98.7)	143 (97.3)	145 (98.6)
Completed 48 weeks treatment	27 (17.8)	27 (17.6)	28 (19.0)	22 (15.0)
Died	5 (3.3)	3 (2.0)	7 (4.8)	3 (2.0)
Removed due to Protocol-mandated change in anemia management prior to 48 weeks	69 (45.4)	82 (53.6)	68 (46.3)	90 (61.2)
ESA dose change	65 (42.8)	69 (45.1)	65 (44.2)	69 (46.9)
IV iron administration	4 (2.6)	14 (9.2)	3 (2.0)	21 (14.3)
Other early withdrawal				
Non-protocol-mandated change in anemia management	17 (11.2)	20 (13.1)	14 (9.5)	6 (4.1)
ESA dose change	13 (8.6)	17 (11.1)	10 (6.8)	5 (3.4)
IV iron administration	6 (3.9)	5 (3.3)	4 (2.7)	1 (0.7)
Withdrew consent	10 (6.6)	3 (2.0)	1 (0.7)	5 (3.4)
Adverse event	5 (3.3)	5 (3.3)	7 (4.8)	2 (1.4)
RBC or whole blood transfusion	1 (0.7)	7 (4.6)	5 (3.4)	5 (3.4)
Protocol violation	3 (2.0)	1 (0.7)	7 (4.8)	4 (2.7)
Principal Investigator decision	3 (2.0)	1 (0.7)	3 (2.0)	1 (0.7)
Sponsor's request	2 (1.3)	0 (0.0)	0 (0.0)	2 (1.4)
Study drug suspended for >12 weeks	0	0	0 (0.0)	1 (0.7)
Lost to follow-up	1 (0.7)	0 (0.0)	0	0
Other	9 (5.9)	4 (2.6)	9 (6.1)	6 (4.1)

Reviewer's table

In both studies, the protocol-mandated change in anemia management criteria that triggered subjects to be removed from randomized Stage 2 phase prior to 48 weeks included the following:

- Hgb < 9.0 g/dL or > 12.0 g/dL confirmed by a consecutive repeat value obtained between ≥ 1 day and ≤ 2 weeks after the first value (this constituted meeting criteria for a Protocol-Mandated Change in Anemia Management (PMAM) due to a need for an ESA dose change)
- Hgb > 11.5 g/dL over ≥ 1 week confirmed by ≥ 2 consecutive weekly measurements AND an associated increase in Hgb by ≥ 1 g/dL over 4 weeks (this also constituted meeting criteria for a PMAM due to a need for an ESA dose change)

- Ferritin < 100 µg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements (this constituted meeting criteria for a PMAM due to a need for IV iron)

Additional analysis was performed for final hemoglobin and serum ferritin values for subjects who withdrew prior to 48 weeks due to protocol-mandated change in anemia management. The following table shows the final hemoglobin and ferritin in the randomized phase (Stage 2) in SFP-4 and SFP-5 studies.

Table 10. Subjects Who Met Criteria for Protocol-Mandated Changes in Anemia Management

	SFP-4		SFP-5	
	SFP N=152 n (%)	**Placebo N=153 n (%)**	**SFP N=147 n (%)**	**Placebo N=147 n (%)**
Overall (PMAM)	69 (45.4)	82 (53.6)	68 (46.3)	90 (61.2)
Final Hgb > 12.0 g/dL	41 (27.0)	32 (20.9)	32 (21.8)	21 (14.3)
Final Hgb < 9.0 g/dL	17 (11.2)	27 (17.6)	22 (15.0)	34 (23.1)
Final Ferritin < 100 mcg/L	5 (3.3)	17 (11.1)	4 (2.7)	23 (15.6)

Reviewer's table

In Study SFP-4, the majority of subjects with protocol mandated changes in anemia management had final Hgb values > 12.0 g/dL with slightly more patients in the SFP group (27%) as compared to the placebo group (20.9%) that needed ESA dose change. There were more subjects withdrawn with final Hgb values < 9 g/dL in the placebo group as compared to the SFP group (17.6% vs. 11.2%, respectively). There were also more subjects who had final serum ferritin level <100 mcg/L in the placebo group as compared to the SFP group (11.1% vs. 3.3%, respectively).

For the remaining subjects who were determined to meet criteria for protocol-mandated changes in anemia management by investigator, 6 subjects in the placebo group had final Hgb >11 g/dL with a previous Hgb >11.5 g/dL. In the SFP group, 6 of 7 subjects had final Hgb >11 g/dL with a previous Hgb >12 g/dL and one subject had final Hgb 10.9 g/dL with the previous value of 10.8 g/dL.

Similarly, in Study SFP-5, there were more subjects with protocol-mandated changes withdrawn with the final Hgb values < 9 g/dL in the placebo group as compared to the SFP group (23.1% vs. 15%, respectively) and more subjects withdrawn with the final Hgb values >12 g/dL in the SFP group as compared to the placebo group (21.8% vs. 14.3%, respectively). There were also more subjects who were withdrawn from Stage 2 due to serum ferritin level <100 mcg/L in the placebo group as compared to the SFP group (15.6% vs. 2.7%, respectively).

For the remaining subjects who were determined to meet criteria for protocol-mandated changes in anemia management by investigator, all 9 subjects in the placebo group had final Hgb >11 g/dL. Of those, 6 had the previous Hgb value >12 g/dL and 2 had Hgb ≥11.8 g/dL. In the SFP

group, all 11 subjects had final Hgb >11 g/dL. Of those, 8 subjects had the previous Hgb value >12 g/dL and 3 subjects had final Hgb >11.5 g/dL.

Reviewer's Comments: *About 50% of study patients in either the SFP or placebo groups were removed from the randomized phase prior to 48 weeks due to protocol mandated anemia management, mainly ESA dose change. However, additional analysis of final Hgb and serum ferritin levels prior to removal showed that more patients in the placebo group had Hgb<9 g/dL or serum ferritin <100 mcg/L than in the SFP group in both studies. This provides some assurance and additional support for the efficacy of SFP for those who were removed prior to 48 weeks.*

Protocol Violations/Deviations

Study SFP-4:

Protocol deviations identified for the randomized subjects are summarized in the Table below. The percentages of subjects with the specific protocol violations cited below were similar in the SFP and placebo groups.

Table 11. Protocol Violations/Deviations in SFP-4

Protocol Deviation	**SFP (N=152) n (%)**	**Placebo (N=153) n (%)**	**Total (N=305) n (%)**
Change in ESA product, dose, or route of administration	62 (40.8)	70 (45.8)	132 (43.3)
Developed withdrawal criteria and were not withdrawn	13 (8.6)	12 (7.8)	25 (8.2)
Did not meet inclusion/exclusion criteria during Stage 2	19 (12.5)	15 (9.8)	34 (11.1)
Received excluded concomitant treatment, such as inappropriate IV iron or oral iron	9 (5.9)	10 (6.5)	19 (6.2)
Received less than the intended full amount of study drug exposure at any visit	32 (21.1)	34 (22.2)	66 (21.6)
Received no study drug on a scheduled day of treatment	84 (55.3)	72 (47.1)	156 (51.1)
Received wrong treatment or incorrect dose of study drug	4 (2.6)	2 (1.3)	6 (2.0)
Satisfied criteria for study drug withholding but study drug not withheld	3 (2.0)	0 (0.0)	3 (1.0)

Reviewer's table

Study SFP-5:

Protocol deviations identified for the randomized subjects are summarized in the Table below. The percentages of subjects with the specific protocol violations cited below were similar in the SFP and placebo groups.

Table 12. Protocol Violations/Deviations in SFP-5

Protocol Deviation	SFP (N=147) n (%)	Placebo (N=147) n (%)	Total (N=294) n (%)
Change in ESA product, dose, or route of administration	56 (38.1)	48 (32.7)	104 (35.4)
Developed withdrawal criteria and were not withdrawn	20 (13.6)	14 (9.5)	34 (11.6)
Did not meet inclusion/exclusion criteria	16 (10.9)	18 (12.2)	34 (11.6)
Eligibility	4 (2.7)	11 (7.5)	15 (5.1)
Received excluded concomitant treatment, such as inappropriate IV iron or oral iron	14 (9.5)	14 (9.5)	28 (9.5)
Received less than the intended full amount of study drug exposure at any visit	36 (24.5)	40 (27.2)	76 (25.9)
Received no study drug on a scheduled day of treatment	96 (65.3)	74 (50.3)	170 (57.8)
Received wrong treatment or incorrect dose of study drug	4 (2.7)	6 (4.1)	10 (3.4)
Satisfied criteria for study drug withholding but study drug not withheld	7 (4.8)	5 (3.4)	12 (4.1)

Reviewer's table

Analyzed populations

The following are definitions of analyzed populations:

- ITT population: All subjects who were randomized to a treatment group in Stage 2.
- MITT population: Randomized subjects who received at least 1 dose of study drug and also had at least 1 post-baseline Hgb value.
- Efficacy-evaluable population: All randomized subjects who either (1) complete ≥36 study drug exposures (expected to be approximately 12 weeks) in Stage 2, or (2) are withdrawn from study prior to 36 study drug exposures in Stage 2 due to suspected study drug toxicity or a protocol-mandated change in anemia management.
- Safety population: Subjects who received any amount of study drug. Subjects receiving an incorrect treatment are summarized as SFP.

The numbers of subjects in analyzed populations for the two studies are shown below.

Table 13. Analyzed Populations

	SFP-4		SFP-5	
Subject Disposition	**SFP**	**Placebo**	**SFP**	**Placebo**
Randomized (ITT)	152	153	147	147
MITT	148 (97.4)	151 (98.7)	142 (96.6)	144 (98.0)
Evaluable	115 (75.7)	121 (79.1)	112 (76.2)	113 (76.9)
Safety	149 (98.0)	151 (98.7)	143 (97.3)	145 (98.6)

Reviewer's table

6.1.4 Analysis of Primary Endpoint(s)

Primary efficacy endpoint

The primary efficacy endpoint was the mean change in Hgb from baseline to end of the treatment (EoT). The Hgb values at EoT were based on all available values obtained during the last 1/6th of each subject's participation in the study regardless of the time or reason subjects were withdrawn or completed randomized, controlled phase (Stage 2) of the study.

ITT Population

The mean changes in hemoglobin from baseline to EoT in the ITT population in the two groups in both studies are presented in Table below. In Study SFP-4, the mean hemoglobin decreased 0.03 g/dL from baseline in the SFP group as compared to 0.38 g/dL in the placebo group. In Study SFP-5, the mean hemoglobin decreased 0.08 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group. The primary efficacy analysis used an ANCOVA model with baseline Hgb as a covariate. The treatment differences in hemoglobin between the SFP and the placebo groups in both studies showed an LS mean difference of 0.35 g/dL and were statistically significant (p =0.01) in both studies.

Table 14. Primary Efficacy Endpoint in ITT population

	SFP-4		**SFP-5**	
	SFP (N = 152)	**Placebo (N = 153)**	**SFP (N = 147)**	**Placebo (N = 147)**
Baseline Hgb (g/dL) Mean (SD)	10.96 (0.59)	10.91 (0.63)	10.96 (0.61)	10.94 (0.62)
EoT Hgb (g/dL), Mean (SD)	10.93 (1.24)	10.53 (1.35)	10.87 (1.36)	10.50 (1.32)
Change in Hgb from Baseline to EOT (g/dL) Mean (SD)	-0.03 (1.15)	-0.38 (1.24)	-0.08 (1.15)	-0.44 (1.16)
ANCOVA analysis with baseline Hgb as the covariate				
LS Mean (SE)	0.06 (0.11)	-0.30 (0.11)	-0.04 (0.11)	-0.39 (0.11)
95% CI of LS Mean	(-0.16, 0.28)	(-0.52, -0.08)	(-0.25, 0.16)	(-0.60, -0.19)
LS Mean Difference (SE)	0.35 (0.14)		0.35 (0.14)	
95% CI of LS Mean Difference	(0.9, 6.2)		(0.8, 6.1)	
P-value	0.010		0.011	

Note: LS Mean (SE) and p-value are from an ANCOVA model with baseline Hgb as the covariate. The model also includes an indicator variable for the baseline ESA dose stratum.
Reviewer's table

MITT population

The primary efficacy endpoint results in the MITT population were similar to the results that were obtained from the ITT analysis (see Table below). In Study SFP-4, the mean hemoglobin decreased 0.04 g/dL in the SFP group as compared to 0.39 g/dL in the placebo group.

Similarly, in Study SFP-5 the mean hemoglobin decreased 0.09 g/dL in the SFP group as compared to 0.45 g/dL in the placebo group. ANCOVA analysis with baseline Hgb as the covariate showed a treatment difference of LS mean difference of 0.36 g/dL in hemoglobin in both studies. The difference between the SFP and the placebo group was statistically significant (p =0.01) in both studies.

Table 15. Primary Efficacy Endpoint in MITT population

	SFP-4		SFP-5	
	SFP (N = 148)	**Placebo (N = 151)**	**SFP (N = 142)**	**Placebo (N = 144)**
Baseline Hgb (g/dL) Mean (SD)	10.96 (0.59)	10.91 (0.63)	10.96 (0.61)	10.93 (0.63)
EoT Hgb (g/dL), Mean (SD)	10.91 (1.25)	10.52 (1.37)	10.87 (1.38)	10.49 (1.33)
Change in Hgb from Baseline to EOT (g/dL) Mean (SD)	-0.04 (1.17)	-0.39 (1.25)	-0.09 (1.18)	-0.45 (1.17)
ANCOVA analysis with baseline Hgb as the covariate				
LS Mean (SE)	0.06 (0.12)	-0.30 (0.11)	-0.05 (0.11)	-0.40 (0.11)
95% CI of LS Mean	(-0.17, 0.28)	(-0.53, -0.08)	(-0.26, 0.17)	(-0.62, -0.19)
LS Mean Difference (SE)	0.36 (0.14)		0.36 (0.14)	
95% CI of LS Mean Difference	(0.08, 0.63)		(0.08, 0.63)	
p-value	0.011		0.011	

Note: LS Mean (SE) and p-value are from an ANCOVA model with baseline Hgb as the covariate. The model also includes an indicator variable for the baseline ESA dose stratum.
Reviewer's table

Evaluable population

In the efficacy-evaluable population, the mean hemoglobin decreased 0.03 g/dL in the SFP group as compared to 0.35 g/dL in the placebo group in Study SFP-4 (see Table below). Similarly, the mean hemoglobin decreased 0.11 g/dL in the SFP group as compared to 0.44 g/dL in the placebo group in Study SFP-5. ANCOVA analysis with baseline Hgb as the covariate showed that the treatment difference in hemoglobin between the SFP and the placebo group with an LS mean difference of 0.32 g/dL in Study SFP-4 and 0.34g/dL in Study SFP-5. The difference between two treatment groups was not statistically significant (p =0.056) in Study SFP-4 but was statistically significant in Study SFP-5 (p=0.039).

Table 16. Primary Efficacy Endpoint in Evaluable Population

	SFP-4		SFP-5	
	SFP (N = 115)	**Placebo (N = 121)**	**SFP (N = 112)**	**Placebo (N = 123)**
Baseline Hgb (g/dL) Mean (SD)	11.01 (0.57)	10.96 (0.64)	10.94 (0.55)	10.92 (0.62)
EoT Hgb (g/dL), Mean (SD)	10.98 (1.33)	10.60 (1.41)	10.84 (1.41)	10.48 (1.38)

Change in Hgb from Baseline to EOT (g/dL) Mean (SD)	-0.03 (1.27)	-0.35 (1.30)	-0.11 (1.25)	-0.44 (1.22)
ANCOVA analysis with baseline Hgb as the covariate				
LS Mean (SE)	0.09 (0.13)	-0.23 (0.14)	-0.05 (0.13)	-0.39 (0.13)
95% CI of LS Mean	(-0.17, 0.36)	(-0.49, -0.04)	(-0.31, 0.16)	(-0.64, -0.14)
LS Mean Difference (SE)	0.32 (0.17)		0.34 (0.16)	
95% CI of LS Mean Difference	(-0.01, 0.65)		(0.02, 0.65)	
P-value	0.056		0.039	

Note: LS Mean (SE) and p-value are from an ANCOVA model with baseline Hgb as the covariate. The model also includes an indicator variable for the baseline ESA dose stratum.
Reviewer's table

6.1.5 Analysis of Secondary Endpoints(s)

Changes in Reticulocyte Hgb Content (CHr), Serum Ferritin and TSAT from baseline to the End-of-Treatment (EoT)

The mean changes from baseline to EoT in CHr, serum ferritin and TSAT in SFP-4 and SFP-5 are presented in Table below.

In the two studies,CHr and serum ferritin at EoT decreased less from baseline in the SFP groups than in the placebo groups. The pre-dialysis TSAT at EoT decreased less from baseline in the SFP groups than in the placebo groups in both studies. The results in iron parameters were consistent with the primary efficacy results in the two studies.

Table 17. Mean change in Reticulocyte Hemoglobin Content and Iron Parameters from Baseline to the End of Treatment in ITT population

	SFP-4		**SFP-5**	
	SFP N=152 Mean (SD)	**Placebo N=153 Mean (SD)**	**SFP N=147 Mean (SD)**	**Placebo N=147 Mean (SD)**
Reticulocyte Hgb Content (pg)	-0.2 (1.19)	-0.9 (1.41)	-0.6 (1.44)	-0.9 (1.47)
Serum Ferritin (mcg/L)	-70.8 (132.41)	-141.2 (187.74)	-65.3 (162.45)	-120.9 (268.19)
Pre-dialysis TSAT (%)	-1.0 (9.07)	-2.9 (7.65)	-0.9 (7.54)	-3.6 (7.29)

Note: TSAT =transferrin saturation
Reviewer's table

Change in iron parameters from pre-dialysis to post-dialysis over the course of the treatment period

The mean changes from pre-dialysis to post-dialysis over the course of the treatment period in serum iron, UIBC, and TSAT are shown in Table below. There were mean increases in serum iron, TSAT from pre-dialysis to post-dialysis in the SFP groups as compared to minimal changes in the placebo groups in both studies. On the other hand, there was a decrease in UIBC in the SFP groups as compared to small increase in UIBC in the placebo groups in both studies. These results were consistent with the primary efficacy results.

Table 18. Change from Pre-dialysis to Post-dialysis in Iron Parameters During the Treatment Period in MITT population

	SFP-4		SFP-5	
	SFP N=142 Mean (SD)	Placebo N=147 Mean (SD)	SFP N=139 Mean (SD)	Placebo N=141 Mean (SD)
Serum iron (mcmol/L)	17.45 (8.70)	0.63 (3.08)	19.68 (6.82)	1.19 (3.47)
TSAT (%)	32.7 (15.8)	-0.4 (6.9)	37.5 (11.5)	0.1 (6.9)
UIBC (mcmol/L)	-11.96 (6.60)	2.38 (3.25)	-13.31 (5.02)	2.57 (3.35)

Note: TSAT =transferrin saturation, UIBC =unsaturated iron binding capacity
Reviewer's table

6.1.6 Other Endpoints

Other protocol specified endpoints were not fully evaluated because many patients withdrew from the randomized controlled phase of the studies due to ESA dose changes.

6.1.7 Subpopulations

Pooled analyses of efficacy data from SFP-4 and SFP-5 studies by subgroup were performed to explore whether the treatment effect differed among the following subgroups of clinical interest.

Age:

There were higher percentages of subjects <65 years of age (72.1% and 63.7%) than subjects ≥65 years of age (27.9% and 36.3%) in both treatment groups (SFP and placebo groups, respectively). In both the <65 year-old subjects and the ≥65 year-old subjects, the SFP group had a smaller mean decrease from baseline (-0.3 g/L and -1.3 g/L, respectively) in Hgb than the placebo group (-3.0 g/L and -6.2 g/L, respectively). The results in both age groups were consistent with the overall study results.

Gender:

There were higher percentages of male subjects (61.0% and 66.1%) than female subjects (39.0% and 33.9%) in both treatment groups. In both the male and female subgroups, the SFP group had a smaller mean decrease from baseline (-0.5 g/L and -0.7 g/L, respectively) in Hgb than the

placebo group (-3.5 g/L and -5.4 g/L, respectively). The results in both gender groups were consistent with the overall study results.

Race:

Similar percentages of subjects were white (52.8% and 55.9%) and nonwhite (47.2% and 44.1%) in the SFP and placebo groups, respectively. In both the white and nonwhite subgroups, the SFP group had a smaller mean decrease from baseline (-0.8 g/L and -0.4 g/L, respectively) in Hgb than the placebo group (-4.8 g/L and -3.4 g/L, respectively). The results in both race groups were consistent with the overall study results.

HD parameters:

Change in Hgb from baseline to the end-of-treatment in subgroups based on HD parameters is shown in the Table below.

Table 19. Change from baseline at EoT in Hemoglobin by HD Parameters

HD parameters		**SFP**	**Placebo**
Type of vascular access			
Catheter	n	28	30
	Mean (SD)	0.1 (11.71)	-5.2 (13.61)
Graft/fistula	n	260	263
	Mean (SD)	-0.7 (11.71)	-4.1 (11.95)
Dialysis flow rate			
≤600 mL/min	n	111	128
	Mean (SD)	-1.0 (12.35)	-5.6 (11.31)
>600 mL/min	n	177	165
	Mean (SD)	-0.4 (11.29)	-3.1 (12.63)
Blood flow rate			
≤400 mL	n	141	145
	Mean (SD)	-0.2 (11.83)	-5.7 (11.94)
>400 mL/min	n	147	148
	Mean (SD)	-1.0 (11.59)	-2.6 (12.12)
Dialysis adequacy			
Kt/V ≤1.6	n	110	126
	Mean (SD)	-2.0 (12.43)	-2.6 (12.24)

Kt/V >1.6	n	130	119
	Mean (SD)	1.3 (11.15)	-4.7 (12.35)
Type of dialyzer membrane			
Cellulose triacetate	n	11	13
	Mean (SD)	-6.6 (11.08)	-5.0 (7.48)
Polyamide	n	8	59
	Mean (SD)	-0.7 (11.05)	-1.4 (12.20)
Polysulfone	n	184	161
	Mean (SD)	-0.9 (12.03)	-5.7 (12.12)
Polyarylethersulfone	n	45	58
	Mean (SD)	1.9 (10.81)	-2.2 (12.39)
Dialyzer reuse			
Yes	n	74	95
	Mean (SD)	-1.5 (11.78)	-3.3 (12.69)
No	n	214	198
	Mean (SD)	-0.3 (11.68)	-4.6 (11.84)

Reviewer's table

Type of vascular access:
Most subjects (90.1%) used the graft/fistula type of vascular access in the study. In both the graft/fistula vascular access subgroup and the catheter vascular access subgroup, the SFP group had a smaller change from baseline (-0.7 g/L and 0.1 g/L, respectively) in Hgb than the placebo group (−4.1 g/L and -5.2 g/L, respectively).

Dialysate flow rate:
There was a slightly higher percentage of subjects with a >600 mL/m in dialysate flow rate at baseline (58.6%) than with a ≤600 mL/min dialysate flow rate at baseline (41.4%) in the studies. In both the dialysate flow rate ≤600 mL/min subgroup and the >600 mL/min subgroup, the SFP group had a smaller mean decrease from baseline (-1.0 g/L and -0.4 g/L, respectively) in Hgb than the placebo group (-5.6 g/L and -3.1 g/L, respectively).

Blood flow rate:
In the blood flow rate ≤400 mL/min subgroup the SFP group had a smaller decrease from baseline in Hgb (-0.2 g/L) than the placebo group (-5.7 g/L). In the higher blood flow rate (>400 mL/min) subgroup, the SFP group also had a mean decrease in Hgb (−1.0 g/L) as compared with placebo group (-2.6 g/L), but the difference was smaller.

Dialysis adequacy:

In the higher measured dialysis adequacy (Kt/V>1.6) subgroup the SFP group had an increase from baseline in Hgb (1.3 g/L) while the placebo group had a decrease in Hgb from baseline (-4.7 g/L). On the other hand, in the lower measured dialysis adequacy (Kt/V ≤1.6) subgroup, the SFP group had a similar decrease in Hgb from baseline (-2.0 g/L) compared with placebo group (-2.6 g/L).

Type of dialyzer membrane:
For both the SFP and placebo groups, the majority of patients used the polysulfone dialyzer membrane at baseline (59.7%). In those using polysulfone dialyzer membrane, the SFP group had a smaller mean decrease from baseline in Hgb (-0.9 g/L) than in the placebo group (-5.7 g/L). In patients using polyarylethersulfone dialyzer membrane subgroup (about 17.6% of study patients), Hgb showed an increase from baseline in the SFP group (1.9 g/L) and a decrease from baseline in the placebo group (-2.2 g/L). In patients using polyamide dialyzer membrane subgroup, the patients in the SFP group had a smaller mean decrease from baseline in Hgb (-0.7 g/L) compared with in the placebo group (-1.4 g/L). On the other hand, in those using the cellulose triacetate dialyzer membrane type subgroups, the patients in the SFP group had a greater decrease from baseline in Hgb (-6.6 g/L) compared with in the placebo group (-5.0 g/L); however, there were few patients in this subgroup (total=24).

Dialyzer reuse:
The majority (70.8%) of patients had no dialyzer reuse at baseline. In the subgroup with no dialyzer reuse at baseline, the SFP group had a smaller mean decrease from baseline in Hgb (-0.3 g/L) than the placebo group (-4.6 g/L). In the subgroup with dialyzer reuse at baseline, the difference between the SFP group and the placebo group was smaller (-1.5 g/L and -3.3 g/L, respectively).

Reviewer's Comments: *The subgroup analyses suggested that dialysis flow rate, blood flow rate, dialysis adequacy, and dialyzer reuse may affect the efficacy of SFP. It appears that these factors may affect the amount of SFP crossing the dialysis membrane during the dialysis. It is noted that patients used cellulose triacetate dialyzer membrane showed more decease in Hgb in the SFP group than in the placebo group. However, the number of patients in this group was relatively small and other factors were unclear in those patients. In a PK/PD study (SFP-8), no consistent trends for net iron delivery by membrane type were observed but the mean net iron delivery was generally greatest for the polyamide membrane, with the exception of low biocarbonate (31 mEq/L) delivery group.*

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A Phase 2 study (SFP-2) was conducted to evaluate the dose response for SFP in patients with HDD-CKD. SFP-2 was a double-blind, randomized, placebo-controlled, dose-finding study. The study randomized patients with HDD-CKD to placebo and 4 parallel-group doses of SFP in the dialysate: 50 mcg iron/L; 100 mcg iron/L; 120 mcg iron/L and 150 mcg iron/L for a treatment period of 26 weeks. The study required that the ESA dose was to be held constant during the entire study, and that no subject was to be given supplemental doses of either IV or oral iron

during the study. However, 17.6% of enrolled subjects had an ESA dose change within the several weeks leading up to randomization and 29.0% of subjects had at least 1 ESA dose change in violation of the protocol.

For the mean change from baseline to final evaluation on study for the MITT population, the increase in Hgb was greatest for the SFP 100 µg iron/dL dose group, for which the change in Hgb relative to the decrease seen for the placebo group was +0.64 g/dL, a difference that was statistically significant (p =0.049) and superior to all other SFP dose groups. For the mean change in serum ferritin, both the SFP 100 µg iron/L and the SFP 120 mcg/L dose groups both experienced a lesser (-7.5%) decrease in ferritin compared with the placebo group (-21.7%). Based on these exploratory efficacy results, a dose of SFP 110 mcg iron/L dialysate was selected for evaluation in the 2 Phase 3 studies.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No specific studies were conducted to evaluate tolerance effect. However, in two Phase 3 clinical trials, the efficacy was evaluated with a mean duration of treatment of about 5 months.

6.1.10 Additional Efficacy Issues/Analyses

None.

6.2 Indication: To reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels

The proposed second indication was to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

6.2.1 Method

One Phase 2 study (NIH-FP-01) was submitted to support the indication to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels.

This was a multicenter, randomized (1:1), double-blind, placebo-controlled, Phase 2 study in adult patients with hemodialysis-dependent CKD (HDD-CKD).

See Section 5.3.1 for detailed study protocols.

6.2.2 Demographics

Demographics

In Study NIH-FP-01, the majority of the subjects were male (57.4% in SFP and 66.7% in placebo) and most were white (59.3% in SFP and 63% in placebo). Mean age was 59.0 years

(range of 25 to 93 years). There were slightly more males and more Caucasians in the placebo group than in the SFP group (see Table below).

Table 20. Demographics in NIH-FP-01 in ITT Population

	SFP (N = 54)	**Placebo (N = 54)**
Age, years Median (range)	59 (37-93)	59 (25-86)
Gender		
Male, n (%)	31 (57.4)	36 (66.7)
Female, n (%)	23 (42.6)	18 (33.3)
Race		
Caucasian, n (%)	32 (59.3)	34 (63.0)
African American, n (%)	21 (38.9)	20 (37.0)
Other	1 (1.8)	0

Reviewer's table

Baseline Characteristics

Baseline hemoglobin and iron parameters

The baseline mean pre-dialysis hemoglobin level was comparable between the SFP and placebo groups (see Table below). The baseline mean TSAT and other iron parameters were also similar between the two groups.

Table 21. Baseline hemoglobin and iron parameters in MITT population

	SFP N=52 Mean (SD)	**Placebo N=51 Mean (SD)**
Hemoglobin (g/dL)	10.96 (0.72)	11.11 (6.87)
Iron parameters		
TSAT (%)	26.7 (7.07)	28.4 (7.54)
TIBC (mcmol/L)	45.72 (6.68)	46.1 (7.83)
UIBC (mcmol/L)	40.77 (5.51)	41.21 (6.81)
Serum iron (mcmol/L)	11.96 (3.03)	13.01 (4.10)
Reticulocyte hemoglobin content (pg)	32.76 (1.84)	32.49 (2.17)

Reviewer's table

Renal history and other medical history:

The baseline renal history parameters were similar for the SFP and placebo groups. At baseline the mean time since the initial diagnosis of renal failure was 5.1 years. At baseline the mean time

since current vascular access started was 2.6 years, and 42.7% of subjects had a history of angioplasty for the current vascular access. All patients received 3 times hemodialysis per week except one patient who received 4 times per week in the placebo group.

The baseline medical history was similar for the SFP and placebo groups. The classes of medical history reported most frequently were vascular disorders (100% of subjects), renal and urinary disorders (99.0%), metabolism and nutrition disorders (98.1%), endocrine disorders (89.3%), and blood and lymphatic system disorders (86.4%). The most frequently reported individual diagnoses were hypertension (95.1%), renal failure chronic (95.1%), hyperphosphatemia (66.0%), procedural hypotension (62.1%), and hyperparathyroidism secondary (60.2%).

Baseline IV iron and ESA use:

The mean times at baseline since the last IV iron therapy and the last oral iron therapy were 9.9 weeks and 37.5 weeks, respectively, with a mean of 99.4 mg of total IV iron administered in the last 6 weeks prior to randomization.

Almost all subjects (101 of 103 subjects) received epoetin for their prescribed ESA dose, with the mean dose being 9412.2 U/week. The majority of patients were in Stratum I (≤13,000 equivalent units/week epoetin: 80 subjects, 77.7%). The mean prescribed ESA dose in equivalent units of epoetin was 9345.9 U/week for the 103 subjects in the safety population, 7191.6 U/week for the 80 subjects in Stratum I, and 16839.1 U/week for the 23 subjects in Stratum II.

Table 22. History of Iron and ESA use and Blood Transfusion

	SFP (N=54)	**Placebo (N=49)**
Any IV Iron Within the 6 weeks prior to study, n (%)	53 (98)	45 (100)
Total iron administered 6 weeks prior to randomization (mg) Mean (SD)	102.1 (128.6)	96.4 (111.9)
Prescribed ESA dose - equivalent units of epoetin (U/week)		
Mean (SD)	9483.2 (5413.86)	9205.9 (5500.05)
ESA Stratum I, n (%)	41 (75.9)	39 (79.6)
ESA Stratum II, n (%)	28 (18.4)	29 (19.0)
History of RBC or whole blood transfusions, n (%)	13 (24.1)	10 (20.4)
Yes	21 (38.9)	20 (40.8)
No	33 (61.1)	29 (59.2)

ESA Stratum I: ≤13,000 equivalent units/week epoetin, Stratum II: >13,000 equivalent units/week epoetin)
Reviewer's table

Concomitant Medications:

All subjects in both groups received one or more concomitant medications during the study. The percentages of subjects receiving concomitant medications were similar for the SFP and placebo groups. The most frequently reported concomitant medications were paricalcitol (60.2%) given for calcium homeostasis, paracetamol (57.3%) given as an analgesic, influenza vaccine (51.5%), sodium chloride (48.5%) given as an IV additive, calcium acetate (48.5%) for treatment of hyperkalemia and hyperphosphatemia, and sevelamer carbonate (48.5%) also given for treatment of hyperkalemia and hyperphosphatemia.

Study Treatment Compliance

The mean duration of exposure to study drug was 212 days (SD=76.1) and 222 days (SD=58.1) in the SFP and placebo groups, respectively (see Table below). The majority of subjects received ≥32 weeks but less than 36 weeks of treatment in the SFP (79%) and placebo groups (80%).

Table 23. Treatment Duration in Randomized Phase in MITT population

	SFP (N=52)	**Placebo (N=51)**
Treatment Duration (days) exposure		
Mean (SD)	212.1 (76.08)	222.1 (58.12)
Min, Max	1, 249	1, 249
Duration of exposure (n (%))		
≥1 day	52 (100.0)	51 (100.0)
≥1 week	50 (96.2)	51 (100.0)
≥2 weeks	49 (94.2)	51 (100.0)
≥4 weeks	48 (92.3)	50 (98.0)
≥8 weeks	47 (90.4)	49 (96.1)
≥12 weeks	46 (88.5)	47 (92.2)
≥16 weeks	45 (86.5)	47 (92.2)
≥20 weeks	45 (86.5)	46 (90.2)
≥24 weeks	42 (80.8)	43 (84.3)
≥28 weeks	41 (78.8)	43 (84.3)
32-35 weeks	41 (78.8)	41 (80.4)

Reviewer's table

In the randomized population, a majority of subjects received less than the intended full amount of study drug exposure at any visit in the SFP group (35 subjects, 64.8%) and in the placebo group (31 subjects, 57.4%).

6.2.3 Subject Disposition

A total of 108 patients with HDD-CKD were randomized, 103 (52 in the SFP group, 51 in the placebo group) received study drug. The majority of the subjects who received study drug completed the study in the SFP (78.8%) and placebo (78.4%) groups. The most frequent primary reasons for withdrawal in both groups included withdrew consent and adverse event.

Table 24. Subject Disposition

	SFP	Placebo
Randomized	54	54
Stratum I	42 (77.8)	42 (77.8)
Stratum II	12 (22.2)	12 (22.2)
Received study drug	52	51
Did not receive study drug	2	3
Primary reason:		
Adverse Event		1
Other	2	
Protocol Violation		2
Completed study	41 (78.8)	40 (78.4)
Discontinued prematurely	11 (21.2)	11 (21.6)
Reason for discontinuation:		
Adverse event	3 (5.8)	3 (5.9)
Death	2 (3.8)	3 (5.9)
Protocol violation	1 (1.9)	1 (2.0)
Lost to follow-up	0 (0.0)	0 (0.0)
Withdrew consent	4 (7.7)	4 (7.8)
Sponsor's request	0 (0.0)	0 (0.0)
Principal Investigator decision	2 (3.8)	0 (0.0)
Other	1 (1.9)	3 (5.9)

Note: Stratum I: ≤13,000 equivalent units/week epoetin; Stratum II: >13,000 equivalent units/week epoetin.
Reviewer's table

Protocol Violations/Deviations

Protocol deviations identified for the randomized subjects are summarized in Table below.

Table 25. Protocol Violations/Deviations

	SFP N=54 n (%)	**Placebo N=54 n (%)**
Received wrong treatment	2 (3.7)	2 (3.7)
Randomized to wrong stratum	1 (1.9)	4 (7.4)
Change in type of ESA	1 (1.9)	0 (0.0)
Did not meet inclusion/exclusion criteria	16 (29.6)	16 (29.6)
Did not receive study drug due to missing visit	25 (46.3)	26 (48.1)
Received less than the intended full amount of study drug exposure at any visit	35 (64.8)	31 (57.4)
IV iron deviation	6 (11.1)	9 (16.7)
Lack of adherence to centralized anemia management center- recommended	22 (40.7)	23 (42.6)
Other	38 (70.4)	44 (81.5)

Reviewer's table

Analyzed populations

MITT population: Randomized subjects who received at least one dose of study drug and also received ESA during the treatment period.

Safety population: Safety population: Subjects who received any amount of study drug. Subjects receiving an incorrect treatment are summarized as SFP.

In NIH-FP-01, 2 subjects randomized to the placebo group who incorrectly received SFP for a few treatments were summarized in the SFP group in the safety population but were analyzed in the placebo group in the MITT population. All of the 103 subjects who received study drug were included in the safety and the MITT populations.

The number of subjects in analyzed populations for the study is shown below.

Table 26. Analyzed Populations

	SFP	Placebo
Randomized (ITT)	54	54
MITT population	52	51
Safety population	54	49

Reviewer's table

6.2.4 Analysis of Primary Endpoints

FDA statistical reviewer performed ITT population analysis in addition to the sponsor's MITT population analysis.

Change in Prescribed ESA Dose:

The mean change in prescribed ESA dose from baseline to end-of-treatment in the ITT and MITT population is shown in Table below. After adjusting for baseline Hgb, at end-of-treatment, the subjects receiving SFP had a mean increase of 5% in prescribed ESA dose while the placebo group had a mean increase of 37.3% in prescribed ESA dose in the ITT population. The treatment difference in percentage change in prescribed ESA dose between the SFP and placebo did not reach statistical significance (p=0.052). The analysis in the MITT population showed that the treatment difference between the two groups was statistically significant (4.9% vs. 39.8%, p-value = 0.045).

Table 27. Change from Baseline in Prescribed ESA Dose in ITT and MITT Population

	SFP N=54		Placebo N=54	
	Mean Epoetin U/wk (SD)	**%Change from Baseline LS mean**	**Mean Epoetin U/wk (SD)**	**%Change from Baseline LS mean**
ITT population	**N=54**		**N=54**	
Baseline Prescribed ESA Dose U/wk (SD)	9295.0 (5415.3)		9316.7 (5444.12)	
End-of-Treatment (EoT) Prescribed ESA Dose U/wk (SD)	9668.5 (7465.49)	5 .0 (11.60)	12549.4 (13602.99)	37.3 (11.60)
p-value	0.052			
MITT population	**N=52**		**N=51**	
Baseline Prescribed ESA Dose U/wk (SD)	9483.2 (5413.9)		9205.9 (5500.1)	
End-of-Treatment (EoT) Prescribed ESA Dose U/wk (SD)	9871.2 (7523.2)	4.9 (12.1)	12628.8 (13967.4)	39.8 (12.2)
p-value	0.045			

Reviewer's table

Change in Actual ESA Dose:

The mean change in actual ESA dose from baseline to end-of-treatment in the ITT and MITT population is shown in Table below. After adjusting for baseline Hgb, at end-of-treatment, the subjects receiving SFP had a mean increase of 11.1% in actual ESA dose while the placebo group had a mean increase of 40.7% in actual ESA dose in the ITT population. The treatment difference in percentage change in actual ESA dose between the SFP and placebo did not reach statistical significance (p=0.111). Similar result was seen in the MITT population (11.3% vs. 43.4%, p-value = 0.098).

Table 28. Change from Baseline in Actual ESA Dose in ITT and MITT Population

	SFP N=54		Placebo N=54	
	Mean Epoetin U/wk (SD)	**%Change from Baseline LS mean**	**Mean Epoetin U/wk (SD)**	**%Change from Baseline LS mean**
ITT population	**N=54**		**N=54**	
Baseline Actual ESA Dose U/wk (SD)	9000.5 (5493.11)		8960.5 (5476.49)	
End-of-Treatment (EoT) Actual ESA Dose U/wk (SD)	9224.3 (7014.03)	11.1 (12.97)	12151.4 (13600.56)	40.7 (12.97)
p-value	0.111			
MITT population	**N=52**		**N=51**	
Baseline Actual ESA Dose U/wk (SD)	9177.5 (5505.07)		8835.6 (5449.02)	
End-of-Treatment (EoT) Actual ESA Dose U/wk (SD)	9409.9 (7070.24)	11.3 (13.51)	12385.8 (13926.29)	43.4 (13.64)
p-value	0.098			

Reviewer's table

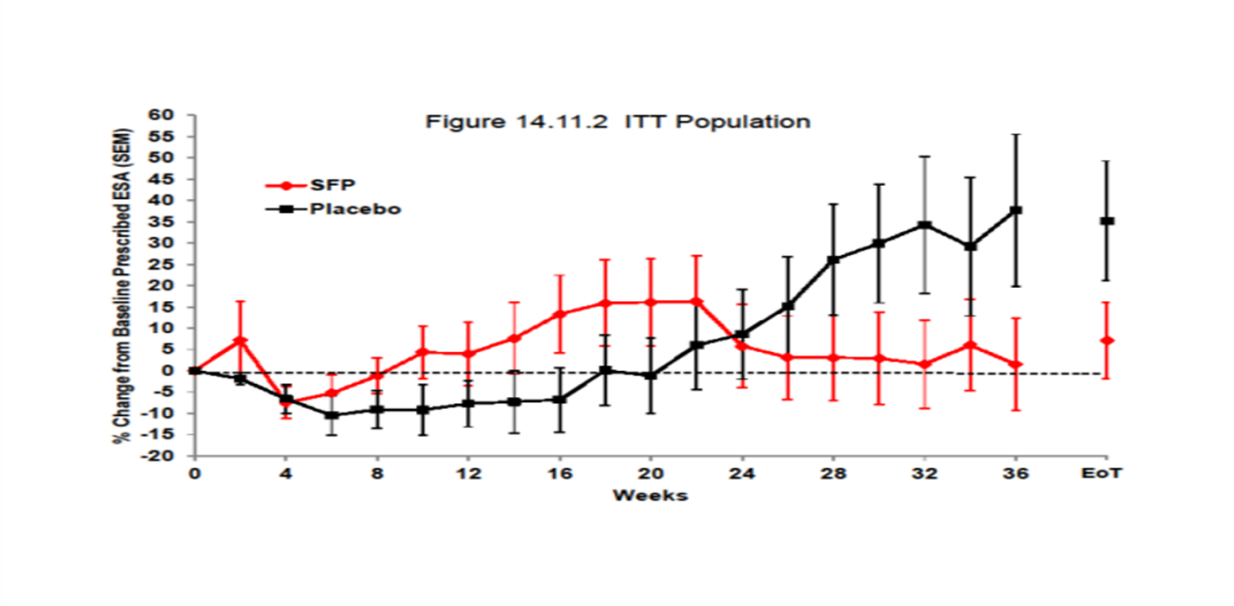
Reviewer's Comments: *Study NIH-FP-01was a relatively small exploratory phase 2 trial without formal sample size and power calculations planned. The interpretation of the study results is difficult. The study results were not persuasive for a benefit of SFP over placebo. The study may be used for hypothesis generation. It should not be used as a confirmative study to support a new indication.*

6.2.5 Analysis of Secondary Endpoints(s)

Changes from baseline in the prescribed ESA dose over time

The percent changes in prescribed ESA dose from baseline over time in the ITT population are displayed in the Figure below. After changes in ESA dosing were allowed at Week 5, the prescribed ESA dose was increased more in the SFP group during the period from Week 10 to Week 24 as compared to the placebo group. After Week 24, the prescribed ESA dose increased more in the placebo group as compared to the SFP group.

Figure 2. Changes from Baseline in Prescribed ESA Dose Over Time



Sponsor's figure

Reviewer's Comments: *The reasons for the increased prescribed ESA dose prior to 24 weeks in the SFP group than in the placebo group were unclear and against the proposed use of SFP to reduce the prescribed ESA dose.*

ESA response index (ERI)

ERI was calculated as prescribed ESA dose (U/wk)/Hgb (g/L). The change in ERI from baseline to the end-of-treatment was smaller in the SFP group (99.9 U/wk/g/L) than in the placebo group (397.4 U/wk/g/L), but the difference was not statistically significant (p=0.304).

Table 29. Change in ESA Response Index

	SFP N=52	**Placebo N=51**
Baseline ERI		
n	52	51
Mean (SD)	868.0 (492.01)	834.6 (503.12)
End-of-Treatment ERI		
n	49	51
Mean (SD)	972.4 (756.04)	1231.9 (1337.54)
Change from baseline in ERI	99.9 (571.94)	397.4 (1132.67)
P-value	0.304	

Reviewer's table

Distribution of changes from baseline in the prescribed ESA dose

The distribution of magnitude of change in prescribed ESA dose from baseline to end-of-treatment did not show a significant difference between SFP and placebo groups (p=0.915) (see Table below).

Table 30. Distribution of changes from baseline in the prescribed ESA dose

Changes from baseline in the prescribed ESA dose	**SFP N=52 n (%)**	**Placebo N=51 n (%)**
Increase ≥ 25%	16 (30.8)	20 (39.2)
Increase 10 to <25%	5 (9.6)	4 (7.8)
Increase or decrease <10%	12 (23.1)	9 (17.6)
Decrease 10% to <25%	3 (5.8)	3 (5.9)
Decrease ≥ 25%	16 (30.8)	15 (29.4)
p-value	0.915	

Reviewer's table

Supplemental IV iron use

The use of supplemental IV iron at end-of-treatment is shown in the Table below. At end-of-treatment, fewer subjects had received supplemental IV iron in the SFP group (11 subjects 21.2%) than in the placebo group (20 subjects, 39.2%). For subjects who received IV iron, the mean dose of supplemental IV iron at the end-of-treatment was similar in the SFP group (111.3 mg/week) and the placebo group (116.4 mg/week).

Table 31. Supplemental IV Iron Use

IV iron use at end of treatment	**SFP N=52**	**Placebo N=51**
Number of subjects who received IV iron (n, %)	11 (21.2)	20 (39.2)
Mean (SD) dose per subject who received IV iron (mg/week)	111.3 (65.2)	116.4 (41.3)
Median (mg/week)	100.0	102.5
Min, Max (mg/week)	63.0, 300.0	62.0, 233.3

Reviewer's table

7 Review of Safety

Safety Summary:

The safety of Triferic was evaluated primarily in two randomized placebo-controlled phase 3 clinical trials (SFP-4 and SFP-5) in patients with HDD-CKD (total of 292 patients received SFP). Overall treatment-emergent adverse events (TEAEs) were reported at similar rates for the

SFP-treated patients and the placebo-treated patients (78.4% and 75.3%, respectively) during the studies. Non-fatal treatment-emergent serious adverse events (SAEs) were reported at similar rates for the two groups (24.0% in SFP-treated patients and 25.3 % in the placebo-treated patients). Thirteen (4.5%) patients had at least one TEAE that led to treatment discontinuation permanently in the SFP group as compared to 7 (2.4%) the placebo group in the clinical trials.

A total of 17 deaths were reported in the two phase 3 clinical trials including 12 (4.1%) among the SFP-treated patients and 5 (1.7%) among the placebo-treated patients. Among the death cases, the duration of on study treatment ranged from 8 to 328 days in the SFP-treated patients and 27 to 227 days in the placebo-treated patients. Time to event leading to death since the last hemodialysis with study drug ranged from 1 to 15 days in the SFP-treated patients and 1 to 3 days in the placebo-treated patients. Almost all patients had significant underlying cardiac conditions in addition to end-stage renal disease. Six patients in the SFP group and one patient in the placebo group died at home or nursing home without detailed information provided. The events leading to death were cardiac arrest in 8 cases (6 in SFP-treated patients and 2 in placebo-treated patients), sudden death or unknown cause in 5 cases (4 in SFP-treated patients and 1 in placebo-treated patients), acute myocardial infarction in 3 cases (1 in SFP-treated patients and 2 in placebo-treated patients), and one case of bronchopneumonia in the SFP group. No deaths were considered to be related to the study treatment by investigator and cases could be most likely attributed to co-morbid disease and/or disease progression.

In the two phase 3 clinical trials, suspected hypersensitivity reaction was reported in one (0.3%) patient in the SFP group as compared to none in the placebo group (0%). The event was considered as moderate and related to study drug. Five additional cases of suspected hypersensitivity reaction were reported in phase 2 and the phase 3 open-label extension treatment studies. Overall, six (0.4%) cases of suspected hypersensitivity reactions were reported in 1411 SFP-treated patients in clinical trials in the SFP development program. In 2 of the 6 cases events occurred at the first dose, were considered to be study drug related and study treatment was discontinued permanently. The remaining 4 patients continued the SFP treatment without recurrent events and the events were not considered to be related to the study drug. Occurrence of other adverse events of special interest, including intradialytic hypotension, composite cardiovascular events, hemodialysis vascular access thrombotic event, and systemic or serious infection, were similar for the SFP group and the placebo group.

The most common TEAEs (≥3% in the SFP-treated patients) that were reported more frequently in the SFP-treated patients than in the placebo-treated patients were procedural hypotension, muscle spasms, headache, dizziness, peripheral edema, pain in extremity, dyspnea, pyrexia, urinary tract infection, hyperkalemia, back pain, asthenia, fatigue, arteriovenous fistula site hemorrhage, arteriovenous fistula thrombosis, and hypertension. The nonfatal SAEs that were reported more frequently in the SFP group as compared to the placebo group included: diabetic foot infection (1% vs. 0%), arteriovenous fistula thrombosis (1.7% vs. 0.7%), and pulmonary edema (1.4% vs. 0.3%). The most common TEAEs (occurred in at least 2 subjects) leading to study discontinuation in the SFP group were asthenia, dizziness and headache.

A total of 1411 patients were exposed to Triferic in all clinical trials including open-label extension studies. The safety profile of Triferic in those patients was similar to that observed in the Phase 3 clinical trials.

Overall, SFP was reasonably tolerated in patients with HDD-CKD.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following table lists the clinical studies used to evaluate overall safety of Triferic. Two Phase 3, randomized, placebo-controlled clinical trials (SFP-4 and SFP-5) in patients with HDD-CKD were used to evaluate the safety of Triferic for the proposed indication. Additional safety data from other clinical trials and open-label extension studies in patient with HDD-CKD were provided to support the safety of Triferic.

Table 32. Clinical Trials Used to Evaluate Safety

	SFP	**Placebo**	Total
Phase 3 Placebo-Controlled Studies			
SFP-4	149	151	300
SFP-5	143	145	288
Total	292	296	588
Other Controlled Studies			
SFP-1	10	11	21
SFP-2	105	26	131
SFP-3	32	0	32
SFP-6 (Crossover study)	693	686	703
NIH-FP-01 (02 DEC 2010 protocol version)	54	49	103
NIH-FP-01 (prior to 02 DEC 2010 protocol version)	5	6	11
Total	899	778	1001
Uncontrolled Open-Label Extension Studies			
SFP-4-OL	98	107 (received SFP)	205
SFP-5-OL	101	113 (received SFP)	214
SFP-6-OL	308	0	308
Total	507	220 (received SFP)	727
Total Number of Unique SFP Subjects in Clinical Trials	1411		

Reviewer's table

7.1.2 Categorization of Adverse Events

Adverse events (AEs) as reported on the case report forms (CRFs) were coded using MedDRA system organ class and preferred term.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Integrated Analysis of Safety included pooled safety data from the two randomized, placebo-controlled Phase 3 studies (SFP-4 and SFP-5) in patients with HDD-CKD. All SFP-treated patients in all clinical trials were also pooled to provide additional safety evaluation.

7.2 Adequacy of Safety Assessments

The Integrated Analysis of Safety included pooled safety data from the two randomized, placebo-controlled Phase 3 studies (SFP-4 and SFP-5) in patients with HDD-CKD. All SFP-treated patients in all clinical trials were also pooled to provide additional safety evaluation.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Extent of Exposure:

Of the 588 patients with HDD-CKD who received at least 1 dose of study drug in the two Phase 3 clinical trials, 292 subjects received SFP and 296 subjects received placebo. The mean (SD) duration of exposure was 159.2 (112.9) days for the SFP group and 162.1 (110.9) days for the placebo group (see Table below). Slightly less than half of study patients received study treatment ≥20 weeks (46.6% in SFP and 50.7% in Placebo). In the SFP and placebo groups, respectively, 21.2% and 18.9% of subjects had ≥44 weeks of exposure. The total exposure to SFP in the pooled Phase 3 studies was 127.3 subject-years.

Table 33. Overall Drug Exposure in Pooled Phase 3 Clinical Studies

	SFP (N=292)	**Placebo (N=296)**
Duration of exposure (days)		
Mean (SD)	159.2 (112.9)	162.1 (110.9)
Median	128.0	143.0
Min, Max	1, 332	1, 333
Total exposure		
Subject-days	46493	47993
Subject-weeks	6641.9	6856.1
Subject-years	127.3	131.4
Distribution of duration of exposure, n (%)		
≥1 day	292 (100.0)	296 (100.0)
≥1 week	288 (98.6)	293 (99.0)
≥2 weeks	282 (96.6)	289 (97.6)
≥4 weeks	264 (90.4)	263 (88.9)

≥8 weeks	227 (77.7)	234 (79.1)
≥12 weeks	182 (62.3)	199 (67.2)
≥16 weeks	161 (55.1)	166 (56.1)
≥20 weeks	136 (46.6)	150 (50.7)
≥24 weeks	123 (42.1)	130 (43.9)
≥28 weeks	106 (36.3)	111 (37.5)
≥32 weeks	88 (30.1)	94 (31.8)
≥36 weeks	78 (26.7)	76 (25.7)
≥40 weeks	70 (24.0)	66 (22.3)
44-47 weeks	62 (21.2)	56 (18.9)

Reviewer's table

In pooled all clinical trials in the SFP clinical development program, a total of 1411 patients with HDD-CKD received at least one dose of SFP. This included three open-label extension safety studies (SFP-4-OL, SFP-5-OL, and SFP-6-OL) in the 120-day safety update submission. The mean (SD) duration of exposure of SFP in 1411 patients was 201.9 (175.9) days. A total of 863 subjects had ≥12 weeks of exposure to SFP, 734 subjects had ≥24 weeks of exposure to SFP, and 238 subjects had ≥52 weeks (1 year) of exposure to SFP (see Table below).

Table 34. Overall Drug Exposure in All Clinical Trials

	N=1411
Duration of exposure, days	
Mean (SD)	201.9 (175.85)
Median	180.0
Min, Max	1, 538
Total exposure	
Subject-days	284885
Subject-weeks	40697.9
Subject-years	780.0
Distribution of duration of exposure, n (%)	
≥1 day	1411 (100.0)
≥1 week	1381 (97.9)
≥2 weeks	1008 (71.4)
≥4 weeks	980 (69.5)
≥8 weeks	898 (63.6)
≥12 weeks	863 (61.2)
≥16 weeks	835 (59.2)
≥20 weeks	798 (56.6)
≥24 weeks	734 (52.0)

≥28 weeks	655 (46.4)
≥32 weeks	636 (45.1)
≥36 weeks	571 (40.5)
≥40 weeks	534 (37.8)
≥44 weeks	508 (36.0)
≥48 weeks	472 (33.5)
≥52 weeks	238 (16.9)
≥56 weeks	227 (16.1)
≥60 weeks	211 (15.0)
≥64 weeks	187 (13.3)
≥68 weeks	164 (11.6)
≥72 weeks	33 (2.3)
≥76 weeks	1 (0.1)

Reviewer's table

Demographics:

In the pooled Phase 3 clinical studies, the demographics in the safety population were similar between the SFP and placebo groups (see Table below). The mean (SD) age of subjects in the SFP and placebo groups was 59.0 (12.6) years (range, 20 to 86 years) and 59.6 (13.7) years (range, 21 to 89 years), respectively. The majority of subjects were Caucasian (52.7% in the SFP group and 56.1% in the placebo group) and male (61.3% in the SFP group and 66.2% in the placebo group).

Table 35. Demographics in Pooled Phase 3 Studies

	SFP (N=292)	**Placebo (N=296)**
Age (years)		
Mean (SD)	57.2 (12.6)	59.6 (13.7)
Median	59.0	60.0
Min, Max	20, 86	21, 89
Age Category, n (%)		
<65 years	210 (71.9)	188 (63.5)
≥65 years	82 (28.1)	108 (36.5)
Gender, n (%)		
Male	179 (61.3)	196 (66.2)
Female	113 (38.7)	100 (33.8)
Race, n (%)		
Caucasian	154 (52.7)	166 (56.1)

African American	112 (38.4)	99 (33.4)
Asian	14 (4.8)	9 (3.0)
Other	12 (4.2)	22 (6.5)

Reviewer's table

Among the total 1411 SFP-treated patients with HDD-CKD in all clinical trials in the SFP development program, the mean (SD) age was 58.8 (13.3) years with a range of 19 to 96 years. There were 967 (68.5%) patients <65 years of age and 444 (31.5%) patients ≥65 years of age. The majority of patients were male (61.7%) and most were Caucasian (50.8%).

7.2.2 Explorations for Dose Response

Only one dose (concentration) of Triferic was studied in two Phase 3 clinical trials.

7.2.3 Special Animal and/or In Vitro Testing

Not performed.

7.2.4 Routine Clinical Testing

Routine clinical testing in clinical trials is adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hypersensitivity/anaphylactic/anaphylactoid reactions and hypotension reactions were evaluated in the clinical trials.

7.3 Major Safety Results

The following table summarizes the overall adverse events in pooled Phase 3 clinical trials (SFP-4 and SFP-5).

Table 36. Overall Treatment-Emergent Adverse Events in Pooled Phase 3 Trials

Subject with Treatment-Emergent Adverse Events (AEs)	**SFP (n=292) n (%)**	**Placebo (n=296) n (%)**
TEAEs	229 (78.4)	223 (75.3)
Deaths	12 (4.1)	5 (1.7)

Nonfatal TESAEs	70 (24.0)	75 (25.3)
TEAEs leading to study discontinuation	13 (4.5)	7 (2.4)

Reviewer's table

7.3.1 Deaths

In the two Phase 3 clinical trials, 12 deaths (4.1%) occurred among the SFP-treated patients and 5 deaths (1.7%) occurred among the placebo-treated patients. The exposure-adjusted mortality rates were 9 deaths per 100 subject-years of exposure for SFP-treated patients and 4 deaths per 100 subject-years of exposure for placebo-treated patients.

The following table presents the all-cause deaths in each Phase 3 clinical trial.

Table 37. All-cause Deaths in Phase 3 Clinical Trials

	SFP-4		**SFP-5**	
	SFP (n=149) n (%)	**Placebo (n=151) n (%)**	**SFP (N=143) n (%)**	**Placebo (N=145) n (%)**
All-cause deaths	5 (3.4)	3 (2.0)	7 (4.9)	2 (1.4)

Reviewer's table

The following table summarizes the patients' information and adverse events leading to deaths for the two treatment groups. Among the death cases, the patient age range was similar between the two treatment groups. All deaths occurred in male patients except for three females in the SFP group. The duration on study treatment ranged from 8 to 328 days in the SFP-treated patients and 27 to 227 days. Time to event leading to death since last study drug ranged from 1 to 15 days in the SFP-treated patients and 1 to 3 days in the placebo-treated patients. The adverse events leading to death were cardiac arrest in 8 cases (6 in the SFP-treated patients and 2 in the placebo-treated patients), sudden death or unknown cause in 5 cases (4 in the SFP-treated patients and 1 in the placebo-treated patients), acute MI in 3 cases (1 in the SFP-treated patients and 2 in the placebo-treated patients), and one case of bronchopneumonia in the SFP group.

Table 38. Analysis of Death Cases in Pooled Two Phase 3 Trials

	SFP (N=292)	**Placebo (N=296)**
Total deaths	12 (4.1%)	5 (1.7%)
Age	44-72 years	47-79 years
Gender	9 Males, 3 Females	5 Males
Treatment duration on study drug	8-328 days	27-227 days
Time to event leading to death since last study drug	1-15 days	1-3 days
Event leading to death/cause of deaths		
Cardiac arrest	6	2
Sudden deaths/unknown	4	1
MI	1	2

Bronchopneumonia	1	0

Reviewer's table

Patient information for the death cases in each study is listed in the following table. Almost all patients had significant underlying cardiac conditions. Six of 12 patients in the SFP group and one of 5 patients in the placebo group died at home or nursing home without sufficient diagnosis made to allow meaningful assessment. None of the death cases was considered to be related to the study treatment by investigator.

Table 39. Listing of Death Cases in Two Phase 3 Clinical Trials

Study name Treatment group	Age/ Gender Patient ID	Treatment duration (days on study)	Time to event leading to death since the last study drug	Time to death since the last study drug	AEs leading to death	Underlying conditions	Causality assessment by investigator
Study SFP-4							
SFP group	68/M 406-032	8 days	5 days	5 days	Found unresponsive at nursing home, cardiac arrest	CAD, CHF, DM	Not related
	65/M 410-007	48 days	1 day	1 day	Unresponsive, died prior to paramedics arrived	CAD, HTN, DM	Not related
	68/M 432-008	45 days	3 days	3 days	SOB, light-headedness, cardiac arrest in ER	CAD, HTN, DM	Not related
	57/F 433-017	69 days	1 day	8 days	Chest pain, SOB, acute MI	CAD, HTN, COPD	Not related
	44/M 437-038	239 days	2 days	2 days	Found dead at home	DM, HTN	Not related
Placebo group	74/M 406-042	31 days	3 days	14 days	Trauma, cardiac arrest	CAD, CHF, DM	Not related
	47/M 436-009	227 days	3 days	6 days	Chest pain, acute MI	CAD, CHF	Not related
	71/M 437-043	220 days	3 days	25 days	SOB, cardiac arrest, CHF	CAD, MI, CVA, DM	Not related
Study SFP-5							
SFP group	66/M 514-002	22 days	1 day	1 day	Collapsed and unresponsive VT, cardiac arrest	CAD, HTN, MI	Not related
	72/M 526-007	188 days	15 days	15 days	Died at home due to cardio-respiratory arrest	DM, HTN, cardiac pacemaker	Not related
	49/M 526-027	328 days	2 days	3 days	Chest pain, cardiac arrest, pulmonary edema	DM, HTN	Not related
	56/F 530-014	148 days	2 days	2 days	Found expired at home	DM, CHF, HTN	Not related
	67/M 531-030	176 days	2 days	4 days	Bronchopneumonia	DM, CHF, testicular cancer	Not related
	66/F 531-040	108 days	2 days	2 days	Died at home "Sudden death"	CAD, DM, HTN	Not related
	59/M 555-021	120 days	14 days	Not provided	Cardiac arrest	DM, CHF, CAD, Stroke	Not related
Placebo group	79/M 512-016	73 days	2 days	2 days	Found dead at home Sudden death	CAD, HTN, Aortic aneurysm	Not related
	75/M 519-019	27 days	1 day	2 days	Chest pain, acute MI	CAD, DM, HTN	Not related

Reviewer's table

The following are summaries of patient narratives in death cases in Phase 3 clinical trials.

Study SFP-4

SFP group: 5 deaths

Subject RMTI-SFP-4 406-032 - Cardiac arrest
This was a 68-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate on (b) (6) (Day 1). Renal history included CKD since 2006 secondary to diabetes mellitus type 2. Other significant medical conditions included hypertension, CAD (stent 2007), CHF, cardiac pacemaker (2003), peripheral vascular disorder, hyperphosphatemia, COPD (2010), leg amputation (below knee 2006), depression, and hypothyroidism. The subject received his last dose of Stage 2 study drug on (b) (6) (Day 8) and his last dialysis treatment during Stage 2 was on (b) (6) (Day 10).

On (b) (6) (Day 13), the subject was found unresponsive at (b) (6) by nursing home personnel (prior to scheduled dialysis) and was pronounced dead. It was reported that the subject had sustained a cardiac arrest (cardiac arrest cause unknown). The subject's nephrologist reported that the subject did not have any recent acute issues. An autopsy was not performed. The Investigator considered the treatment-emergent event of cardiac arrest to be severe and unlikely related to study drug. The Sponsor medical monitor considered the treatment-emergent event of cardiac arrest to be serious, unexpected, and not related to study drug.

Subject RMTI-SFP-4 410-007 - Death
This was a 65-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history included CKD since 2006. Other significant medical conditions included diabetes mellitus (1987), hypertension, coronary artery disease, CHF (2009), leg and foot amputation (2000), hyperparathyroidism, hyperlipidemia, hyperphosphatemia, peripheral vascular disorder (2009), and hypothyroidism. His last dialysis treatment prior to the event of death was on (b) (6) (Day 48). The subject's last dose of Stage 2 study drug was on the same day (Day 48).

On (b) (6) (Day 49), the subject was found unresponsive in the morning. The subject had expired by the time paramedics arrived. No autopsy was performed. There had been no complaints during his last dialysis session. The cause of death was unknown. The Investigator considered the treatment-emergent event of death to be severe and unlikely related to study drug, but related to coronary artery disease and hypertension. The Sponsor medical monitor considered the treatment-emergent event of death to be serious and not related to study drug.

Subject RMTI-SFP-4 432-008 - Cardiac arrest
This was a 68-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 09 Oct 2007 secondary to diabetes mellitus type 2. Other significant medical conditions included right bundle branch block (2011), cardiac ischemia, hypertension, hyperlipidemia, and hyperparathyroidism, gout and hyperphosphatemia. The subject's last dose of Stage 2 study drug and last dialysis treatment during Stage 2 were on (b) (6) (Day 45).

On (b) (6) (Day 48), the subject was taken to the emergency room (ER) due to shortness of breath and light-headedness. Upon arrival to hospital, the subject became pulseless and breathless, and he collapsed. His finger stick glucose was 110 mg/dL. It was reported that the subject had a cardiac arrest with pulseless electrical activity (PEA). Cardiopulmonary resuscitation (CPR) was initiated and the subject was treated with oxygen, epinephrine, and atropine. The subject remained with PEA until going into ventricular fibrillation for approximately 2 minutes before asystole. Resuscitation efforts including treatment with epinephrine, atropine, calcium gluconate, sodium bicarbonate, regular insulin, and defibrillation were unsuccessful, and the subject was pronounced dead. The cause of death was determined to be cardiac arrest. An autopsy was not performed. The Investigator considered the treatment-emergent event of cardiac arrest to be severe and unlikely related to study drug, but rather related to

coronary artery disease, hypertension and end stage renal disease. The Sponsor medical monitor considered the treatment-emergent event of cardiac arrest to be serious and not related to the study drug.

Subject RMTI-SFP-4 433-017 - Acute myocardial infarction
This was a 57-year-old woman with HDD-CKD who received her first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 10 Dec 2010 secondary to diabetes mellitus (since 1982). Other significant medical conditions included coronary artery disease, coronary artery bypass (2000), hypertension, hyperlipidemia, obesity, COPD, asthma and depression, and hyperparathyroidism. Her last dialysis treatment during Stage 2 was on (b) (6) (Day 69) and she received her last dose of Stage 2 study drug on the same day (Day 69).

On (b) (6) (Day 70), the subject presented to the ER with complaints of shortness of breath, cough, and pain in her left chest radiating to her jaw. An ECG showed ST segment elevation in the lead aVR with ST segment depression on lateral precordial leads, and she was hospitalized. On the same day, the subject's troponin I was 2.929 ng/mL and serum creatine kinase (CK) was 198 IU/L. The subject was diagnosed with acute myocardial infarction. The subject underwent cardiac catheterization with stent placement to the saphenous vein graft to the posterior descending artery. A thrombin injection was given and the subject was transferred to the intensive care unit (ICU). On (b) (6), the subject's troponin I was noted to be 123 ng/mL and CK was 1319 IU/L. An echocardiogram showed an ejection fraction of 40%. On (b) (6), the subject developed hypotension and fever and was treated with piperacillin/tazobactam. She was also treated with intravenous (IV) dopamine, dobutamine, Levophed®, and vasopressin for BP support. On (b) (6), she was put on extracorporeal membrane oxygenation (ECMO). On (b) (6), the subject's ejection fraction decreased to 10 - 15%, with a globally akinetic heart. Her family decided to stop all resuscitative efforts and continue only with comfort care. On (b) (6), the subject died due to acute myocardial infarction. The Investigator considered the event of acute myocardial infarction to be severe and not related to study drug but rather due to the subject's underlying cardiac condition. The Sponsor medical monitor considered the event of acute myocardial infarction to be serious and not related to study drug.

Subject RMTI-SFP-4 437-038 - Sudden death
This was a 44-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history included CKD since 2007 secondary to diabetes mellitus type 2 (since 2004). Other significant medical conditions included hypertension, dyslipidemia, hyperphosphatemia, diabetic retinopathy (2009), and peripheral edema. On (b) (6) (Day 239), the subject received his last dose of Stage 2 study drug and his last dialysis treatment during Stage 2 was on the same day.

On (b) (6) (Day 241), the site was notified that the subject was found dead at his home, and that 14 cans of alcohol were discovered with the body. The patient had no history of alcoholism or depression. No resuscitation measures were taken and no autopsy was done. The cause of death was reported as unknown. The Investigator considered the treatment-emergent event of sudden death to be severe and not related to study drug, but possibly due to hyperkalemia. The Sponsor medical monitor considered treatment-emergent event of sudden death to be serious and not related to study drug.

Placebo group: 3 death cases

Subject RMTI-SFP-4 406-042 – Cardiac arrest
This was a 74-year-old man with HDD-CKD who received his first dose of placebo (standard dialysate without SFP) on (b) (6) (Day 1). Renal history for the subject included CKD since 2007 secondary to diabetes mellitus (since 1986). Other significant medical conditions included coronary artery disease, congestive cardiac failure, hypertension, retinal hemorrhage, hyperlipidemia, hypothyroidism, peripheral edema, peripheral neuropathy, retinopathy, hyperparathyroidism secondary and hyperphosphatemia. His last dialysis treatment prior to the event of cardiac arrest was on (b) (6) (Day 31) and he received his last dose of Stage 2 study drug on the same day.

On (b) (6) (Day 34), the subject was allegedly involved in an altercation leading to possible trauma and had an unwitnessed cardiac arrest. Advanced cardiovascular life support (ACLS) was initiated by emergency response

services and the subject was admitted to hospital on (b) (6) (Day 35). Upon admission, the subject was administered two additional cardiac shocks and he was intubated and placed on a respirator. The subject had fixed and dilated pupils indicative of severe neurological injury. On (b) (6) (Day 45), the subject died. It was unknown whether an autopsy was performed. The Investigator considered the treatment-emergent event of cardiac arrest to be severe and not related to study drug. The Sponsor medical monitor considered the treatment-emergent event of cardiac arrest to be serious and not related to study drug.

Subject RMTI-SFP-4 436-009 – Acute myocardial infarction
This was a 47-year-old man with HDD-CKD who received his first dose of placebo (standard dialysate without SFP) on (b) (6). Renal history for the subject included CKD since 2007 secondary to hypertension. Other significant medical conditions included coronary artery disease, congestive heart failure, hyperlipidemia, obesity, peripheral artery disease, and secondary hyperparathyroidism. The subject received his last dose of the Stage 2 study drug on (b) (6) (Day 227) and his last dialysis treatment during Stage 2 was on the same day.
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On (b) (6) (Day 230), the subject developed chest pain and respiratory distress. On the same day (Day 230), the subject was diagnosed with acute myocardial infarction and was hospitalized in the ICU. His laboratory test results showed CK-MB of 205.42 and troponin I of 63.77. On the same day (Day 230) the subject underwent cardiac catheterization, which showed all coronary trees with heavy calcifications. The proximal left anterior descending artery (LAD) was occluded and the right coronary artery (RCA) was occluded at the proximal end, with intracoronary and intercoronary collaterals from the left coronary artery (LCA). On the same day (Day 230), the subject underwent coronary angioplasty with atherectomy and was on mechanical ventilation due to respiratory failure. On (b) (6) (Day 236), the subject went into cardiac arrest. Cardiopulmonary resuscitation was unsuccessful, and the subject was pronounced dead. It was reported that the cause of death was due to severe acute coronary syndrome and an autopsy report was not available. The Investigator considered the treatment-emergent events of acute myocardial infarction to be severe and not related to study drug. The Sponsor medical monitor considered the treatment-emergent events of acute myocardial infarction to be serious and not related to study drug.

Subject RMTI-SFP-4 437-043 - Cardio-respiratory arrest, congestive heart failure
This was a 71-year-old man with HDD-CKD who received his first dose of placebo (standard dialysate without SFP) on (b) (6) (Day 1). Renal history for the subject included CKD since 2011 secondary to diabetes mellitus type 2 (since 2000). Other significant medical conditions included coronary artery disease, myocardial infarction, cerebrovascular accident, hyperlipidemia, diabetic neuropathy, osteoarthritis, peripheral vascular disorder, hypertension, and leg amputation (2009). His last dialysis treatment prior to the events of cardio-respiratory arrest and congestive cardiac failure (fourth occurrence) and his last dialysis treatment that he underwent during Stage 2 were on (b) (6) (Day 220). The subject received his last dose of Stage 2 study drug on the same day.

On (b) (6) (Day 223), the subject developed shortness of breath and was hospitalized for recurrent cardio-respiratory arrest. Troponins were noted as 0.46 and 0.163. Chest X-ray showed bilateral pleural effusion. The subject was intubated. Right thoracentesis was performed and over 2 L of yellow fluid was removed. On (b) (6) (Day 234), the subject developed bradycardia and was treated with nitrates and beta blockers. He was noted to have waxing and waning mental status. On (b) (6) (Day 239), his BUN was noted as 68 mg/dL and creatinine as 5.46 mg/dL. On (b) (6) (Day 241), the subject refused further medical treatment, and on (b) (6) (Day 245), he was discharged from the hospital to a nursing home. On (b) (6) (Day 256), the subject died and the events of cardio-respiratory arrest and congestive cardiac failure were ongoing at the time of subject's death. The events of cardio-respiratory arrest and congestive cardiac failure were considered fatal and were assessed as the cause of death of the subject. The Investigator considered the treatment-emergent events of congestive cardiac failure (second and fourth occurrences) and cardio-respiratory arrest to be severe and not related to study drug, but rather related to subject's prior event of acute myocardial infarction. The Sponsor medical monitor considered the treatment-emergent events of cardio-respiratory arrest to be serious and not related to study drug.

Study SFP-5:

SFP treatment group: 7 death cases

Subject RMTI-SFP-5 514-002 - Cardiac arrest
This was a 66-year-old man with HDD-CKD who received his first dose of soluble ferric pyrophosphate (SFP) 2 µM (110 µg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 2010 secondary to diabetes mellitus type 2. Other significant medical conditions included coronary artery disease, myocardial infarction (1998 and 2002), hypertension, and hyperparathyroidism. His last dialysis treatment prior to the event of cardiac arrest was on (b) (6) (Day 22). The subject's last dose of Stage 2 study drug and last dialysis treatment during Stage 2 were the same day.

On (b) (6) (Day 23), around 14:30 hours, the subject collapsed and was found unresponsive. The subject was noted to have ventricular tachycardia and was diagnosed with cardiac arrest by the emergency medical technician. The subject was treated with 50% dextrose, amiodarone 300 mg, 3 ampules of epinephrine, vasopressin 40 mg, and 0.9% normal saline. Cardiopulmonary resuscitation (CPR) and defibrillation were performed. The subject died on the same day at (b) (6) hours due to cardiac arrest. An autopsy was not performed. Investigator considered the treatment-emergent event of cardiac arrest to be severe and not related to study drug, but rather related to the subject's underling cardiac condition and end stage renal disease. The Sponsor medical monitor considered the treatment-emergent event of cardiac arrest to be serious and not related to study drug.

Subject RMTI-SFP-5 526-007 – Fluid overload, Cardio-respiratory arrest
This was a 72-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 2006 secondary to hypertension and diabetes mellitus type 2. Other significant medical conditions included right bundle branch block, cardiac pacemaker placement, hyperphosphatemia, and hyperparathyroidism.The subject had been noncompliant with hemodialysis treatments; from mid (b) (6) to early (b) (6), he received dialysis only once a week. As a result, he was discontinued from the study and he received his last dose of study drug on (b) (6) (Day 188). The subject's last dialysis treatment during the Stage 2 treatment period was also on the same day (Day 188). After the decision to discontinue the subject, the study staff had been trying to perform the early termination visit since (b) (6) (Day 195); however, the subject never returned to the unit for dialysis.

On (b) (6) (Day 203), the subject died at home due to cardio-respiratory arrest. The Investigator considered this treatment-emergent event of cardio-respiratory arrest to be severe and not related to study drug. The Sponsor medical monitor considered the treatment-emergent event of cardio-respiratory arrest to be serious and not related to study drug.

Subject RMTI-SFP-5 526-027 - Cardiac arrest
This was a 49-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 2008 secondary to diabetes mellitus type 2 (since 1984) and hypertension (since 2006). Other significant medical conditions included left bundle branch block, hyperlipidemia, diabetic retinopathy, diabetic neuropathy, and hyperphosphatemia. The subject received his last dose of Stage 2 study drug on (b) (6) (Day 328) and his last dialysis treatment during Stage 2 was also on the same day (Day 328).

On (b) (6) (Day 329), the subject had chest pain for the whole day. On (b) (6) (Day 330), the subject developed altered speech and then immediately became apneic, and had a cardiac arrest. The subject underwent CPR and was placed on endotracheal intubation. He was brought to the ER where he regained his pulse and later had a recurrent ventricular tachycardia with loss of pulse in the ER. He underwent CPR and was treated with epinephrine, atropine, insulin, albuterol, calcium gluconate, sodium bicarbonate, magnesium, dopamine, amiodarone 300 mg, amiodarone drip, lidocaine, and lidocaine drip. His rhythm eventually converted to atrial fibrillation with a ventricular rate of 93 beats per minute (bpm). A chest X-ray revealed pulmonary edema and pulmonary vascular congestion. An ECG showed atrial fibrillation with ST segment depression in the lateral leads. A cardiac

echocardiogram showed impaired left ventricular systolic wall motion with ejection fraction of 45%. He was admitted to the intensive care unit (ICU) where cooling measures were initiated according to the hypothermia protocol. On (Day 331), neurologist evaluation revealed that the subject was likely having brain death. On the same day (Day 331), the subject was pronounced dead. An autopsy was not performed. The Investigator considered the treatment-emergent event of cardiac arrest to be severe and unlikely related to study drug, but rather related to his underlying medical conditions. The Sponsor medical monitor considered the treatment-emergent event of cardiac arrest to be serious and not related to study drug.

Subject RMTI-SFP-5 530-014 - Death, Arteriovenous fistula thrombosis, Anemia
This was a 56-year-old woman with HDD-CKD who received her first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 12 Jan 2010 secondary to diabetes mellitus type 2 (since 2006). Other significant medical conditions included congestive cardiac failure, hypertension, vulval cancer and status post chemotherapy in 1996, obesity, hyperparathyroidism, and peripheral edema. Her last dialysis treatment prior to the events of arteriovenous fistula thrombosis and anemia was on (b) (6) (Day 132).

On (b) (6) (Day 137), the subject was brought to the ER after she had a fall and hit her neck, associated with numbness in her legs. She also complained of not feeling a thrill in her AV fistula 2-4 days prior to the fall. The subject's laboratory investigations showed hemoglobin (Hgb) of 8.9 g/dL. A CT scan revealed no findings, and she was admitted to the hospital on (b) (6) (Day 138) for further evaluation. Chest X-ray showed pulmonary edema. She was diagnosed with arteriovenous fistula thrombosis (Day 138). She was also found to have cardiomyopathy with an ejection fraction of 35 - 39%. On (b) (6) (Day 140), the subject underwent thrombectomy and stenting. On the same day (Day 140), the subject was transfused with 4 units of packed red blood cells (PRBCs) due to anemia. On (b) (6) (Day 142), Hgb was 8.5 g/dL. The subject was treated with midazolam, fentanyl, mepivacaine 2%, and Vicodin® for arteriovenous fistula thrombosis; and salbutamol and ipratropium for pulmonary edema. The subject was treated with iron dextran for anemia. The events of arteriovenous fistula thrombosis and anemia were considered resolved without sequelae on (b) (6) (Day 147) and the subject was discharged from the hospital on the same day.

On (b) (6) (Day 148), the decision was made to permanently discontinue study drug as the subject had received intravenous (IV) iron and PRBCs; and the subject received her last dose of Stage 2 study drug on the same day (Day 148). However, the subject expired prior to undergoing the early termination visit. On (b) (6) (Day 150), after completion of her dialysis, the subject did not feel well. On (b) (6), at (b) (6), the subject was found to have expired at home; the cause of death was unknown. No autopsy was performed. The Investigator considered the treatment-emergent event of death to be not related to the study drug, but rather related to a recent hospital admission for a non-working dialysis access and underlying medical conditions. The Sponsor medical monitor considered the treatment-emergent events of arteriovenous fistula thrombosis, anemia, and death to be serious and not related to study drug.

Subject RMTI-SFP-5 531-030 – Bronchopneumonia, Testis cancer, Postoperative wound infection
This was a 67-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 2006 secondary to diabetes mellitus type 2 (since 1986). Other significant medical conditions included coronary artery disease, cardiomyopathy, congestive cardiac failure (2005), atrial fibrillation, hyperlipidemia, hypotension, testis cancer, right radical orchiectomy, pulmonary hypertension, sleep apnea syndrome, peripheral vascular disease, gout, and hyperphosphatemia. The subject received his last dose of Stage 2 study drug on (b) (6) (Day 176). His last dialysis treatment prior to the event of bronchopneumonia was on the same day (Day 176).

On (b) (6) (Day 178), the subject was hospitalized for bronchopneumonia. No action was taken with the study drug in response to this event. On (b) (6) (Day 180), the subject died of bronchopneumonia. Investigator considered the treatment-emergent event of bronchopneumonia to be severe and not related to study drug, but rather due to an alternative etiology of pneumonia or bronchitis and a previous history of postoperative hernia wound

infection. The Sponsor medical monitor considered the treatment-emergent events of testis cancer, postoperative wound infection and bronchopneumonia to be serious and not related to study drug.

Subject RMTI-SFP-5 531-040 - Sudden death
This was a 66-year-old woman with HDD-CKD who received her first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 2005 secondary to diabetes mellitus type 2 (since 1980). Significant medical conditions included coronary artery disease, congestive cardiac failure, cerebrovascular accident (2000), hypertension, diabetic retinopathy, diabetic neuropathy, hypothyroidism, hyperlipidemia, restless legs syndrome, hyperparathyroidism and hyperphosphatemia, spinal laminectomy (lumbar laminectomy), and colectomy. The subject received her last dose of Stage 2 study drug on (b) (6) (Day 108) and her last dialysis treatment during Stage 2 was on the same day.

On (b) (6) (Day 110), the subject died (sudden death) at her residence. No autopsy was performed and her death certificate was unavailable. The Investigator considered the treatment-emergent event of sudden death to be severe and unlikely related to study drug, but rather related to the subject's end stage renal disease, coronary artery disease, and diabetes mellitus type 2. The Sponsor medical monitor considered the treatment-emergent events of sudden death to be serious and not related to study drug.

Subject RMTI-SFP-5 555-021 - Cardiac arrest
This was a 59-year-old man with HDD-CKD who received his first dose of SFP 2 mcM (110 mcg of iron/L of dialysate) on (b) (6) (Day 1). Renal history for the subject included CKD since 14 Jun 2004. Other significant medical conditions included coronary artery disease with stent insertion, hemorrhagic stroke, congestive cardiac failure, hypertension, diabetic retinopathy, rheumatoid arthritis, and hypocalcemia and hyperphosphatemia. The subject underwent last dialysis with SFP on (b) (6) (Day 120) and was discontinued from Stage 2 due to a non-protocol-mandated change in anemia management due to the erythropoiesis stimulating agent (ESA) dose change due to recent hospitalization for pneumonia, and underwent the early termination visit on (b) (6) (Day 132).

On (b) (6) (Day 134), 14 days after the last dose of study drug and 2 days after completion of the study, the subject went into cardiac arrest and paramedics were called. On examination, paramedics found that the subject was apneic with a ventricular fibrillation rhythm. CPR was done and pulse was regained after 20 minutes. He was intubated and brought to the ER. That same day, he was hospitalized for anoxic encephalopathy, which was due to cardiac arrest. The subject was treated with norepinephrine bitartate, epinephrine, and ventilator support for hypotension. The subject later died due to cardiac arrest. The Investigator considered the treatment-emergent event of cardiac arrest to be severe and not related to study drug, but rather related to end stage renal disease, stroke, hypertension, and diabetes mellitus type 2. The Sponsor medical monitor considered the treatment-emergent events of cardiac arrest to be serious and not related to study drug.

Placebo group: 2 death cases

Subject RMTI-SFP-5 512-016 – Sudden death
This was a 79-year-old man with HDD-CKD who received his first dose of placebo (standard dialysate without SFP) on (b) (6) (Day 1). Renal history for the subject included CKD since 21 Apr 2010 secondary to arteriosclerosis (since an unknown date). Other significant medical conditions included coronary artery disease, hypertension, aortic aneurysm, gout, hyperlipidemia, and left bundle branch block, secondary hyperparathyroidism, basal cell carcinoma (2011), and renal cell carcinoma and nephrectomy (1998 and 1999).
His last dialysis treatment prior to the event of sudden death was on (b) (6) (Day 73).

On (b) (6) (Day 75), the subject was found dead (sudden death) at home on (b) (6) (Day 75). There was no report of any signs or symptoms prior to his death. The Investigator considered the treatment-emergent event of sudden death to be severe and not related to study drug but rather but related to cardiac disease. The Sponsor medical monitor considered the treatment-emergent event of sudden death to be serious and not related to study drug.

Subject RMTI-SFP-5 519-019 – Acute myocardial infarction
This was a 75-year-old man with HDD-CKD who received his first dose of placebo (standard dialysate without SFP) on (b) (6) (Day 1). Renal history for the subject included CKD since 02 Feb 2009 secondary to hypertension (since 1994). Other significant medical conditions included ischemic heart disease, diabetes mellitus type 2, hypertension, hypercholesterolemia, and secondary hyperparathyroidism. His last dialysis treatment prior to the event of acute myocardial infarction was on (b) (6) (Day 27).

On (b) (6) (Day 28), the subject developed chest pain around midnight and stopped breathing. Immediately, emergency medical service was called and the subject was taken to a nearby hospital, where he was pronounced dead. The date of death was (b) (6) (Day 29) and the cause of death was reported as acute myocardial infarction. The Investigator considered the treatment-emergent event of acute myocardial infarction to be severe and not related to study drug, but rather related to ischemic heart disease (as a result of long standing diabetes mellitus and hypertension). The Sponsor medical monitor considered the treatment-emergent event of acute myocardial infarction to be serious and not related to study drug.

One patient died in the placebo group prior to receiving the study treatment. The patient narrative is shown below.

Subject RMTI-SFP-5 530-003 – Convulsion
This was a 48-year-old man with HDD-CKD who did not receive study drug. Renal history for the subject included CKD since 26 Nov 2003 secondary to hypertension (since Nov 2003). Other significant medical conditions included convulsion disorder, syncope, hypertension , and pleural effusion.

His last dialysis treatment prior to the event of convulsion was on (b) (6). On (b) (6), prior to administration of the first dose of study drug, the subject developed convulsion and died immediately. The Investigator considered the treatment-emergent event of convulsion to be severe and not related to study drug, but rather due to the subject's history of seizure. The Sponsor medical monitor considered the treatment-emergent event of convulsion to be serious and not related to study drug, as the subject had never received any study drug.

In NIH-HP-01 trial, 2 deaths were reported in the SFP group (3.7%) and 3 deaths in the placebo group (6.1%) during the study. One additional placebo patient died after completion of study participation.

In SFP-6 cross-over study, 3 patients died during the placebo treatment period.

In all clinical trials including the open-label extension studies in 1411 SFP-treated patients with HDD-CKD, 51 (3.6%) deaths were reported. The exposure-adjusted mortality rate for all SFP-treated subjects was 6.5 deaths per 100 subject exposure years). Most deaths were considered to be cardiac related. No deaths were considered by the investigator to be related to SFP treatment. The following table summarizes the patient's demographics and AEs leading to deaths.

Table 40. Summary of Deaths in SFP-treated Patients in All Clinical Trials

	All SFP-treated Patients (n=1411)
Total deaths	51 (3.6%)
Age	25-93 years
Gender	33 Males, 18 Females
Treatment duration on study drug	12-491 days
Reported Events Leading to Death	
Cardiac arrest	17
Cardio-respiratory arrest	7
Death	4
Myocardial infarction	4
Arteriosclerosis coronary artery	3
Sudden death	3
Hypoxic-ischemic encephalopathy	2
Septic shock	2
Acute respiratory failure	1
Azotemia	1
Bronchopneumonia	1
Electrolyte imbalance	1
Gastroenteritis	1
Gastrointestinal hemorrhage	1
Hepatic failure	1
Intestinal perforation	1
Pneumonia	1
Sepsis	1
Shock	1
Subdural hematoma	1
Ventricular arrhythmia	1

Reviewer's table

The following summarizes all death cases in SFP-treated patients in clinical studies.

Table 41. Listing of Death Cases in SFP-treated Patients in All Clinical Studies

Study/ Site-Subject No.	Date of First Dose of SFP	Date (Study Day) of Last Dose of SFP	Date (Study Day) of Death	Cause of Death (Verbatim Term)/ Start Date (Study Day) of Cause of Death	Causality Assessed by Investigator
NIHFP01/ 05-019	(b) (6)	(b) (6) (105)	(b) (6) 121)	ANOXIC BRAIN INJURY (b) (6) (111)	NOT RELATED
NIHFP01/ 16-023		(b) (6) (150)	(b) (6) 151)	CARDIAC ARREST (b) (6) (151)	NOT RELATED
RMTISFP2 514-005		(b) (6) (110)	Not provided	CARDIOPULMONARY ARREST (b) (6) (112)	NOT RELATED
RMTISFP2 601-004		(b) (6) (185)	Not provided	HEPATIC FAILURE (b) (6) (192)	NOT RELATED
RMTISFP3 001-039		(b) (6) (29)	(b) (6) 31)	ATHEROSCLEROTIC HEART DISEASE (b) (6) (31)	UNLIKELY
RMTISFP4 402-016		(b) (6) (13)	(b) (6) 38)	CARDIAC ARREST DUE TO STROKE (b) (6) (38)	NOT RELATED
RMTISFP4 406-012		(b) (6) (426)	(b) (6) (427)	CARDIOPULMONARY ARREST DUE TO (426)	NOT RELATED
RMTISFP4 406-016		(b) (6) (271)	(b) (6) (285)	CARDIORESPIRATORY ARREST CAUSE UNKNOWN (b) (6) (285)	NOT RELATED
RMTISFP4 406-032		(b) (6) (8)	(b) (6) (13)	CARDIAC ARREST CAUSE UNKNOWN (b) (6) (13)	UNLIKELY
RMTISFP4 407-064		(b) (6) (120)	(b) (6) (126)	CARDIAC ARREST (b) (6) (126)	UNLIKELY
RMTISFP4 410-007		(b) (6) (48)	(b) (6) (49)	DEATH, CAUSE UNKNOWN (b) (6) (49)	UNLIKELY
RMTISFP4 411-026		(b) (6) (55)	(b) (6) (58)	CARDIOPULMONARY ARREST (b) (6) (57)	NOT RELATED
RMTISFP4 411-043		(b) (6) (90)	(b) (6) (93)	CARDIAC ARREST LIKELY RELATED TO METABOLIC ACIDOSIS (b) (6) (92)	NOT RELATED
		(b) (6) (90)	(b) (6) 93)	GASTROENTERITIS (b) (6) (92)	NOT RELATED
		(b) (6) (90)	(b) (6) (93)	HYPOTENSIVE SHOCK (b) (6) (92)	NOT RELATED
RMTISFP4 417-014		(b) (6) (157)	(b) (6) (163)	CARDIAC ARREST (b) (6) (163)	NOT RELATED
RMTISFP4 421-026		(b) (6) (479)	(b) (6) (492)	CARDIOPULMONARY ARREST (b) (6) (492)	NOT RELATED
RMTISFP4 426-029		(b) (6) (15)	(b) (6) (40)	UNKNOWN CAUSE OF DEATH (b) (6) (40)	NOT RELATED
RMTISFP4/ 429-024		(b) (6) (66)	(b) (6) (71)	MYOCARDIAL INFARCTION (b) (6) (71)	NOT RELATED
RMTISFP4/ 432-008		(b) (6) (45)	(b) (6) (48)	CARDIAC ARREST (b) (6) (48)	UNLIKELY
RMTISFP4/ 433-017		(b) (6) (69)	(b) (6) (77)	ACUTE MYOCARDIAL INFARCTION (b) (6) (70)	NOT RELATED
RMTISFP4/ 437-038		(b) (6) (239)	(b) (6) (241)	SUDDEN DEATH(CAUSE UNKNOWN) (b) (6) (241)	NOT RELATED
RMTISFP5/ 514-002		(b) (6) (22)	(b) (6) (23)	CARDIAC ARREST (b) (6) (23)	NOT RELATED
RMTISFP5/ 517-005		(b) (6)	(b) (6) (363)	CARDIAC ARREST (b) (6) (363)	NOT RELATED
RMTISFP5/ 524-017		(b) (6) (458)	Not provided	MYOCARDIAL INFARCTION (b) (6) (468)	NOT RELATED
RMTISFP5/ 526-007		(b) (6) (188)	(b) (6) (203)	CARDIOPULMONARY ARREST (b) (6) (203)	NOT RELATED
RMTISFP5/ 526-027		(b) (6) (328)	(b) (6) (331)	UNKNOWN CARDIAC ARREST (b) (6) (330)	UNLIKELY

RMTISFP5/528-020	(b) (6) (b) (6) (162)	(b) (6) (175)	WORSENING OF UREMIA (b) (6) (171)	NOT RELATED
RMTISFP5/529-048	(b) (6) (127)	Not provided	PNEUMONIA (b) (6) 2 (127)	NOT RELATED
RMTISFP5/529-072	(b) (6) (36)	(b) (6) (38)	CARDIORESPIRATORY ARREST (b) (6) (38)	NOT RELATED
RMTISFP5/530-014	(b) (6) (148)	(b) (6) (151)	DEATH OF UNKNOWN ETIOLOGY (b) (6) (151)	NOT RELATED
RMTISFP5/531-001	(b) (6) (206)	(b) (6) (211)	ACUTE MYOCARDIAL INFARCTION (b) (6) (206)	NOT RELATED
	(b) (6) (206)	(b) (6) (211)	CARDIAC ARREST (b) (6) (210)	NOT RELATED
RMTISFP5/531-030	(b) (6) (176)	(b) (6) (180)	BRONCHOPNEUMONIA (b) (6) (178)	NOT RELATED
RMTISFP5/531-040	(b) (6) (108)	(b) (6) 110)	SUDDEN DEATH (b) (6) (110)	UNLIKELY
RMTISFP5/534-032	(b) (6) (66)	(b) (6) (74)	CARDIAC ARREST (b) (6) (68)	NOT RELATED
RMTISFP5/546-006	(b) (6) (365)	(b) (6) (386)	UNKNOWN DEATH (b) (6) (386)	NOT RELATED
RMTISFP5/555-021	(b) (6) (120)	Not provided	CARDIAC ARREST (b) (6) (134)	NOT RELATED
RMTISFP6/1132-009	(b) (6) (281)	(b) (6) (283)	CARDIAC ARREST (b) (6) (283)	NOT RELATED
RMTISFP6/1181-016	(b) (6) (269)	(b) (6) (272)	ATHEROSCLEROSIS HEART DISEASE (b) (6) (272)	NOT RELATED
RMTISFP6/1181-037	(b) (6) (255)	(b) (6) (256)	ATHEROSCLEROSIS HEART DISEASE (b) (6) (256)	NOT RELATED
RMTISFP6/1182-007	(b) (6) (458)	(b) (6) (465)	CARDIAC ARREST (b) (6) (465)	NOT RELATED
RMTISFP6/1182-024	(b) (6) (173)	(b) (6) (174)	SUDDEN DEATH (b) (6) (174)	NOT RELATED
RMTISFP6/1182-027	(b) (6) (379)	(b) (6) (379)	CARDIAC ARREST (b) (6) (379)	NOT RELATED
RMTISFP6/1211-053	(b) (6) (281)	(b) (6) (301)	SEPTIC SHOCK (b) (6) (282)	UNLIKELY
RMTISFP6/1211-077	(b) (6) (274)	(b) (6) (365)	VENTRICULAR ARRHYTHMIA (b) (6) (365)	NOT RELATED
RMTISFP6/1371-007	(b) (6) (71)	(b) (6) (77)	PERFORATED BOWEL (b) (6) (73)	UNLIKELY
RMTISFP6/1441-007	(b) (6) (169)	(b) (6) (180)	ELECTROLYTE DISTURBANCES DUE TO CESSATION OF DIALYSIS (b) (6) (180)	NOT RELATED
RMTISFP6/1451-007	(b) (6) (314)	(b) (6) (322)	SEPSIS (b) (6) (43)	NOT RELATED
RMTISFP6/1461-004	(b) (6) (284)	(b) (6) (288)	SEPTIC SHOCK (b) (6) (287)	NOT RELATED
RMTISFP6/1541-006	(b) (6) (365)	(b) (6) (367)	GI BLEED (b) (6) (367)	NOT RELATED
RMTISFP6/1551-009	(b) (6) (371)	(b) (6) (373)	ACUTE RESPIRATORY FAILURE (b) (6) (373)	NOT RELATED
RMTISFP6/1561-006	(b) (6) (150)	(b) (6) (153)	CARDIAC ARREST (b) (6) (153)	NOT RELATED
RMTISFP6/1601-007	(b) (6) (10)	Not provided	SUBDURAL HEMATOMA (b) (6) (26)	NOT RELATED

Sponsor's Table

One of the deaths occurred at the same day Triferic was administered during hemodialysis. The patient narrative is shown below.

Subject Number 1182-027
This a 68-year-old black or African American man with HDD-CKD who was enrolled in the RMTI-SFP-6 double-blind crossover study on (b) (6) (Study Day -21). He was randomly assigned on 08 Oct 2012 to receive SFP from Weeks 1-2 and placebo from Weeks 4-5. The subject received his first dose of study drug in the double-blind crossover study on (b) (6) (Study Day 1). On 16 Nov 2012, the subject signed the informed consent for the RMTI-SFP-6 open-label long-term extension study and received his first dose of open-label SFP on (b) (6) (Study Day 64; Extension Study Day 1). Chronic kidney disease had been diagnosed on 11 Feb 2012 and the subject had received his first dialysis treatment on 11 Feb 2012. Additional significant medical history included myocardial infraction, congestive cardiac failure, type 2 diabetes mellitus, diabetic neuropathy, hyperlipidemia, hypertension, leg amputation, peripheral vascular disorder, secondary hyperparathyroidism, and unilateral blindness.

The subject's last dose of SFP had been administered on (b) (6) (Study Day 379; Extension Study Day 316). On (b) (6), the subject started dialysis at his usual time of 05:30 AM. Dialysis was completed at (b) (6), and at the end of the subject's 4-hour dialysis session, the vital signs were recorded as pulse rate 91 bpm, blood pressure 117/70 mm Hg, and respiratory rate 16 breaths per minute. Post-treatment, the subject passed out and cardiopulmonary resuscitation was performed until an ambulance arrived to transport him to the hospital. On the way to the hospital, the subject experienced a cardiac arrest. At 10:11 AM, the subject arrived at the emergency room in a ventricular fibrillation rhythm with cardiopulmonary resuscitation in progress. A cardiac arrest code was performed. Treatment for the event included amiodarone hydrochloride. At (b) (6), the code was called off and the subject was pronounced dead. An autopsy was not performed. According to the death certificate, the cause of death was cardiopulmonary arrest and atherosclerotic heart disease. The event was not considered to be related to study drug by the investigator.

7.3.2 Nonfatal Serious Adverse Events

In the pooled SFP-4 and SFP-5 studies, 24.0% of the SFP-treated patients and 25.3% of the placebo-treated patients experienced at least one nonfatal treatment-emergent serious adverse events (TESAEs). A total of 120 TESAEs were reported in the SFP group and 154 TESAEs were reported in the placebo group. The following table includes nonfatal TESAEs reported in ≥1% of SFP-treated patients.

The nonfatal TESAEs that were reported more frequently in the SFP group as compared to the placebo group were diabetic foot infection (1% vs. 0%), arteriovenous fistula thrombosis (1.7% vs. 0.7%), and pulmonary edema (1.4% vs. 0.3%). There were no nonfatal TESAEs in the SFP or placebo groups that were considered by the investigator to be related to study treatment.

Table 42. Nonfatal Treatment-Emergent Serious Adverse Events Reported ≥1% of SFP-treated Subjects in Pooled SFP-4 and SFP-5 Studies

System organ class Preferred term	SFP N=292 n (%)	Placebo N=296 n (%)
Number of subjects with ≥1 nonfatal TESAE	70 (24.0)	75 (25.3)
Cardiac disorders	12 (4.1)	22 (7.4)
Cardiac failure congestive	5 (1.7)	7 (2.4)

General disorders and administration site conditions	6 (2.1)	7 (2.4)
Non-cardiac chest pain	3 (1.0)	7 (2.4)
Infections and infestations	21 (7.2)	22 (7.4)
Pneumonia	5 (1.7)	8 (2.7)
Diabetic foot infection	3 (1.0)	0 (0.0)
Injury, Poisoning and Procedural Complications	14 (4.8)	10 (3.4)
Arteriovenous fistula thrombosis	5 (1.7)	2 (0.7)
Metabolism and Nutrition Disorders	8 (2.7)	20 (6.8)
Fluid overload	4 (1.4)	13 (4.4)
Respiratory, Thoracic and Mediastinal Disorders	5 (1.7)	6 (2.0)
Pulmonary edema	4 (1.4)	1 (0.3)

Reviewer's table

Of the 1411 SFP-treated subjects in SFP clinical development program, 412 subjects (29.2%) experienced a total of 899 nonfatal TESAEs. The most common TESAEs, occurring in ≥1% of subjects were fluid overload (2.3%), hyperkalemia (2.0%), pneumonia (1.8%), congestive heart failure (1.7%), arteriovenous fistula thrombosis (1.3%), pulmonary edema (1.3%), acute myocardial infarction (1.1%), atrial fibrillation (1.1%), non-cardiac chest pain (1.1%), coronary artery disease (1.0%), and vascular graft thrombosis (1.0%).

A total of 5 subjects (0.4%) experienced TESAEs considered by the investigator to be related to study treatment. These TESAEs were pneumonia in 2 patients, abdominal pain, pyrexia, and leukocytoclastic vasculitis each in one patient.

7.3.3 Dropouts and/or Discontinuations

Overall, 13 (4.5%) patients had at least one TEAE that led to treatment discontinuation in the SFP group as compared to 7 (2.4%) patients in the placebo group in the Phase 3 studies. The most common TEAEs leading to study discontinuation in the SFP group were asthenia, dizziness, and headache, occurring in 2 subjects each (0.7%). All other TEAEs that led to study discontinuation occurred in single subjects including thrombocytopenia, cardiac arrest, coronary artery disease, blurry vision, constipation, feeling cold, feeling hot, flushing, nausea, hypotension, hypersensitivity, vascular graft complication (arm pain during administration), hemoglobin decreased, worsening peripheral neuropathy, flushing, and pruritus generalized.

Table 43. Treatment-Emergent Adverse Events Leading to Study Discontinuation in ≥1 SFP-treated Subject

System organ class Preferred term	**SFP N=292**	**Placebo N=296**
Number of subjects with ≥1 TEAE leading to study discontinuation	13 (4.5)	7 (2.4)
Blood and Lymphatic System Disorders	1 (0.3)	0 (0.0)
Thrombocytopenia	1 (0.3)	0 (0.0)

Cardiac Disorders	2 (0.7)	0 (0.0)
Cardiac arrest	1 (0.3)	0 (0.0)
Coronary artery disease	1 (0.3)	0 (0.0)
Eye Disorders	1 (0.3)	0 (0.0)
Vision blurred	1 (0.3)	0 (0.0)
Gastrointestinal Disorders	1 (0.3)	2 (0.7)
Constipation	1 (0.3)	0 (0.0)
General Disorders and Administration Site Conditions	2 (0.7)	2 (0.7)
Asthenia	2 (0.7)	1 (0.3)
Feeling cold	1 (0.3)	0 (0.0)
Feeling hot	1 (0.3)	0 (0.0)
Injury, Poisoning and Procedural Complications	2 (0.7)	0 (0.0)
Procedural hypotension	1 (0.3)	0 (0.0)
Vascular graft complication	1 (0.3)	0 (0.0)
Investigations	1 (0.3)	1 (0.3)
Hemoglobin decreased	1 (0.3)	1 (0.3)
Nervous System Disorders	4 (1.4)	2 (0.7)
Dizziness	2 (0.7)	1 (0.3)
Headache	2 (0.7)	0 (0.0)
Neuropathy peripheral	1 (0.3)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	1 (0.3)	0 (0.0)
Pruritus generalized	1 (0.3)	0 (0.0)

Reviewer's table

In 7 of 13 SFP-treated patients, treatment-related TEAEs that led to study discontinuation determined by investigator were asthenia, dizziness, and headache, blurry vision, thrombocytopenia (also on heparin), flushing, nausea, cramping, hypotension, constipation, feeling cold, feeling hot, and procedural hypotension.

The patient who experienced procedural hypotension was also considered to be a suspected hypersensitivity reaction by the investigator.

In all clinical trials in a total of 1411 SFP-treated subjects in the SFP development program, 49 subjects (3.5%) experienced a total of 62 TEAEs that led to study treatment discontinuation. The most common TEAEs leading to study discontinuation were acute myocardial infarction and headache (3 subjects each, 0.2%), cardiac arrest, coronary artery disease, dizziness, asthenia, constipation, and generalized pruritus (2 subjects, 0.1%).

Fourteen (1.0%) of the 1411 SFP-treated subjects had treatment-related TEAEs that led to study discontinuation. The treatment-related TEAEs that led to study discontinuation were headache (3 subjects, 0.2%); constipation, asthenia, and dizziness (2 subjects each, 0.1%); and thrombocytopenia (on heparin), vision blurred, nausea, feeling cold, feeling hot, pyrexia,

hyperbilirubinemia, drug hypersensitivity, procedural hypotension, hepatic enzyme increased, and generalized pruritus (1 subject each, 0.1%).

The treatment-related TEAE of drug hypersensitivity that led to study discontinuation was also considered to be a suspected hypersensitivity reaction by the investigator.

The TEAEs of hyperbilirubinemia and hepatic enzyme increased that led to study discontinuation were experienced by the same subject and were assessed as possibly related to study drug by the investigator. A significant increase in alkaline phosphatase (1710 U/L) and total bilirubin (111.15 mcmol/L) above baseline levels with lesser increases in transaminases (ALT 79 U/L and AST 72 U/L; <2 xULN) was reported. This subject had elevated enzymes prior to the first dose of SFP and was subsequently diagnosed with cholelithiasis.

7.3.4 Significant Adverse Events

Adverse events of special interest (AESIs)

The AESIs included the following adverse events:

- Intradialytic hypotension (IDH)
- Suspected Hypersensitivity Reactions
- Composite Cardiovascular Events
- HD Vascular Access Thrombotic Events
- Other Venous or Arterial Thrombotic Events
- Systemic/Serious Infections

The following table summarizes the AESIs in pooled two phase 3 clinical trials.

Table 44. Treatment-Emergent Adverse Events of Special Interest in Pooled Phase 3 Trials

TEAEs of Special Interest	SFP N=292	Placebo N=296
Intradialytic hypotension, n (%)	62 (21.2)	57 (19.3)
Symptomatic	26 (8.9)	19 (6.4)
Requiring Intervention	35 (12.0)	36 (12.2)
Suspected Hypersensitivity Reactions, n (%)	1 (0.3)	0 (0.0)
Composite Cardiovascular Events, n (%)	26 (8.9)	27 (9.1)
HD Vascular Access Thrombotic Events, n (%)	15 (5.1)	11 (3.7)
Arteriovenous fistula or graft thrombosis	13 (4.5)	10 (3.4)
HD catheter thrombosis	2 (0.7)	2 (0.7)
Other Thrombotic Events, n (%)	3 (1.0)	6 (2.0)
Systemic/Serious Infections, n (%)	24 (8.2)	26 (8.8)

Reviewer's table

Intradialytic hypotension (IDH):

In the pooled two Phase 3 trials, 292 SFP-treated patients received a total of 19950 HD sessions and 296 placebo-treated patients received a total of 20398 HD sessions. IDH episodes occurred at the same rate (2.1% of the total HD sessions) in both treatment groups. There were similar frequencies of IDH episodes resulting in premature termination or interruption of dialysis in the SFP and placebo groups. Of those, the IDH episodes of a severity or frequency that exceeded the subject's established pattern of IDH prior to entering the study were also reported at similar frequencies: 1.4% of HD sessions in the SFP group and 1.2% in the placebo group. The overall incidence of subjects experiencing ≥1 IDH episode was 28.8% in the SFP group and 30.4% in the placebo group. However, the CRF did not have separate questions for whether the SBP decrease met the protocol definition of IDH and whether it exceeded the subject's established pattern of IDH prior to entering the study.

Table 45. Intradialytic Hypotension Episodes in Hemodialysis Sessions

	SFP (N=292) n (%)	**Placebo (N=296) n (%)**
Actual total number of HD sessions	19950	20398
Actual total number of HD sessions per subject (mean [SD])	68.3 (48.4)	68.9 (47.1)
HD sessions with an IDH episode (number of sessions [%])	416 (2.1)	420 (2.1)
Hypotension resulting in premature termination or interruption of dialysis	170 (0.9)	199 (1.0)
Decrease in SBP meeting the protocol definition of IDH	267 (1.3)	244 (1.2)
HD sessions with an IDH episode of a severity or frequency that exceeded the subject's established pattern of IDH prior to entering the study (number of sessions [%])	273 (1.4)	246 (1.2)
Hypotension resulting in premature termination or interruption of dialysis	17 (0.1)	19 (0.1)
Decrease in SBP meeting the protocol definition of IDH*	267 (1.3)	244 (1.2)
Number of subjects experiencing ≥1 IDH episode (n [%])	84 (28.8)	90 (30.4)
Hypotension resulting in premature termination or interruption of dialysis	48 (16.4)	48 (16.2)
Decrease in SBP meeting the protocol definition of IDH	57 (19.5)	58 (19.6)

*The CRF did not ask separate questions for whether the SBP decrease met the protocol definition of IDH and whether it exceeded the subject's established pattern of IDH prior to entering the study.
Reviewer's table

Intradialytic hypotension episodes that met both protocol-specified criteria for IDH reportable as an AE were reported as procedural hypotension in 62 subjects (21.2%) in the SFP group and 57 subjects (19.3%) in the placebo group (see Table below). There were 316 IDH events total (269 asymptomatic events and 47 symptomatic events) reported in the SFP group and 284 (236 asymptomatic events and 48 symptomatic events) in the placebo group. A subject may have experienced asymptomatic IDH episodes and symptomatic IDH episodes in different HD sessions during the treatment period.

Of subjects who had IDH episodes reported as TEAEs, 26 subjects (8.9%) in the SFP group as compared to 19 subjects (6.4%) in the placebo group reported ≥1 symptom; 35 subjects (12.0%) in the SFP group and 36 subjects (12.2%) in the placebo group required intervention.

The most commonly reported symptoms in both groups were dizziness or fainting, followed by muscle cramps, and nausea. The most common type of intervention in both groups was IV saline or other isotonic solution and terminating or reducing ultrafiltration. See Table below.

Table 46. Treatment-Emergent Intradialytic Hypotension Adverse Events

	SFP (N=292)		Placebo (N=296)	
	Events n	**Subjects n (%)**	**Events n**	**Subjects n (%)**
Any TEAE that met both protocol criteria for IDH reportable as an AE	316	62 (21.2)	284	57 (19.3)
Asymptomatic IDH TEAE with ≥1	141	23 (7.9)	111	27 (9.1)
IDH TEAE with ≥1 symptom	47	26 (8.9)	48	19 (6.4)
Symptomatic IDH TEAE with at least 1 intervention	38	23 (7.9)	43	17 (5.7)
Asymptomatic	269	49 (16.8)	236	49 (16.6)
Not requiring intervention	127	38 (13.0)	125	33 (11.1)
Requiring intervention[a]	141	23 (7.9)	111	27 (9.1)
IV saline or other isotonic solution	69	19 (6.5)	47	23 (7.8)
Terminating or reducing ultrafiltration	100	12 (4.1)	75	12 (4.1)
Stopping dialysis altogether	3	2 (0.7)	2	2 (0.7)
Low temperature dialysate	1	1 (0.3)	0	0 (0.0)
Other	20	4 (1.4)	11	5 (1.7)
Symptomatic	47	26 (8.9)	48	19 (6.4)
Dizziness or fainting	24	16 (5.5)	14	10 (3.4)
Muscle cramps	9	6 (2.1)	11	6 (2.0)
Nausea	4	4 (1.4)	5	3 (1.0)
Abdominal discomfort	1	1 (0.3)	0	0 (0.0)
Vomiting	0	0 (0.0)	3	3 (1.0)
Other	19	13 (4.5)	25	10 (3.4)
Not requiring intervention	9	8 (2.7)	5	5 (1.7)
Requiring intervention[a]	38	23 (7.9)	43	17 (5.7)
IV saline or other isotonic solution	21	17 (5.8)	37	16 (5.4)
Terminating or reducing ultrafiltration	17	13 (4.5)	19	9 (3.0)
Stopping dialysis altogether	7	3 (1.0)	9	5 (1.7)

Other	7	3 (1.0)	8	4 (1.4)

[a] An IDH AE may have more than one symptom or intervention.
Reviewer's table

One subject (0.3%) in the SFP group reported a TEAE of IDH (PT: procedural hypotension) that led to study discontinuation; no TEAEs of IDH that led to study discontinuation were reported in the placebo group. The event was determined by the investigator to be a suspected hypersensitivity event (described in section below). Recorded symptoms included nausea, dizziness or fainting, and other symptoms. The subject was treated with IV saline and the event resolved on the same day.

IDH was considered to be TESAE in one subject in the placebo group and in none in the SFP group.

In all clinical trials in 1411 SFP-treated subjects in SFP development program, 262 (18.6%) experienced any TEAE of IDH including 142 subjects (10.1%) who were asymptomatic requiring intervention and 141 subjects (10.0%) who reported ≥1 symptom. Similarly, the most common type of intervention was IV saline or other isotonic solution (112 of 142 asymptomatic subjects who required intervention and 108 of 131 symptomatic subjects who required intervention), and terminating or reducing ultrafiltration (78 of 142 asymptomatic subjects who required intervention and 71 of 131 symptomatic subjects who required intervention). The most commonly reported symptoms were dizziness or fainting (66 of 141 symptomatic subjects). Treatment-emergent SAEs of IDH occurred in 6 of 1411 SFP-treated subjects (0.4%).

Suspected hypersensitivity reactions

In Phase 3 trials, a suspected hypersensitivity reaction was reported in one (0.3%) patient (procedural hypotension) in the SFP group and none in the placebo group.

The following is patient narrative of this case.

Subject RMTI-SFP-5 544-001
This was a 61-year old man with HDD-CKD who was randomized on 19 Sep 2011 (Day -2) and received the first dose of SFP 2 mcM (11 mcg of iron/dL of dialysate) on 21 Sep 2011 (Day 1). Renal history for the subject included CKD since an unknown date secondary to diabetes mellitus type 2 (since 2002). Other significant medical conditions included renal cell carcinoma (in remission), hypertension, aortic valve stenosis, right bundle branch block, allergic rhinitis and hepatitis, drug hypersensitivity (hydralazine), dyslipidemia, depression, and peripheral edema. Concomitant medications at the time of the event were simvastatin, glipizide, sevelamer carbonate, Vicodin®, alprazolam, cinacalcet hydrochloride, ergocalciferol, calcitriol, Renaplex ®, and sodium chloride.

The subject's last dialysis treatment prior to the event and his last dose of stage 2 study drug was on 21 Sep 2011 (Day 1). On 21 Sep 2011 (Day 1), the subject experienced flushing two minutes after starting dialysis. Flushing lasted for a few seconds and then subsided. The subject's BP at the start of dialysis (2 minutes prior to the onset of flushing) was 160/85 mmHg and was 141/73 mmHg 23 minutes after the onset of flushing. Two hours and 40 minutes after the start of dialysis, the subject developed decreased BP of 85/54 mmHg and was diagnosed with procedural hypotension associated with cramping, nausea, and dizziness. On the same day 21 Sep 2011 (Day 1), the

study drug was permanently discontinued in response to this event (procedural hypotension). The subject was treated with a normal saline IV bolus, which resulted in increase in BP to 104/56 mmHg within 10 minutes. The subject also received diphenhydramine and metoclopramide for flushing and nausea, respectively. The event of procedural hypotension was suspected to be an hypersensitivity reaction. The subject completed dialysis with SFP after a total of 4 hours and left the dialysis center in stable condition. The event of procedural hypotension was considered resolved without sequelae on 21 Sep 2011 (Day 1). The Investigator considered the treatment-emergent event of procedural hypotension as moderate and related to study drug.

In overall 1411 SFP-treated patients in clinical trials in the SFP development program, TEAEs of suspected hypersensitivity reactions were reported for 6 (0.4%) of 1411 subjects including one case in Phase 3 trials mentioned above. These events were reported as procedural hypotension [3 subjects], drug hypersensitivity [1 subject], syncope [1 subject], procedural pain [1 subject], and muscle spasms [1 subject]). There were 3 additional patients (RMTI-SFP-4 402-013, RMTI-SFP-4 437-033, and RMTI-SFP-5 530-048) with AEs of procedural hypotension, procedural hypotension, and hypoesthesia [2 events], respectively) reported in the initial NDA submission. The sponsor later indicated that the suspected hypersensitivity reaction questions on the AE CRFs had been marked in error in the ongoing open-label extension studies, and were corrected prior to database lock.

Two of 1411 subjects (0.1%) had treatment-related TEAEs of suspected hypersensitivity reaction (PTs: procedural hypotension and drug hypersensitivity) including one case in Phase 3 trials. Both events led to study discontinuation. There were no treatment-related TESAEs of suspected hypersensitivity reaction in any SFP-treated subjects.

Two of 6 suspected hypersensitivity reactions were considered to be treatment-related TEAEs (procedural hypotension and drug hypersensitivity) including one case in Phase 3 trials mentioned above. Both patients experienced TEAEs right after starting the first hemodialysis with SFP and those TEAEs led study treatment discontinued permanently.

The patient narrative for the additional case is presented below.

Subject RMTI-SFP-4 410-025
This was a 54-year-old woman with HDD-CKD who had previously received placebo during Stage 2. The subject entered the open-label long-term Stage 3 extension study on 30 APR 2012 and received her first and only dose of SFP on 02 MAY 2012 (Day 43; Extension Day 1). At the first visit at which the subject was exposed to SFP study drug, she experienced a non-serious event of drug hypersensitivity (allergic reaction to study drug). She had started dialysis at 05:02 and immediately developed symptoms of itching and a sensation of neck swelling; she also developed a rash around the cheeks and neck. There were no symptoms of wheezing or chest tightness. She was being dialyzed using an Asahi Rexeed Polysulfone (HF) 25R dialyzer that had been previously used 3 times and cleaned with Renalin. She was given diphenhydramine 50 mg IV, and the bicarbonate jug was switched from one containing SFP to one without SFP. The event resolved without sequelae within 18 minutes at 05:20 on the same day (Day 43; Extension Day 1). Her blood pressure was 152/76 mmHg prior to dialysis at 04:57, and was 155/74 mmHg at 05:24. Dialysis was continued without further incident, ending at 08:10, and the subject left the clinic at 08:30. The subject was called later that day at 11:00 and it was confirmed that she remained clinically stable. The study drug was permanently discontinued on the same day (Day 43; Extension Day 1) in response to this event. The investigator considered the treatment-emergent event of drug hypersensitivity to be of moderate severity and probably related to study drug. The Sponsor medical monitor considered this treatment-emergent event to be non-

serious and relatively mild, as it was not associated with decreased blood pressure and resolved with 50 mg diphenhydramine, and possibly related to study drug.

The following table summarizes the all six cases of suspected hypersensitivity reactions reported in all clinical trials.

Table 47. Cases of Suspected Hypersensitivity Reactions in All Clinical Trials

Study Subject ID Age/Gender	Time to onset of AEs	SFP dose/duration	Adverse Events	Required Treatment/Outcome	Causality assessment by investigator
SFP-4 OL 410-025 54 yrs/F	immediately	Extension Day 1 1st dose (received Placebo at Stage 2)	Itching, sensation of neck swelling, rash around cheeks and neck	Diphenhydramine 50 mg IV Switched to standard dialysate Resolved within 18 minutes Discontinued treatment permanently	Probably Related
SFP-5 544-001 62 yrs/M	2 min	1st dose	Flushing, Hypotension (2 hr 40 min) Cramping, nausea, and dizziness	Normal saline 400 ml IV bolus Ultrafiltration turned off BP increased in 10 minutes Diphenhydramine 25 mg orally Metoclopramide 5 mg orally Completed dialysis after a total of 4 hrs Resolved Discontinued treatment permanently	Related
NIH-FP-01 16-40 61 yrs/M	4 hrs	Day 160 on study	Worsening of intradialytic hypotension after completing dialysis	No treatment Resolved Continued SFP for 3 more months until completing the study	Not related
SFP-4 OL 421-021 46 yrs/M	Pre-dialysis	Extension Day 353 (Received SFP group at Stage 2)	Hypertension treated with clonidine and taken off dialysis Unresponsive/syncope with decreased BP in 1 hr 16 min	Hospitalized for syncope Resolved Completed Stage 3 to Day 491	Not related
SFP-6 1301-023 66 yrs/F	9 min	2nd dose	Intradialytic back pain Decreased SBP	Acetaminophen Decreased dialysis blood flow rate to 250 mL/min Resolved in 2 hours 20 minutes Completed dialysis	Not related
SFP-6 1461-015 60 yrs/M	3 hours	2nd dose	Intradialytic hypotension and worsening muscle cramping	IV normal saline 200 ml Dialysis interrupted temporally Completed dialysis Resolved Enrolled extension study and received 40 week treatment	Not related

Reviewer's table

Composite Cardiovascular Events

In the pooled Phase 3 studies, the rate of treatment-emergent composite cardiovascular events was similar between the two treatment groups. Overall, 26 subjects (8.9%) experienced 30 composite cardiovascular events in the SFP group as compared to 27 subjects (9.1%) experienced 42 composite cardiovascular events in the placebo group. Most events were considered to be serious. The most common cardiovascular TEAEs were congestive cardiac failure, cardiac arrest, and acute myocardial infarction. The cardiac arrest events were reported as fatal events that were discussed in the earlier section.

Table 48. TEAEs of Composite Cardiovascular Events in Pooled Phase 3 Studies

	SFP (N=292) n (%)	Placebo (N=296) n (%)
Number of Subjects with At Least One Treatment-Emergent Adverse Event of Composite Cardiovascular Event	26 (8.9)	27 (9.1)
Cardiac Disorders	23 (7.9)	25 (8.4)
Cardiac Failure Congestive	5 (1.7)	8 (2.7)
Cardiac Arrest	5 (1.7)	1 (0.3)
Acute Myocardial Infarction	4 (1.4)	6 (2.0)
Coronary Artery Disease	2 (0.7)	3 (1.0)
Angina Pectoris	2 (0.7)	2 (0.7)
Angina Unstable	2 (0.7)	0 (0.0)
Atrial Fibrillation	1 (0.3)	3 (1.0)
Cardio-Respiratory Arrest	1 (0.3)	2 (0.7)
Myocardial Infarction	1 (0.3)	2 (0.7)
Supraventricular Tachycardia	1 (0.3)	2 (0.7)
Cardiomegaly	1 (0.3)	0 (0.0)
Atrial Flutter	0 (0.0)	2 (0.7)
Atrioventricular Block First Degree	0 (0.0)	1 (0.3)
Cardiogenic Shock	0 (0.0)	1 (0.3)
Cardiomyopathy	0 (0.0)	1 (0.3)
Palpitations	0 (0.0)	1 (0.3)
General Disorders And Administration Site Conditions	2 (0.7)	1 (0.3)
Sudden Death	2 (0.7)	1 (0.3)
Nervous System Disorders	1 (0.3)	1 (0.3)
Cerebrovascular Accident	1 (0.3)	1 (0.3)

Reviewer's table

In all clinical trials in the overall 1411 SFP-treated subjects with HDD-CKD in the SFP development program, 139 subjects (9.9%) reported at least 1 composite cardiovascular event and 126 subjects (8.9%) had ≥1 serious composite cardiovascular TEAE. The most common composite cardiovascular TEAEs were congestive cardiac failure (2.1%), acute myocardial infarction (1.4%), cardiac arrest (1.3%), atrial fibrillation (1.1%), and coronary artery disease (1.0%).

HD Vascular Access Thrombotic Events and Other Thrombotic Events

In the pooled Phase 3 trials, overall HD vascular thrombotic events/other thrombotic events were reported at a similar rate between the two groups (see Table below). In the SFP group, 18 (6.2%) subjects experienced 22 HD vascular access/other thrombotic events; six (2.1%) had events that were considered to be serious. In the placebo group, 17 (5.7%) subjects experienced 23 HD vascular access/other thrombotic events; six (6, 2.0%) had events that were considered to be serious. The only event occurring more frequently in the SFP group as compared to the placebo was arteriovenous fistula thrombosis (3.4% and 2.0%, respectively).

Table 49. Hemodialysis Vascular Access Thrombotic Events and Other Thrombotic Events in Pooled Phase 3 Studies

	SFP (N=292) n (%)	Placebo (N=296) n (%)
Number of Subjects with At Least One Treatment-Emergent Adverse Event of HD Vascular Access/Other Thrombotic Event	18 (6.2)	17 (5.7)
General Disorders and Administration Site Conditions	5 (1.7)	5 (1.7)
Thrombosis In Device	5 (1.7)	5 (1.7)
Injury, Poisoning and Procedural Complications	13 (4.5)	10 (3.4)
Arteriovenous Fistula Thrombosis	10 (3.4)	6 (2.0)
Vascular Graft Thrombosis	3 (1.0)	4 (1.4)
Vascular Disorders	0 (0.0)	3 (1.0)
Deep Vein Thrombosis	0 (0.0)	3 (1.0)

Reviewer's table

In all clinical trials in 1411 SFP-treated subjects, 157 subjects (11.1%) had ≥1 TEAE of HD vascular access thrombotic events or other thrombotic events. The most common events were arteriovenous fistula thrombosis (63, 4.5%), vascular graft thrombosis (53, 3.8%), and thrombosis in device (45, 3.2%). Treatment-emergent SAEs of HD vascular access thrombotic events/other thrombotic events occurred in 37 subjects (2.6%).

Systemic/Serious Infections

In the pooled Phase 3 trials, the overall rate of systemic/serious infection reported was similar between the SFP and the placebo group (see Table below). In the SFP group, 24 (8.2%) subjects experienced 28 systemic/serious infection events; 23 (7.9%) had events that were considered serious events. In the placebo group, 26 (8.8%) subjects experienced 28 systemic/serious infection events; 25 (8.4%) had events that were considered serious events. The most common events were pneumonia (2.1%), urinary tract infection (1%), and diabetic foot infection (1%) in the SFP-treated patients.

Table 50. Systemic/Serious Infections in Pooled Phase 3 Studies

	SFP (N=292) n (%)	Placebo (N=296) n (%)
Number of Subjects with At Least One Treatment-Emergent Adverse Event of Systemic/Serious Infection	24 (8.2)	26 (8.8)
Pneumonia	6 (2.1)	8 (2.7)
Urinary Tract Infection	3 (1.0)	1 (0.3)
Diabetic Foot Infection	3 (1.0)	0 (0.0)
Cellulitis	2 (0.7)	1 (0.3)
Lobar Pneumonia	2 (0.7)	1 (0.3)
Device Related Sepsis	2 (0.7)	0 (0.0)
Sepsis	2 (0.7)	0 (0.0)
Gastroenteritis Viral	1 (0.3)	1 (0.3)
Osteomyelitis	1 (0.3)	1 (0.3)
Postoperative Wound Infection	1 (0.3)	0 (0.0)
Septic Shock	1 (0.3)	0 (0.0)
Urosepsis	1 (0.3)	0 (0.0)
Viral Upper Respiratory Tract Infection	1 (0.3)	0 (0.0)
Arteriovenous Graft Site Infection	0 (0.0)	2 (0.7)
Bacteremia	0 (0.0)	2 (0.7)
Upper Respiratory Tract Infection	0 (0.0)	2 (0.7)
Arteriovenous Fistula Site Infection	0 (0.0)	1 (0.3)
Bronchitis	0 (0.0)	1 (0.3)
Device Related Infection	0 (0.0)	1 (0.3)
Diverticulitis	0 (0.0)	1 (0.3)
Influenza	0 (0.0)	1 (0.3)
Klebsiella Sepsis	0 (0.0)	1 (0.3)
Pseudomonal Bacteremia	0 (0.0)	1 (0.3)
Acute Pyelonephritis	0 (0.0)	1 (0.3)
Renal Cyst Infection	0 (0.0)	1 (0.3)

Reviewer's table

In all clinical trials in the 1411 SFP-treated subjects, 143 subjects (10.1%) reported ≥1 TEAE of systemic/serious infection. The most common TEAEs of systemic/serious infection were pneumonia (1.9%), cellulitis (0.9%), sepsis (0.9%), and urinary tract infection (0.9%).

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In pooled Phase 3 studies, the overall TEAEs occurred at similar frequencies between the SFP group (78.4%) and the placebo group (75.3%). The TEAEs occurring in ≥1% of subjects in the SFP group in the pooled Phase 3 trials is presented in Table below.

Table 51. TEAEs Reported in ≥1% of Subjects in Pooled Phase 3 Trials

System organ class Preferred term	SFP N=292 n (%)	Placebo N=296 n (%)
Number of subject with at least one TEAE	229 (78.4)	223 (75.3)
Blood and Lymphatic System Disorders	14 (4.8)	18 (6.1)
Anemia	8 (2.7)	13 (4.4)
Cardiac Disorders	35 (12.0)	42 (14.2)
Cardiac arrest	6 (2.1)	1 (0.3)
Congestive heart failure	5 (1.7)	8 (2.7)
Angina pectoris	5 (1.7)	5 (1.7)
Acute myocardial infarction	4 (1.4)	6 (2.0)
Bradycardia	4 (1.4)	5 (1.7)
Tachycardia	3 (1.0)	5 (1.7)
Gastrointestinal Disorders	74 (25.3)	79 (26.7)
Diarrhea	23 (7.9)	29 (9.8)
Nausea	22 (7.5)	29 (9.8)
Vomiting	16 (5.5)	24 (8.1)
Dyspepsia	7 (2.4)	5 (1.7)
Abdominal pain upper	6 (2.1)	9 (3.0)
Abdominal pain	6 (2.1)	6 (2.0)
Constipation	6 (2.1)	3 (1.0)
General Disorders and Administration Site Conditions	75 (25.7)	58 (19.6)
Peripheral edema	20 (6.8)	11 (3.7)
Pyrexia	13 (4.5)	9 (3.0)
Asthenia	12 (4.1)	9 (3.0)
Fatigue	11 (3.8)	6 (2.0)
Chest pain	6 (2.1)	5 (1.7)
Chills	6 (2.1)	1 (0.3)
Non-cardiac chest pain	5 (1.7)	11 (3.7)
Thrombosis in device	5 (1.7)	5 (1.7)
Face edema	4 (1.4)	3 (1.0)
Pain	3 (1.0)	5 (1.7)
Malaise	3 (1.0)	4 (1.4)
Chest discomfort	3 (1.0)	2 (0.7)
Catheter site hemorrhage	3 (1.0)	0 (0.0)

Feeling cold	3 (1.0)	0 (0.0)
Edema	3 (1.0)	0 (0.0)
Infections and Infestations	72 (24.7)	72 (24.3)
Urinary tract infection	13 (4.5)	4 (1.4)
Upper respiratory tract infection	12 (4.1)	15 (5.1)
Nasopharyngitis	7 (2.4)	15 (5.1)
Pneumonia	7 (2.4)	9 (3.0)
Bronchitis	6 (2.1)	5 (1.7)
Cellulitis	4 (1.4)	4 (1.4)
Diabetic foot infection	4 (1.4)	0 (0.0)
Sinusitis	3 (1.0)	2 (0.7)
Arteriovenous fistula site infection	3 (1.0)	1 (0.3)
Injury, Poisoning, and Procedural Complications	129 (44.2)	125 (44.2)
Procedural hypotension	63 (21.6)	57 (19.3)
Arteriovenous fistula site complication	32 (11.0)	35 (11.8)
Arteriovenous fistula thrombosis	10 (3.4)	6 (2.0)
Arteriovenous fistula site hemorrhage	10 (3.4)	5 (1.7)
Contusion	8 (2.7)	6 (2.0)
Fall	7 (2.4)	5 (1.7)
Vascular graft complication	6 (2.1)	5 (1.7)
Procedural pain	6 (2.1)	3 (1.0)
Procedural dizziness	5 (1.7)	3 (1.0)
Wound	4 (1.4)	0 (0.0)
Arteriovenous graft site hemorrhage	3 (1.0)	3 (1.0)
Procedural nausea	3 (1.0)	3 (1.0)
Hemodialysis complication	3 (1.0)	2 (0.7)
Postoperative anemia	3 (1.0)	0 (0.0)
Metabolism and Nutrition Disorders	45 (15.4)	49 (16.6)
Fluid overload	14 (4.8)	21 (7.1)
Hyperkalemia	13 (4.5)	13 (4.4)
Hypoglycemia	7 (2.4)	8 (2.7)
Decreased appetite	3 (1.0)	4 (1.4)
Diabetic foot	3 (1.0)	2 (0.7)
Hypokalemia	3 (1.0)	1 (0.3)
Hyperlipidemia	2 (0.7)	3 (1.0)
Musculoskeletal and Connective Tissue Disorders	70 (24.0)	66 (22.3)
Muscle spasms	28 (9.6)	24 (8.1)
Pain in extremity	20 (6.8)	17 (5.7)
Back pain	13 (4.5)	10 (3.4)
Arthralgia	8 (2.7)	8 (2.7)
Musculoskeletal pain	3 (1.0)	4 (1.4)
Myalgia	3 (1.0)	2 (0.7)
Neck pain	3 (1.0)	2 (0.7)
Muscular weakness	3 (1.0)	0 (0.0)

Nervous System Disorders	63 (21.6)	45 (15.2)
Headache	27 (9.2)	16 (5.4)
Dizziness	22 (7.5)	21 (7.1)
Hypoesthesia	8 (2.7)	1 (0.3)
Syncope	4 (1.4)	5 (1.7)
Peripheral neuropathy	4 (1.4)	1 (0.3)
Psychiatric Disorders	12 (4.1)	20 (6.8)
Anxiety	3 (1.0)	6 (2.0)
Renal and Urinary Disorders	5 (1.7)	7 (2.4)
Dysuria	3 (1.0)	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	53 (18.2)	54 (18.2)
Cough	21 (7.2)	24 (8.1)
Dyspnea	17 (5.8)	13 (4.4)
Pulmonary edema	6 (2.1)	1 (0.3)
Productive cough	4 (1.4)	5 (1.7)
Epistaxis	4 (1.4)	3 (1.0)
Wheezing	4 (1.4)	2 (0.7)
Oropharyngeal pain	4 (1.4)	1 (0.3)
Pleural effusion	3 (1.0)	2 (0.7)
Exertional dyspnea	3 (1.0)	1 (0.3)
Asthma	3 (1.0)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	25 (8.6)	18 (6.1)
Pruritus	3 (1.0)	3 (1.0)
Rash	3 (1.0)	2 (0.7)
Vascular Disorders	33 (11.3)	23 (7.8)
Hypertension	9 (3.1)	8 (2.7)
Hypotension	8 (2.7)	5 (1.7)
Orthostatic hypotension	5 (1.7)	0 (0.0)

Reviewer's table

The TEAEs reported by ≥3% in the SFP group and reported at least 1% more commonly in the SFP group than in the placebo group based on system organ class are listed in the Table below.

Table 52. Common Adverse Events Reported ≥3% in SFP-Treated Subjects and >1% More Frequent in SFP-Treated Subjects by SOC

System organ class Preferred term	**SFP N=292 n (%)**	**Placebo N=296 n (%)**
Number of subject with at least one TEAE	229 (78.4)	223 (75.3)
General Disorders and Administration Site Conditions		
Peripheral edema	20 (6.8)	11 (3.7)

Pyrexia	13 (4.5)	9 (3.0)
Asthenia	12 (4.1)	9 (3.0)
Fatigue	11 (3.8)	6 (2.0)
Infections and Infestations		
Urinary tract infection	13 (4.5)	4 (1.4)
Injury, Poisoning, and Procedural Complications		
Procedural hypotension	63 (21.6)	57 (19.3)
Arteriovenous fistula thrombosis	10 (3.4)	6 (2.0)
Arteriovenous fistula site hemorrhage	10 (3.4)	5 (1.7)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	28 (9.6)	24 (8.1)
Pain in extremity	20 (6.8)	17 (5.7)
Back pain	13 (4.5)	10 (3.4)
Nervous System Disorders		
Headache	27 (9.2)	16 (5.4)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	17 (5.8)	13 (4.4)

Reviewer's table

The TEAEs reported ≥3% in the SFP group and reported more frequently in the SFP group as compared to the placebo group were procedural hypotension, muscle spasms, headache, dizziness, peripheral edema, pain in extremity, dyspnea, pyrexia, urinary tract infection, hyperkalemia, back pain, asthenia, fatigue, arteriovenous fistula site hemorrhage, arteriovenous fistula thrombosis, and hypertension. See Table below.

Table 53. TEAEs Reported ≥3% in the SFP-treated Subjects and Reported More in the SFP Group

System organ class Preferred term	**SFP N=292 n (%)**	**Placebo N=296 n (%)**
Procedural hypotension	63 (21.6)	57 (19.3)
Muscle spasms	28 (9.6)	24 (8.1)
Headache	27 (9.2)	16 (5.4)
Dizziness	22 (7.5)	21 (7.1)
Peripheral edema	20 (6.8)	11 (3.7)
Pain in extremity	20 (6.8)	17 (5.7)
Dyspnea	17 (5.8)	13 (4.4)
Pyrexia	13 (4.5)	9 (3.0)
Urinary tract infection	13 (4.5)	4 (1.4)
Hyperkalemia	13 (4.5)	13 (4.4)
Back pain	13 (4.5)	10 (3.4)
Asthenia	12 (4.1)	9 (3.0)
Fatigue	11 (3.8)	6 (2.0)
Arteriovenous fistula thrombosis	10 (3.4)	6 (2.0)
Arteriovenous fistula site hemorrhage	10 (3.4)	5 (1.7)

Hypertension	9 (3.1)	8 (2.7)

Reviewer's table

In all clinical trials in 1411 SFP-treated subjects, 1020 of 1411 (72.3%) experienced ≥1 TEAE. The most common TEAEs were procedural hypotension (20.3%), nausea (13.0%), diarrhea (12.5%), and arteriovenous fistula site complication (12.2%). The total number of subjects who experienced a treatment-related TEAE was 136 of 1411 subjects (9.6%). The most common treatment-related TEAEs were procedural hypotension (4.2%) and nausea (1.1%).

7.4.2 Laboratory Findings

Iron Parameters for Possible Iron Overload:

TSAT ≥50% or Serum Ferritin ≥1200 mcg/L

In the pooled Phase 3 trials, 42 (14.9%) subjects developed pre-dialysis TSAT ≥50% in the SFP group as compared to 18 (6.2%) in the placebo group in the randomized phase of the studies (see table below).

There were a few patients who developed pre-dialysis serum ferritin ≥1200 mcg/L in both treatment groups (1.3% in the SFP group and 3.1% in the placebo group) during the randomized phase of the studies.

Table 54. TSAT ≥50% or Serum Ferritin ≥1200 mcg/L in Phase 3 Studies

	SFP N=292 n (%)	**Placebo N=296 n (%)**
TSAT ≥50%	42/282 (14.9)	18/289 (6.2)
Ferritin ≥1200 mcg/L	4/282 (1.4)	9/289 (3.1)

Reviewer's table

Among subjects with TSAT ≥50%, only 6 subjects had their TSAT value confirmed by 2 consecutive values measured at any time within a 2-week period (3 each in the SFP and placebo groups). In 3 of those patients (2 in the SFP group and 1 in the placebo group), study drug administration was withheld per protocol. The remaining 3 patients (1 in the SFP group and 2 in the placebo group) continued study drug treatment (see Table below).

Among subjects with serum ferritin ≥1200 mcg/L, 5 subjects had their serum ferritin value confirmed by 2 consecutive values measured at any time within a 2-week period (1 in the SFP group and 4 in the placebo groups). In all 5 patients, study drug administration was withheld per protocol (see Table below).

Table 55. Subjects with Confirmed TSAT ≥50% or Serum Ferritin ≥1200 mcg/L in Pooled Phase 3 Studies

	SFP N=292 n (%)	Placebo N=296 n (%)
TSAT ≥50%	42/282 (14.9)	18/289 (6.2)
Confirmed by 2 consecutive values measured at any time within a 2-week period (per protocol)	3/282 (1.1)	3/289 (1.0)
Study drug administration was withheld (per protocol)[a]	2/282 (0.7)	1/289 (0.3)
Continued study drug treatment	1/282 (0.4)	2/289 (0.7)
Ferritin ≥1200 mcg/L	4/282 (1.4)	9/289 (3.1)
Confirmed by 2 consecutive values measured at any time within a 2-week period (per protocol)	1/282 (0.4)	4/289 (1.4)
Study drug administration was withheld (per protocol)[a]	1/282 (0.4)	4/489 (1.4)
Continued study drug treatment	0	0

[a] Defined for the purposes of this analysis as having >80% of study drug doses withheld starting within 28 days of the date of the 2nd consecutive value and ending 28 days after start of study drug withholding or at the last Stage 2 treatment period visit, whichever comes first. Withdrawal from Stage 2 within 28 days of the date of the 2nd consecutive value and not commencing Stage 3 study drug for 28 days after the last dose of study drug in Stage 2 was also counted as having had study drug withheld.
Reviewer's table

The frequency of treatment-emergent adverse events was analyzed by TSAT value and patients with TSAT ≥50% experienced slightly more overall events than those with TSAT<50% in both the SFP and the placebo groups. However, in patients with TSAT ≥50%, the frequency of events was similar between the SFP and the placebo group.

Table 56. Overall TEAEs by TSAT Value in Pooled Phase 3 Studies

	SFP		Placebo	
	TSAT≥50% N=42 n(%)	TSAT<50% N=240 n(%)	TSAT≥50% N=18 n(%)	TSAT<50% N=271 n(%)
TEAEs	35 (83.3%)	186 (77.5%)	16 (88.9%)	205 (75.6%)
TESAEs	12 (28.6%)	64 (26.7%)	7 (38.9%)	70 (25.8%)
Deaths	3 (7.1%)	8 (3.3%)	1 (5.6%)	4 (1.5%)
AEs leading to discontinuation	0 (0.0%)	11 (4.6%)	1 (5.6%)	6 (2.2%)

Sponsor's table submitted on 10/7/14

In all clinical trials in 1411 SFP-treated subjects, 291 (22.1%) subjects had at least one TSAT value ≥50% and 129 (9.7%) subjects had at least one serum ferritin value ≥1200 mcg/L.

Liver function tests

The reported laboratory abnormalities of ALT, AST and total bilirubin in pooled Phase 3 studies is relatively low and no differences were observed between the two groups.

Table 57. Abnormalities in AST, ALT and Total Bilirubin in Pooled Phase 3 Studies

	SFP N=264 n (%)	Placebo N=266 n (%)
ALT >2 x ULN	1 (0.4)	3 (1.1)
ALT >3 x ULN	0 (0.0)	3 (1.1)
AST >2 x ULN	2 (0.8)	4 (1.5)
AST >3 x ULN	1 (0.4)	0 (0.0)
Total bilirubin >2 x ULN	0 (0.0)	1 (0.4)

Reviewer's table

In all clinical trials in 1411 SFP-treated patients, the laboratory abnormalities of ALT, AST and total bilirubin is summarized in the Table below. The overall rate is also low and there were no subjects who met the laboratory criteria for Hy's Law (ALT > 3xULN and total bilirubin ≥ 2xULN).

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Table 58. Abnormalities in AST, ALT and Total Bilirubin in All Clinical Trials

	SFP N=1411 n (%)
ALT >2 x ULN	10/1306 (0.8)
ALT >3 x ULN	2/1306 (0.2)
AST >2 x ULN	17/1302 (1.3)
AST >3 x ULN	6/1302 (0.5)
Total bilirubin >2 x ULN	3/1306 (0.2)

Note: SFP-1 subjects are excluded from the denominators because normal ranges were not provided for that study.

Reviewer's table

Other chemistry laboratory tests

In Pooled phase 3 studies, mean clinical chemistry values at EoT were generally similar to baseline, with slight changes from baseline observed for most parameters; mean changes were similar between the SFP and placebo groups.

For the parameters of albumin, alkaline phosphatase, bilirubin, blood urea nitrogen (BUN), calcium, gamma glutamyl transferase (GGT), AST, ALT, and sodium, the proportion of subjects with PCS values was low at baseline, EoT, and at any time postbaseline, and was also similar between the SFP and placebo groups.

7.4.3 Vital Signs

Mean values for SBP and diastolic blood pressure (DBP) were lower post-dialysis compared with pre-dialysis; however, only slight changes were observed from baseline to EoT for pre-dialysis and from baseline to EoT for post-dialysis and changes observed were similar between the SFP and placebo treatment groups. Similar mean changes from baseline to EoT were observed for pulse, weight, and temperature. No notable trends were observed for changes in vital signs.

7.4.4 Electrocardiograms (ECGs)

A similar proportion of subjects had abnormal ECGs in the SFP and placebo groups at baseline and at EoT and no significant difference was found between the SFP and the placebo groups.

7.4.5 Special Safety Studies/Clinical Trials

Not performed.

7.4.6 Immunogenicity

Not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only one dose was studied in clinical trials.

7.5.2 Time Dependency for Adverse Events

In phase 3 trials, the treatment-emergent AEs by duration of exposure in the Phase 3 trials are shown in Table below. Overall, there was no significant difference in percentage of subjects who experienced any TEAE across the duration of exposure intervals in the SFP groups and in the placebo groups. The most common TEAEs in subjects are included in the summary table below. The rate of procedural hypotension reported increased with the duration of exposure in the SFP group. There was no notable trend observed for other events.

Table 59. TEAEs by Duration of Exposure in Pooled Phase 3 Studies

	SFP			Placebo		
	≤12 weeks N=292	>12 to <36 weeks N=182	≥36 weeks N=78	≤12 weeks N=196	>12 to <36 weeks N=199	≥36 weeks N=76
Number of subjects with ≥1 TEAE	196 (67.1)	127 (69.8)	48 (61.5)	192 (64.9)	134 (67.3)	35 (46.1)
Procedural hypotension	43 (14.7)	29 (15.9)	16 (20.5)	37 (12.5)	33 (16.6)	8 (10.5)
Arteriovenous fistula site complication	18 (6.2)	16 (8.8)	3 (3.8)	20 (6.8)	17 (8.5)	3 (3.9)
Headache	15 (5.1)	11 (6.0)	2 (2.6)	9 (3.0)	7 (3.5)	1 (1.3)
Diarrhea	13 (4.5)	9 (4.9)	4 (5.1)	18 (6.1)	11 (5.5)	2 (2.6)
Nausea	10 (3.4)	13 (7.1)	4 (5.1)	19 (6.4)	13 (6.5)	2 (2.6)

Reviewer's table

In all clinical trials in 1411 SFP-treated patients, treatment-emergent AEs by duration of exposure by PT are summarized in the Table below. The proportion of subjects who experienced any TEAE across the duration of exposure intervals was slightly higher for the 12 to <36 weeks (81.0%) and ≥36 weeks (80.0%) intervals compared to the ≤12 weeks interval (56.3%). Similarly, the rate of procedural hypotension reported increased with the duration of exposure.

Table 60. TEAEs by Duration of Exposure in SFP-treated Patients in All Clinical Trials

	Duration of Exposure		
	≤12 weeks N=1411	12 -35 weeks N=863	≥36 weeks N=571
Number of subjects with ≥1 TEAE	795 (56.3)	699 (81.0)	457 (80.0)
Procedural hypotension	151 (10.7)	163 (18.9)	117 (20.5)
Arteriovenous fistula site complication	74 (5.2)	74 (8.6)	56 (9.8)
Headache	59 (4.2)	89 (10.3)	74 (13.0)
Diarrhea	56 (4.0)	91 (10.5)	79 (13.8)
Nausea	76 (5.4)	78 (9.0)	69 (12.1)
Diarrhea	56 (4.0)	91 (10.5)	79 (13.8)

Reviewer's table

7.5.3 Drug-Demographic Interactions

No study was specifically conducted to evaluate drug-demographic interactions. The following are based on subgroup analyses from clinical trials.

Age

Most patients were <65 years of age (210 in the SFP group and 188 in the placebo group) in the safety population in pooled Phase 3 studies. There were 82 patients in the SFP group and 108 patients in the placebo group with age ≥65 years. The frequency of TEAEs was analyzed by age group (<65 years and ≥65 years). The proportion of subjects with age ≥65 years reported slightly more overall TEAEs than those with age <65 years in the SFP group [159 (75.7%) in <65 years and 70 (85.4%) in ≥65 years]. In the placebo group, there was a similar frequency of TEAEs reported for both age groups [141 (75%) in <65 years and 82 (75.9%) in ≥65 years].

Gender

Overall, the majority of subjects in the Phase 3 Studies were males [179 (61%) in the SFP group and 196 (66%) in the placebo group]. The overall incidence of TEAEs reported in the SFP group was slightly higher in the female subjects than in male subjects (male 77.1%, female 80.5%). Similarly, the overall incidence of TEAEs reported in the placebo group was also slightly higher in the female subjects than in the male subjects (male 71.9%, female 82.0%).

Race

The overall incidence of TEAEs reported in SFP-treated subjects was similar between Caucasian (79.2%) and non-Caucasian (77.5%). In the placebo group, the overall incidence of TEAEs was also similar in Caucasian (73.5%) and non-Caucasians (77.7%).

7.5.4 Drug-Disease Interactions

Drug-disease interaction studies were not conducted. No studies of SFP have been conducted in patients with moderate or severe hepatic impairment.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted for SFP.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity study was conducted.

7.6.2 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data are provided.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted for SFP. The applicant submitted a pediatric study plan and requested a deferral of pediatric studies between birth and 17 years to meet the requirements of Pediatric Research Equity Act (PREA). The proposed studies included one PK/PD study and one efficacy and safety study. The plan is currently under discussion.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No formal studies have been conducted to evaluate the abuse potential, withdrawal and rebound effect. Because this product will only be administered in dialysis centers by trained healthcare providers, the risk for abuse potential is likely to be low. No overdose was reported.

7.7 Additional Submissions / Safety Issues

The 120-day Safety Update was submitted on 8/1/2014 and the sponsor included additional safety analysis from recently completed three open-label extension safety studies (SFP-4-OL, SFP-5-OL, and SFP-6-OL). All results are incorporated in the safety review.

8. Postmarket Experience

SFP is not currently marketed outside of the U.S.

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

The following recommendations have been discussed in labeling meetings during the review.

1. Section 1 Indication and Usage
   - Revise the indication to: Triferic® is indicated for the treatment of iron loss in adult patients with hemodialysis-dependent chronic kidney disease (HDD-CKD).
   - (b) (4)
2. Section 2 Dosage and Administration
   - Revise to provide clear instruction for all steps involved in preparing Triferic in dialysis solution for use in clinical practice.

3. Section 5 Warnings and Precautions
   - Include 5.1 Hypersensitivity Reactions to add the following standard language as for other intravenous iron products as shown below:

     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. Monitor patients for signs and symptoms of hypersensitivity during and after and after hemodialysis (b) (4) until clinically stable. Personnel and therapies should be immediately available for the treatment of serious hypersensitivity reactions. [see Adverse Reactions (6)].

     Hypersensitivity reactions have been reported in 1 (0.3%) of 292 patients receiving Triferic® in two randomized clinical trials.

   - (b) (4)

4. Section 6 Adverse Reactions
   - Revise the text and table to be consistent with current labeling guidance to present adverse reactions by body system and frequency of reactions.
   - Refer Hypersensitivity Reactions to Section 5 Warnings and Precautions.
   - Revise adverse reactions leading to treatment discontinuation section to list all adverse reactions leading to treatment discontinuation observed in the clinical trials.
5. Section 8 Use in Specific Populations
   - Revise Pediatric Use and Geriatric Use section to be consistent with current guidance.

6. Section 10 Overdosage
   - Revise to be consistent with current guidance.

7. Section 14 Clinical Studies
   - Revise the text to provide demographics, study endpoint, treatment, and the percentage of patients who completed 48 weeks of the treatment.
   - Revise the efficacy Table to present results from the ITT population analysis.
   - Remove the (b) (4) for the secondary efficacy endpoints.
   - Remove the section describing the (b) (4)

9.3 Advisory Committee Meeting

An Oncologic Drugs Advisory Committee (ODAC) meeting was held on November 6, 2014 for this NDA submission. Two questions were discussed by the committee during the meeting:

1. *Do the efficacy and safety results in Studies SFP-4 and SFP-5 support a positive benefit/risk for use of ferric pyrophosphate to treat iron loss?*

   Vote Result: Yes: 8, No: 3, Abstain: 0

The majority of the committee members voted "yes." Those committee members who voted positively described confidence that the trial supported that ferric pyrophosphate was superior to placebo in the context of the trials and that it was effective in delivering iron to those patients. Many of the same members also acknowledged a somewhat artificial setting from the trial as compared to clinical practice, but cited comfort with the demonstrated safety profile of this agent and an unmet need for maintenance iron replacement in dialysis patients as supportive factors.

Those committee members who voted "no" described difficulty in translating the conclusions from the trials to clinical practice, given the differences in treatment in this setting. Individual committee members who voted negatively also stated concerns regarding appropriate dosing and the low rate of patients who completed the planned 48 week treatment duration.

2. *Considering the limitations of the NIH-FP-01 study, should additional studies be required to establish efficacy of ferric pyrophosphate for this claim? Discuss important aspects of trial design for studies to substantiate clinical benefit for this use.*

Committee members generally agreed that additional studies would be necessary to establish the efficacy of ferric pyrophosphate to reduce the prescribed dose of ESA. Committee members suggested that a larger trial would be necessary, and further stated that a double-blind, randomized structure would be appropriate. Another committee member emphasized that any additional trials should be designed to assess clinical endpoints, rather than laboratory measures.

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/s/

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12/19/2014

KATHY M ROBIE SUH
12/19/2014

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Date: October 17, 2014
Drug Name: soluble ferric pyrophosphate
NDA: 206317
Applicant: Rockwell Medical, Inc.
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Amy Chi, RPM, Division of Hematology Products
Subject: Consult regarding NDA 206317 for soluble ferric pyrophosphate

Background
Soluble ferric pyrophosphate (SFP; Triferic) is an iron compound in which iron (III) is covalently bound to pyrophosphate and citrate. SFP is added to the liquid bicarbonate used to generate dialysate. During hemodialysis, SFP diffuses across the dialysis membrane into the blood compartment, thus providing exogenous iron.

On March 24, 2014, Rockwell Medical, Inc. submitted NDA 206317for SFP for the "treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD)." The applicant has also proposed a claim related to a reduction in the dose of erythropoiesis stimulating agent (ESA) needed to maintain desired hemoglobin levels. NDA 206317 is currently under review in the Division of Hematology Products. The Division of Hematology Products requests that the Division of Cardiovascular and Renal Products examine the submitted clinical trials from a nephrology perspective and comment on the utility and anticipated clinical significance/impact of the product on hemodialysis practice and procedures. In addition, they have requested review of the draft labeling with particular attention to the proposed Dosage and Administration section.

Materials Reviewed
The following materials were reviewed:
1. Clinical Study Reports for SFP-4, SFP-5, SFP-6, and SFP-8
2. Integrated Summary of Efficacy and Integrated Summary of Safety
3. Mid-cycle clinical, statistical, and clinical pharmacology slides (*CLIN_NDA 206317 – Mid-Cycle Slides-3.ppt; STAT_midcycle_Triferic_1.ppt; Clin Pharm_NDA206319_Midcycle_Briefing_19aug2014.pptx*)
4. Applicant's draft labeling dated June 2014 and draft labeling with reviewer edits dated September 24, 2014
5. Clinical pharmacology review by Olanrewaju Okusanya dated April 28, 2014

Overview of Phase 3 Program
The applicant's phase 3 program included two phase 3 efficacy and safety trials (SFP-4 and SFP-5) and a short-term safety trial (SFP-6) (Table 1). Each of these trials has an ongoing open-label extension period (Table 2).

The phase 3 program was conducted in patients with chronic kidney disease on maintenance hemodialysis and evaluated a dose of 110 µg SFP-iron per liter of dialysate provided continuously during each dialysis treatment. The design of trials SFP-4 and SFP-5 is discussed further below; see the appendix for a discussion of trial SFP-6.

Table 1: Phase 3 trials submitted in support of efficacy and/or safety

Study	Design	Subjects	Planned Duration
SFP-4 (CRUISE 1)	Phase 3, randomized, single-blind (subject), parallel two-arm, placebo-controlled	SFP 152 Placebo 153	Up to 48 weeks
SFP-5 (CRUISE 2)	Phase 3, randomized, single-blind (subject), parallel two-arm, placebo-controlled	SFP 147 Placebo 147	Up to 48 weeks
SFP-6 (short-term safety)	Phase 3, randomized, double-blind, placebo-controlled, two-way crossover	718 (crossover)	5 weeks

Table 2: Ongoing open-label extension studies

Study	Subjects[1]	Planned Duration
SFP-4-OL (extension of CRUISE 1)	207	6-17 months[2]
SFP-5-OL (extension of CRUISE 2)	214	6-17 months[2]
SFP-6-OL (extension of short-term safety study)	310	48 weeks

[1]Subjects completing the randomized trial in both the SFP and placebo arms who met eligibility criteria could enroll in the open-label extension.
[2]Duration of open-label treatment depends on length of time patient remained in randomized component (SFP-4-RC, SFP-5-RC), to achieve a total duration of 18 months.

Other Trials Submitted in Support of Efficacy

In addition to the phase 3 trials, the applicant submitted the results of NIH-FP-01, an exploratory, phase 2, randomized, placebo-controlled, double-blind trial in patients with chronic kidney disease on hemodialysis with a Hb of ≥ 9.0 to ≤ 12 g/L to support a claim related to decreased ESA use. In this trial, eligible subjects were randomized to SFP or placebo for up to 36 weeks. IV iron and ESA dose could be adjusted after 4 weeks. The primary endpoint was a percent change in the average weekly ESA dose from baseline to end-of-treatment.

The applicant also conducted a phase 1 mass balance study (SFP-8) in 12 patients on hemodialysis to quantify iron transfer from the dialysate during a single dialysis treatment under varying conditions.

Design of Phase 3 Efficacy Trials (SFP-4 and SFP-5)

SFP-4-RC and SFP-5-RC were both multicenter, randomized, placebo-controlled, single-blind (patient) trials. SFP-4-RC was conducted in the United States while SFP-5-RC was conducted in the United States and Canada.

Key inclusion criteria for both trials included patients age ≥ 18 years undergoing chronic hemodialysis with mean hemoglobin (Hb) of ≥ 9.5 to ≤ 11.5 g/dL; transferrin saturation (TSAT) of ≥ 15% to ≤ 40%; serum ferritin of ≥ 200 to ≤ 800 µg/L; and stable dose of erythropoiesis stimulating agent (ESA) of epoetin alfa ≤ 45,000 U/week, darbepoetin alfa ≤ 200 µg/week, or continuous erythropoietin receptor activator (CERA) ≤ 400 µg/month during the run-in period; a urea reduction ratio of ≥ 65% or single-pool Kt/V ≥ 1.2 for thrice weekly dialysis or ≥ 0.9 for 4x weekly dialysis; and a dialyzer blood flow at the mid-point of dialysis averaged over 3 to 4 weeks of ≥ 250 mL/min. In addition, the patient must have received IV iron therapy between 6 months and 2 weeks prior to enrollment. Key exclusion criteria included administration of >800 mg IV iron during the 8 weeks prior to enrollment or any IV iron during the previous 2 weeks; a change in ESA dose of >35% in the previous 2 weeks; RBC or whole blood transfusion in the previous 12 weeks; and known active bleeding.

Reviewer's comment:
1. In chronic kidney disease, the diagnostic utility of serum ferritin and TSAT is believed to be poor for estimating iron stores or predicting a hemoglobin response to iron supplementation. According to clinical guidelines, there is little evidence available to define values below which iron supplementation is indicated. Regardless, current guidelines suggest a trial of iron supplementation if an increase in hemoglobin or a decrease in ESA dose is desired, and the TSAT is ≤ 30% and the ferritin is ≤ 500 ng/mL. This recommendation is primarily based on observations that, below these values, hemoglobin may increase with iron supplementation. The eligibility criteria would allow enrollment of patients who were "iron-replete" by these standards as well as patients with lower values who may have functional iron deficiency.

2. Per the current epoetin alfa label, the median maintenance dose necessary to maintain hemoglobin in clinical studies of dialysis patients was approximately 75 U/kg thrice weekly (15,750 U/week for a 70 kg patient) with 10% of patients receiving a dose of more than 200 U/kg thrice weekly (42,000 U/week for a 70 kg patient). The eligibility criteria would allow enrollment of patients who required a broad range of ESA doses.

Each trial was conducted in two stages:

- Stage 1: Run-in period of up to 4 weeks. Subjects either achieved a stable ESA dose or were considered a run-in failure
- Stage 2: Eligible subjects from Stage 1 were randomized 1:1 to receive SFP or placebo for up to 48 weeks, stratified by baseline Hb and ESA dose

Patients randomized to Stage 2 were eligible to transition to Stage 3 (SFP-4-OL, SFP-5-OL) if they were less than four weeks from completion of Stage 2 and had either completed 48 weeks of treatment or were withdrawn for protocol-mandated changes in ESA or iron dose (see below). The duration of Stage 3 could vary from 6 to 17 months based on the amount of time the patient remained in Stage 2, for a total duration of Stages 2 and 3 of 18 months.

Use of Erythropoiesis-Stimulating Agents and Iron

During Stage 1, no study drug was administered and oral or IV iron was not allowed. In Stage 2, no oral or IV iron was allowed. In addition, no changes were allowed to ESA product, dose, or route of administration. Early withdrawal from Stage 2 was mandated per protocol for the following:

ESA dose change:

- Hb < 9.0 g/dL or > 12.0 g/dL confirmed by repeat obtained ≥ 1 day and ≤ 2 weeks after the first
- Hb > 11.5 g/dL confirmed by ≥ 2 consecutive weekly measurements AND an increase in Hb by ≥ 1 g/dL over 4 weeks

IV iron administration:

- Ferritin < 100 µg/L over ≥ 1 week confirmed by ≥ 2 consecutive measurements

During Stage 3, no oral iron was allowed, intravenous iron was dosed per protocol, and ESA was administered per local practice.

Endpoints

The primary efficacy endpoint was the mean change in Hb from baseline to the end-of-treatment (EoT). End-of-treatment was defined as the last $1/6^{th}$ of the time in the randomized treatment period before the end of the study or early withdrawal, or a minimum of the last two post-baseline treatment period Hb values.

Key secondary endpoints included the mean change in Hb from baseline every 4 weeks and the mean percentage change in ferritin from baseline to end-of-treatment.

Results of phase 3 trials

Subject Disposition

It is not clear from the submission how many subjects entered the run-in period (Stage 1) or the reasons they were not eligible for randomization (Stage 2). Of the subjects who entered Stage 2, 80% of subjects withdrew prior to 48 weeks of treatment (Table 3). Most were withdrawn because of protocol-mandated changes in anemia management.

Table 3: Subject disposition (n[%])

	SFP-4-RC		SFP-5-RC		Total
	SFP (N=152)	**Placebo (N=153)**	**SFP (N=147)**	**Placebo (N=147)**	**(N=599)**
Received at least one dose of study drug	149 (98.0)	151 (98.7)	143(97.2)	145(98.6)	588 (98.2)
Completed 48 weeks	27 (17.8)	27 (17.6)	28 (19.0)	22 (15.0)	104 (17.4)
Withdrawn	120 (78.9)	123 (80.4)	119 (81.0)	125 (85.0)	495 (82.6)
Protocol-mandated change in anemia management prior to 48 weeks	69 (45.4)	82 (53.6)	68 (46.3)	90 (61.2)	309 (51.6)
ESA dose	65 (42.8)	69 (45.1)	65 (44.2)	69 (46.9)	268 (44.7)
IV iron	4 (2.6)	14 (9.2)	3 (2.0)	21 (14.3)	42 (7.0)
Non-protocol-mandated change in anemia management prior to 48 weeks	17 (11.2)	20 (13.1)	14 (9.5)	6 (4.1)	57 (9.5)
ESA dose	13 (8.6)	17 (11.1)	10 (6.8)	5 (3.4)	45 (7.5)
IV iron	6 (3.9)	5 (3.3)	4 (2.7)	1 (0.7)	16 (2.7)
RBC or whole blood transfusion	1 (0.7)	7 (4.6)	5 (3.4)	5 (3.4)	18 (3.0)
Adverse event	5 (3.3)	5 (3.3)	7 (4.8)	2 (1.4)	19 (3.2)
Died	5 (3.3)	3 (2.0)	7 (4.8)	3 (2.0)	16 (2.7)
Withdrew consent	10 (6.6)	3 (2.0)	1 (0.7)	5 (3.4)	19 (3.2)
Protocol violation	3 (2.0)	1 (0.7)	7 (4.8)	4 (2.7)	15 (2.5)
Lost to follow-up	1 (0.7)	0 (0.0)	0	0	1 (0.2)
Entered Stage 3 open-label extension	98 (64.5)	108 (70.6)	101 (68.7)	113 (76.9)	420 (70.0)

Source: Applicant, Clinical Study Reports for SFP-4-RC and SFP-5-RC, Table 3, 5; Integrated Summary of Efficacy, Table 6.

SFP subjects were more likely to be withdrawn for Hb >12 g/dL and less likely to be withdrawn for Hb <9 g/dL or ferritin <100 µg/L than placebo subjects (Table 4).

Table 4: Protocol-mandated changes in anemia management (n[%])

	SFP (N=299)	**Placebo (N=300)**	**Total (N=599)**
Overall	137 (45.8)	172 (57.3)	309 (51.6)
Hb >12 g/dL	73 (24.4)	53 (17.7)	126 (21.0)
Hb <9.0 g/dL	39 (13.0)	61 (20.3)	100 (16.7)
Ferritin <100 µg/L	11 (3.7)	44 (14.7)	55 (9.2)

Source: Applicant, Integrated Summary of Efficacy, Table 7.

Baseline Subject Characteristics

The baseline characteristics of subjects who received ≥ 1 dose of SFP and had ≥ 1 post-baseline Hb value (modified intent-to-treat population) are shown in Table 5. Key baseline characteristics were generally well balanced between treatment arms in both trials. Study subjects were anemic at baseline with a mean Hb of ~ 11 g/dL. Mean baseline ferritin was ~500 µg/L, mean TSAT was ~22-25%, and over 75% of subjects had received IV iron within the previous two months. The median epoetin equivalent dose was ~6,500 U/week.

Reviewer's comment: These summary statistics suggest that many subjects did not meet guideline criteria for absolute or functional iron deficiency at the time of study enrollment.

Over 98% of subjects were on thrice weekly dialysis with a mean dialysis duration of approximately 3.6 hours, mean mid-point blood flow rate of 420 mL/min, and mean dialysate flow rate 700 mL/min (not shown).

Table 5: Baseline subject characteristics (MITT[1])

	SFP-4-RC		SFP-5-RC	
	SFP (N=148[2])	**Placebo (N=151[2])**	**SFP (N=142[2])**	**Placebo (N=144[2])**
Age (mean[SD])	57 (13)	60 (13)	58 (13)	59 (14)
Male (n[%])	98 (66)	104 (69)	79 (56)	91 (63)
White (n[%])	81 (55)	84 (56)	72 (51)	81 (56)
Black (n[%])	50 (34)	46 (31)	61 (43)	53 (37)
Hemoglobin (g/dL) (mean[SD])	10.96 (0.6)	10.90 (0.6)	10.96 (0.6)	10.93 (0.6)
TSAT (%) (mean[SD])	25 (7)	22 (6)	25 (7)	23 (8)
Serum iron (µmol/L) (mean[SD])	12 (4)	11 (3)	12 (3)	11 (3)
Ferritin (µg/L) (mean[SD])	510 (194)	511 (210)	514 (201)	480 (202)
Any IV iron within last 2 months (n[%])	110 (74)	114 (76)	116 (82)	123 (85)
Total IV iron within last 2 months (mg) (mean[SD])	325 (241)	331 (240)	381 (224)	389 (295)
Prescribed weekly epoetin equivalent (U/week) (median [range])	6,000 (0 to 49,600)	6,600 (0 to 67,500)	6,900 (0 to 49,600)	7,200 (0 to 80,600)

Source: Applicant, Clinical Study Reports for SFP-4-RC and SFP-5-RC, Tables 6 , 8, 11, 13, 17, 18.
[1]MITT: Modified intent-to-treat population includes all randomized subjects receiving ≥ 1 dose SFP and having ≥ 1 post-baseline Hb value.
[2]N varies for individual baseline parameters because of missing data

Efficacy

Per the mid-cycle statistical review slides by Dr. Luo, both trials met their primary endpoint based on the intent-to-treat analysis of the change in hemoglobin from baseline to end-of-treatment using an ANCOVA model including baseline hemoglobin and ESA dose (Table 6).

Table 6: Primary efficacy analysis: Change in hemoglobin from baseline to the end-of-treatment (ITT)

	SFP-4-RC		SFP-5-RC	
ANCOVA	**SFP (N=152)**	**Placebo (N=153)**	**SFP (N=147)**	**Placebo (N=147)**
LS mean (SE) (g/dL)	0.06 (0.11)	-0.30 (0.11)	-0.04 (0.11)	-0.39 (0.11)
LS mean difference (SE) (g/dL)	0.35 (0.14); p=0.01		0.35 (0.14); p=0.01	

Source: Statistical mid-cycle presentation, slide 5.

Per the mid-cycle review slides by Dr. Luo, both trials also met their secondary efficacy endpoints. In the placebo arms of trials SFP-4 and SFP-5, hemoglobin fell by -0.39 and -0.45 g/dL, respectively, while mean hemoglobin remained relatively stable in the SFP arms (Table 7).

Table 7: Key secondary endpoints: change in hemoglobin and ferritin (MITT[1])

	SFP-4-RC			SFP-5-RC		
	SFP (N=148)	**Placebo (N=151)**	**P-value**	**SFP (N=143)**	**Placebo (N=145)**	**P-value**
Hb change from baseline (SD) (g/dL)	-0.04 (1.17)	-0.39 (1.25)	0.009	-0.09 (1.18)	-0.45 (1.17)	0.004
Ferritin change from baseline (SD) (ng/mL)	-72 (133)	-143 (188)	<0.001	-67(164)	-123 (270)	<0.001

Source: Statistical mid-cycle presentation, slide 6.
[1]MITT: Modified intent-to-treat population includes all randomized subjects receiving ≥ 1 dose SFP and having ≥ 1 post-baseline Hb value.

Reviewer's comment: Ferritin fell in the SFP arm of both trials, which suggests that SFP alone did not adequately replace ongoing iron losses.

Results of Study NIH-FP-01

According to the mid-cycle statistical review slides by Dr. Luo, in study NIH-FP-01, the prescribed dose of ESA decreased from baseline to the end of treatment in the SFP arm as compared with the placebo arm with a LS mean difference of -35.0 U/week (95% confidence interval of -69.1 to -0.8; p= 0.045). The LS mean difference in actual

ESA use between treatment arms was -31.1 U/week with a 95% confidence interval of -70.3 to 6.1 and a p-value of 0.098.

Reviewer's comment: Assuming this finding is reliable, the clinical significance of decreasing the mean prescribed ESA dose by 35 U/week is unclear.

Data Supporting the Amount of Iron Delivered

The applicant conducted a phase 1 mass balance study (SFP-8) in 12 patients on hemodialysis to quantify iron transfer from dialysate containing 2 μM (110 μg/L) SFP-iron during a single dialysis treatment under varying conditions: control dialysis (Treatment A: no SFP); reference dialysis (B: SFP, new membrane, blood flow ≥ 350 mL/min, dialysate flow ≥ 600 mL/min, and 37 mEq bicarbonate); dialyzer re-use (C); bicarbonate of 31 mEq/L (D), blood flow 250 mL/min and dialysate flow 400 mL/min (E); and polyarylethersulfone (PAES) membrane (F). There was wide variability in cumulative net iron delivery both within and between treatment conditions (Table 8). Iron delivery was the lowest with low blood and dialysate flow.

Table 8: Cumulative net iron delivery by treatment in micrograms

	Mean (SD)	**Median (range)**
Reference	692 (1,010)	348 (-296 to 3,320)
Dialyzer re-use	578 (1,380)	251 (-665 to 4,230)
Low bicarbonate	587 (994)	481 (-518 to 2,760)
Low flow	130 (594)	232 (-1,010 to 1,280)
PAES membrane	350 (1,940)	248 (-4,130 to 3,910)

Source: Applicant, Clinical Study Report SFP-8, Table 7.

Reviewer's comment: The applicant predicted that SFP would deliver between 1.9 and 15.4 mg of iron per dialysis session, which they believed would approximately match iron losses (see clinical pharmacology review by Olanrewaju Okusanya dated April 28, 2014). If our understanding of the results of SFP-8 is correct, assuming a patient is treated with the reference dialysis treatment and achieves the median cumulative net iron delivery of 348 μg/treatment, SFP treatment thrice weekly for a year would be expected to provide 54.3 mg of iron (i.e., 348 μg/treatment x 156 treatments/year). Hemodialysis patients are estimated to lose 1 to 2 grams of iron per year. In this case, SFP would contribute very little towards replacement of chronic losses. In comparison, a single dose of intravenous iron provides ≥ 100 mg of iron with a typical course of therapy delivering ≥ 1000 mg over days to weeks.

Safety

Overall, a total of 1,411 unique patients have been exposed to SFP in the phase 2/3 clinical development program. Of these, 725 subjects (51%) have had ≥ 24 weeks of exposure, and 229 subjects (16%) have had ≥ 52 weeks of exposure (Source: Applicant, Integrated Summary of Safety, Table 10). According to the applicant, a total of 346 patients have been exposed to SFP and 345 to placebo in the phase 2/3 randomized, controlled trials.

In the placebo-controlled phase 2/3 studies, there was a numerical imbalance in deaths (SFP 14 [4%] vs. placebo 9 [2.6%]). The causes of death in the SFP arm were seven cardiac arrests, two sudden deaths, one myocardial infarction, one bronchopneumonia, one cancer, and two unknown. There were a similar number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in the SFP and placebo arms of the two phase 3 trials (Table 9). More subjects in the SFP group discontinued study drug due to AEs. The most common AEs leading to discontinuation were cardiac (cardiac arrest, cardiac failure, cardio-respiratory arrest, and coronary artery disease.) and nervous system disorders (dizziness, headache, hypoxic-ischemic encephalopathy, and neuropathy peripheral) (Source: Applicant, Integrated Summary of Safety, Table 16).

Reviewer's comment: The majority of deaths were cardiac, which is not unexpected for the dialysis population. No deaths were attributed to hypersensitivity reactions, a safety concern seen with other IV products; however, the cases should be carefully reviewed.

Table 9: Subjects with adverse events (n[%])

	SFP (N=346)	Placebo (N=345)	All SFP (N=1,411)
Treatment-emergent adverse events	276 (79.8)	268(77.7)	962 (68.2)
Serious adverse events	95 (27.5)	98 (28.4)	396 (28.1)
Death	14 (4.0)	9 (2.6)	44 (3.1)
Adverse events leading to study discontinuation	17 (4.9)	8 (2.3)	45 (3.2)

Source: Applicant, Integrated Summary of Safety, Tables 11 and 12.

The following adverse events of particular interest have been identified by the applicant or primary review division, or are concerns with other agents in the pharmacologic class:

Vascular Access Thrombosis

Hemodialysis vascular access thrombotic events were defined as TEAEs having a MedDRA preferred term of arteriovenous fistula thrombosis, a lower level term of arteriovenous graft (AVF) thrombosis, or a lower level term of catheter thrombosis or thrombus in catheter where the thrombosis was known to be associated with the subjects hemodialysis access. AVF and AVG thrombosis, but not catheter thrombosis, was reported in a slightly higher proportion of subjects in the SFP arm than in the placebo arm.

Table 10: Thrombosis-related events (n[%])

	SFP (N=346)	Placebo (N=345)	All SFP (N=1,411)
Hemodialysis vascular access thrombotic events/ other thrombotic events	24 (6.9)	20 (5.8)	24 (8.8)
Arteriovenous fistula thrombosis	12 (3.5)	8 (2.3)	51 (3.6)
Arteriovenous graft thrombosis	7 (2.0)	5 (1.4)	37 (2.6)
Thrombosis in device	5 (1.4)	6 (1.7)	34 (2.4)

Source: Applicant, Integrated Summary of Safety, pages 75-76.

Reviewer's comment: The excess of vascular access thrombosis events in the SFP arm represents a small number of cases and it is unclear whether the finding is real. General risk factors for vascular access thrombosis include low access blood flow (e.g., fistula or graft stenosis, hypotension, hypovolemia, external compression) and hypercoagulability (e.g., increase in hemoglobin). It is possible that SFP could contribute to this risk by supporting hemoglobin levels.

Iron Overload

Iron deposition and overload is a potential safety concern with parenteral iron formulations. More subjects in the placebo group than the SFP group exceeded a ferritin of 1,200 µg/L and four subjects in the placebo group had an AST or ALT > 3 x ULN at any point post baseline compared with one subject in the SFP group compared to (Table 11).

Table 11: Laboratory values exceeding specified limits at any time post baseline (n[%])

	SFP (N=346)	Placebo (N=345)	All SFP (N=1,411)
Ferritin > 1200 µg/L	9/333 (2.7)	13/338 (3.8)	151/1,370 (11.0)
AST > 3 x ULN	1/314 (0.3)	0/314	5/1,349 (0.4)
ALT > 3 x ULN	0/314	3/314 (1.0)	1/1,352 (0.1)
Total Bilirubin > 2 mg/dL	0/314	1/314 (0.3)	8/1,353 (0.6)

Source: Applicant, Integrated Summary of Safety, Tables 47 and 56.

Reviewer's comment: It does not appear that subjects in the SFP treatment group developed iron overload or related liver abnormalities in the placebo-controlled trials. This is consistent with the efficacy analyses, which suggest that SFP alone did not adequately replace ongoing iron losses as evidenced by a decreasing ferritin. The trial data do not address the risk of iron overload in patients receiving supplemental iron through multiple sources,

since no oral or IV iron was allowed during the trials and patients requiring iron supplementation were withdrawn from SFP per protocol; however, given the amount of iron provided by SFP and the ability to monitor iron parameters and adjust other therapies accordingly, this may not be a significant issue.

Other Adverse Events of Interest

Intravenous iron has been associated with hypersensitivity reactions, infections, and cardiovascular events. A similar number of such events were reported in the SFP and placebo groups (Table 12).

Table 12: Adverse events of interest

	SFP (N=346)	**Placebo (N=345)**	**All SFP (N=1,411)**
Suspected hypersensitivity reactions	2 (0.6)	1 (0.3)	9 (0.6)
Procedural hypotension	80 (23.1)	77 (22.3)	241 (17.1)
Symptomatic	37 (10.7)	32 (9.3)	123 (8.7)
Requiring intervention	52 (15.0)	53 (15.4)	179 (12.7)
Infections and infestations[1]	26 (7.5)	29 (8.4)	127 (9.0)
Composite cardiovascular events[2]	29 (8.4)	35 (10.1)	121 (8.6)

Source: Applicant, Integrated Summary of Safety, Tables 18 and 19.

[1]Treatement-emergent adverse event with a MedDRA SOC of infections and infestations for which the subject was administered at least 3 doses of an IV antibiotic or a treatment emergent serious adverse event with a MedDRA SOC of infections and infestations.

[2] Includes death due to a cardiac cause, nonfatal myocardial infarction, congestive heart failure, ischemic cerebrovascular accident, and hospitalization due to a cardiac cause.

Consult Question

DHP would like DRCP to examine the efficacy and safety of Triferic in the submitted clinical trials for the proposed indications from a nephrologist's perspective and comment on the utility and any anticipated clinical significance/impact of this product on hemodialysis practice and procedures. In addition, they have requested review of the draft labeling with particular attention to the proposed Dosage and Administration section.

DCRP Response to Consult Questions:

Many patients on dialysis require regular supplemental iron because of chronic losses related to dialysis (e.g., blood remaining in the dialyzer and blood lines, frequent blood draws) and reduced iron absorption; therefore, exogenous iron is often administered. Although we cannot speak for the nephrology community, we believe that a drug that contributes in a meaningful way to replacing iron losses in dialysis patients has merit, even if it does not meet a patient's full replacement needs.

Data from the pivotal trials for SFP suggest that SFP was effective in providing exogenous iron and supporting hemoglobin levels in the trial population; however, we are having some difficulty reconciling the relatively small amount of iron delivered in SFP-8 with the clinical efficacy data from trials SFP-4 and SFP-5. If not already addressed, the review team should consider this issue further.

Although the trial data suggest that SFP can be used as an exogenous source of iron in patients on dialysis, it is also important to note that the dosing regimen did not adequately replace iron losses in study subjects. In both trials, mean ferritin levels decreased from baseline in both the SFP and placebo arms although to a lesser degree in the SFP arm (SFP-4: -72 vs. -143 ng/mL; SFP-5: -67 vs. -123 ng/mL). These data suggest that patients on SFP are likely to require additional sources of exogenous iron. Hence, if approved, we believe the product's label should indicate that patients are likely to require additional sources of iron. Since subjects in the trial could not receive oral or IV iron, it is difficult to characterize this need in the real world setting. Data from the ongoing open-label extension studies may provide additional insight into the need for supplemental iron. In addition, we believe the following analyses may be helpful (if not already conducted):

- *An analysis looking at the distribution of the change in iron parameters from baseline to end of treatment by treatment arm*
- *An analysis that looks at changes in iron parameters over time by treatment arm*

Regarding the Dosage and Administration section of the proposed label, we note that the current version instructs (b) (4) *There are different formulations of liquid and powder bicarbonate concentrate that are produced by different manufacturers. As we understand, Rockwell, the applicant, markets one of these products (SteriLyte Liquid Bicarbonate). There are also different dialysate proportioning systems (i.e., ratios for mixture of bicarbonate concentrate solution, acid concentrate solution, and water within the dialysis machine.) We recommend that you ask Rockwell to address the applicability of their current dosing instructions to the various bicarbonate sources and systems in use in the United States. Regarding the convention of gallons vs. liters, both units are commonly used when referring to dialysate volume; however, liters are generally used when referring to concentration (e.g., micrograms per liter).*

Other comments:

We note that the label proposes use as a treatment for iron deficiency anemia. The analyses that we reviewed suggest that SFP may not keep up with ongoing iron losses in patients, which suggests that the product may not contribute sufficient iron to be useful in treating patients with a true deficiency. If data are available in subjects with iron deficient anemia, we encourage you to conduct efficacy analyses in this subset (if not already conducted).

We recommend including information in labeling on the actual amount of iron that is delivered during a single dialysis session, such as data on net iron delivery from study SFP-8. We also believe it is important to include information on how dialysis conditions such as blood and dialysate flow may affect iron delivery. Again, we believe that data from SFP-8 and possibly additional analyses of the phase 3 trial data by baseline dialysis prescription could be used to address this issue.

Appendix

SFP-6 was a multicenter, randomized, placebo-controlled, double-blind, crossover safety study in patients with chronic kidney disease on hemodialysis conducted in the United States and Canada between 2011 and 2013. Key eligibility criteria included age ≥ 18 years undergoing chronic hemodialysis with stable mean predialysis Hb of ≥ 9.0 to ≤ 12.5 g/L, stable predialysis TSAT of ≥ 15% to ≤ 45%, and stable predialysis serum ferritin of ≥ 100 to ≤ 1200 μg/L. Eligible subjects were randomized 1:1 to treatment with SFP or placebo during weeks 1 and 2 (Treatment Period 1), followed by a 10 to 12 day washout period with standard dialysate, followed by the alternate treatment for weeks 4 and 5 (Treatment Period 2), followed by an additional week of standard dialysate. The primary objective was evaluation of safety.

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/s/

KIMBERLY A SMITH
10/17/2014

ALIZA M THOMPSON
10/17/2014

NORMAN L STOCKBRIDGE
10/17/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206317 **Applicant:** Rockwell Medical, Inc. **Stamp Date:** March 24, 2014

Drug Name: Triferic (Soluble Ferric Pyrophosphate) **NDA/BLA Type:** S-0000

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: RMTI-SFP-2 Study Title: A Dose Ranging Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) Versus Control in Subjects with ESRD Receiving Chronic Hemodialysis Sample Size: 136 Arms: SFP in the dialysate 50 µg iron/L; 100 µg iron/L; 120 µg iron/L, 150 µg iron/L, and placebo. Location in submission: 5.3.5.1. SFP-2 - STF-A Dose Ranging Study of Dialysate Containing Soluble Ferric	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N A	Comment
	Pyrophosphate (SFP) Versus Control in Subjects with ESRD Receiving Chronic Hemodialysis"				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: RMTI-SFP-4 Title: A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 1) Study Pivotal Study #2: RMTI-SFP-5 Title: A Randomized, Placebo-Controlled, Phase 3 Study of Dialysate Containing Soluble Ferric Pyrophosphate (SFP) in Chronic Kidney Disease Patients Receiving Hemodialysis: The Continuous Replacement Using Iron Soluble Equivalents (CRUISE 2) Study Indication: Treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD).	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		U. S. /Canada studies
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		x		
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N A	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse event dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		U. S. /Canada studies
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			Also see Statistical review
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			Also see Statistical review
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			Also see Statistical review
34.	Are all datasets to support the critical safety analyses available and complete?	x			Also see Statistical review

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N A	Comment
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			Also see Statistical review
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

NA.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- **For the proposed indication for reduction of the ESA and (b) (4) requirements in CKD 5HD patients, the submitted NIH-FP-01 study was an exploratory Phase 2 study and the results may not be adequate to support the indication.**
- **Provide detailed analysis (with dataset) for patients who withdrew from study due to "Protocol Mandated Changes in Anemia Management" for Studies RMTI-SFP-4 and RMTI-SFP-5. The analysis should be based on criteria defined in the protocol for ESA dose change (Hgb < 9.0 g/dL, Hg > 12.0 g/dL) and for IV iron administration (serum ferritin < 100 µg/L).**
- **Provide detailed analysis (with dataset) for patients who withdrew from study due to Non-protocol-mandated change in anemia management (ESA dose change, IV iron administration). The analysis should include detailed reasons for ESA dose change and for IV iron administration.**

Min Lu, M.D., M.P.H. /electronic signature/

Reviewing Medical Officer Date

Kathy Robie-Suh, M.D., Ph.D. /electronic signature/

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIN LU
05/16/2014

KATHY M ROBIE SUH
05/16/2014