CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206317Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA (SDN)	206317/000 (1)
Submission Date(s):	03/24/2014; 08/04/2014
Brand Name	TRIFERIC
Generic Name	Soluble Ferric Pyrophosphate
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OCP Division	Division of Clinical Pharmacology V
OND Division	Division of Hematology Products
Applicant	Rockwell Medical Inc.
Relevant IND(s)	51290
Submission Type; Code	Original-1 (Type 5- New Formulation or New Manufacturer)
PUDFA Date:	01/24/2015
Formulation; Strength(s)	Single Use ampoules (27.2 mg Fe/5 mL)
Indication	Treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD)

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1 EXECUTIVE SUMMARY

The Applicant seeks approval of TRIFERIC® (Soluble ferric pyrophosphate) 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). Soluble ferric pyrophosphate (SFP) is an iron-compound in which Fe^{3+} is bound to pyrophosphate and citrate and administered via dialysis. Iron is transferred from the dialysate to the blood compartment by diffusion across the dialyzer membrane over the duration of the hemodialysis treatment. The proposed dose is one vial (27.2mg Fe^{3+}/5 mL) per 2.5 gallon of liquid bicarbonate via hemodialysis to yield a hemodialysate containing iron (as SFP) at a concentration of 110 µg Fe/L.

The Clinical Pharmacology Section of the NDA is supported by 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. Dose-response analyses for effectiveness and safety using dose escalation data did not show any relationship between increasing the dose of SFP and an increase in the magnitude of change in hemoglobin (efficacy) or incidence of moderate to severe adverse events. Concentration-response analyses could not be performed because pharmacokinetic sampling was not performed in efficacy and safety studies.

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. In addition, renal or hepatic studies were not conducted as patients with chronic renal disease requiring hemodialysis are the target population and patients with significant hepatic impairment requiring dialysis are more likely to receive kidney transplant rather than maintained by chronic dialysis.

Recommendation

This NDA is acceptable from a clinical pharmacology perspective.

Drug Development Decision	**Acceptable to OCP?**			**Comment**
Overall	Yes ☒	No ☐	NA ☐	
Evidence of Effectiveness†	Yes ☒	No ☐	NA ☐	2 positive efficacy/safety trials
Proposed dose for general population	Yes ☒	No ☐	NA ☐	1 vial (27.2 mg Fe^{3+}/5 mL) in 2.5 gallons of bicarbonate dialysate
Proposed dose selection for others	Yes ☒	No ☐	NA ☐	No dose adjustments recommended
Pivotal BE	Yes ☐	No ☐	NA ☒	To-be-marketed formulation used for the 2 pivotal efficacy and safety studies and all studies contributing clinical pharmacology data to the package insert
Labeling	Yes ☒	No ☐	NA ☐	Revisions to be negotiated with applicant

†Clinical Pharmacology perspective: although dose-response was not apparent, SFP resulted in the maintenance of hemoglobin levels compared to placebo.

1.1 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The drug is an iron-product administered via dialysis. The dose–escalation trial showed a dose-dependent increase in the concentrations of serum iron for SFP doses of up to 100 µg Fe/L. At doses greater than 100 µg Fe/L, no remarkable increase in serum iron with an increase in dose was observed. The dose for the pivotal phase 3 trials was 1 vial (27.2mg Fe^{3+}/5 mL) in each 2.5 gallon of bicarbonate dialysate yielding hemodialysate iron concentration of 110 µg Fe/L. Dose-response evaluation did not show an increase in efficacy (change in hemoglobin) or moderate to severe adverse events with dose.

Absorbed iron is not metabolized or appreciably excreted, so SFP is not expected to be subject to drug interactions. As SFP is used to maintain plasma iron within a normal range, it is not expected to perpetrate drug interactions.

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 (b) (4) mg (range = (b) (4) 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 (b) (4) mL/min vs. (b) (4) mL/min) in the aforementioned study was estimated to be (b) (4) mg (range= (b) (4) mg). The other factors did not appear to remarkably impact the net iron delivered.

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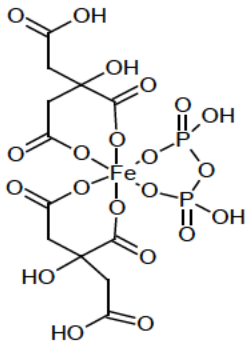
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Ferric pyrophosphate (SFP) has the following physical and chemical characteristics:

- Established name: Ferric pyrophosphate citrate
- Molecular Formula: $Fe_4(C_6H_5O_7)_3(P_2O_7)_3$
- Relative Molecular Mass: Approximately 1312.5 Daltons
- Chemical Name (CAS): 1,2,3-propanetricarboxylic acid, 2-hydroxy-, iron (3+), diphosphate
- Structural Formula:



Ferric pyrophosphate citrate is supplied as clear, green or greenish-yellow, sterile solution containing 5.44 mg Fe/mL in water (Water for Injection, USP). All clinical drug development was accomplished using the to-be-marketed formulation.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ferric pyrophosphate is an iron compound in which Fe^{3+} is bound to pyrophosphate and citrate. It is transferred from the dialysate to the blood compartment by diffusive transport across the dialyzer membrane over the duration of the hemodialysis treatment.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose of ferric pyrophosphate is one vial (27.2 mg Fe^{3+}/5 mL) per 2.1 to 2.5 gallon of liquid bicarbonate via hemodialysis to yield a hemodialysate containing iron (as SFP) at a concentration of 110 µg Fe/L.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

As shown in **Table 1**, several clinical trials were conducted in healthy volunteers and patients with chronic kidney disease on hemodialysis (CKD-HD). A total of three dose-ranging studies, of which two were conducted in patients with CKD-HD (SFP-1 and SFP-2) and one in healthy volunteers (SFP-9) were conducted. These three studies were intended to assess the dose-response characteristics of SFP. The impact of different dialysis conditions on the mass transfer of SFP-iron was studied in Study SFP-8.

To demonstrate the clinical efficacy of SFP, the applicant conducted two pivotal, randomized, single-blind, placebo-controlled Phase 3 studies (SFP-4 and SFP-5) in hemodialysis-dependent stage 5 chronic kidney disease (CKD-5HD) patients and one supportive double-blind placebo controlled study in CKD-5HD

patients (NIH-1). In these studies, 110 µg Fe/mL of SFP was administered via dialysate 3 to 4 times a week for up to 48 weeks.

Table 1. Clinical pharmacology and clinical trials conducted to support the marking approval of SFP

Study ID	Study Design	Study Objectives	Test Product Dose, Route, and Regimen	Patient Diagnosis
SFP-1	randomized, placebo-controlled, open-label, parallel dose escalation study	safety and pilot efficacy	SFP at 20, 40, 80, and 120 µg iron/L dialysate	CKD-HD
SFP-2	randomized, double-blind, parallel, placebo-controlled dose ranging study	safety and dose-ranging efficacy	SFP at 0, 50, 100, 120 and 150 µg iron/L for 26 wks	CKD-HD
SFP-3	randomized, double-blind, crossover, single-dose SFP_{GMP}[1], SFP_{FG}[2]	safety	SFP_{GMP} 130 µg iron/L dialysate SFP_{FG} 130 µg iron/L dialysate	CKD-HD
NIH-FP-01	randomized, double-blind, placebo-controlled, parallel-group study	efficacy and safety	SFP: 110 µg iron/L dialysate fixed dose 36 weeks	CKD-HD
SFP-4-RC	randomized, single-blind, placebo-controlled, parallel study	Pivotal efficacy and safety	SFP: 110 µg iron/L dialysate	CKD-HD
SFP-4-OL	open-label extension control: baseline from beginning of SFP-4-OL	Open-label safety		
SFP-5-RC	randomized, single-blind, placebo-controlled, parallel study	pivotal efficacy and safety	SFP: 110 µg iron/L dialysate	CKD-HD
SFP-5-OL	open-label extension control: baseline from beginning of SFP-5-OL	Safety		
SFP-8	randomized, placebo controlled, open-label, sequential treatment study	mass transfer of SFP-iron from dialysate	SFP: 110 µg iron /L dialysate	CKD-HD
SFP-9	randomized, double-blind, placebo-controlled, single, escalating dose study	PK of single IV doses of SFP	SFP 2.5, 5, 7.5, and 10.0 mg iron/4h and SFP 15 and 20 mg iron/12h via IV infusion	healthy volunteers

SFP_{GMP}: Dialysate used SFP manufactured using GMP standard (to-be-marketed formulation); SFP_{FG}: Dialysate used SFP manufactured using food-grade standard

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Iron supplementation typically results in an increase in serum iron, transferrin-bound iron, and iron stored in the form of ferritin in hepatocytes and macrophages. The available iron is typically used in the bone marrow for hemoglobin synthesis.

Efficacy Endpoint

The primary endpoint in the pivotal trials (SFP-4 and SFP-5) was the mean change in Hgb from baseline to the end of treatment (EofT) evaluated for the modified Intent-To-Treat (MITT) population by treatment group, based on an ANCOVA model with baseline Hgb as the covariate. EofT was defined as the last one-sixth of the time in the randomized treatment period per subject (approximately 8 weeks for those that completed the full course of the 26 week study). The demographic characteristics of the patients in these studies were similar for the SFP and placebo groups. Subjects were predominantly male (63.6%) and not Hispanic or Latino (65.0%). There were more subjects in the white racial category (54.4%) than in the other racial categories. The mean age of subjects was 58.4 years (range, 20 to 89 years). The majority of subjects (≥97.3%) received dialysis 3 times a week and the mean baseline prescribed erythropoietic-stimulating agent (ESA) weekly dose was similar between the SFP and placebo groups. As shown in **Table 2**, the applicant reports that at the EoT, the SFP groups had treatment differences in Hgb from placebo with lease squares (LS) mean values of 3.6 g/L that were statistically significant (p =0.011) in both placebo-controlled studies.

Table 2. Change from Baseline Hgb at EoT, Stage 2, MITT Population (Applicant's analysis)

	SFP-4-RC				SFP-5-RC			
	SFP N=148		Placebo N=151		SFP N=142		Placebo N=144	
	Timepoint Value	Change from Baseline	Timepoint Value	Change from Baseline	Timepoint Value	Change from Baseline	Timepoint Value	Change from Baseline
Baseline Hgb (g/L)								
n	148		151		142		144	
Mean (SD)	109.6 (5.91)		109.0 (6.36)		109.6 (6.09)		109.3 (6.25)	
EoT Hgb (g/L)								
n	147	147	150	150	141	141	143	143
Mean (SD)	109.1 (12.53)	-0.4 (11.67)	105.2 (13.65)	-3.9 (12.52)	108.7 (13.81)	-0.9 (11.76)	104.9 (13.33)	-4.5 (11.71)
ANCOVA with covariate of baseline Hgb								
LS mean (SE)[a]		0.6 (1.15)		-3.0 (1.14)		-0.5 (1.08)		-4.0 (1.09)
95% CI of LS mean		(-1.7, 2.8)		(-5.3, -0.8)		(-2.6, 1.7)		(-6.2, -1.9)
LS mean difference from placebo (SE)[a]		3.6 (1.40)				3.6 (1.39)		
95% CI of LS mean difference from placebo		(0.8, 6.3)				(0.8, 6.3)		
P-value[a]		0.011				0.011		

Abbreviations: ANCOVA = analysis of covariance, CI = confidence interval, EoT = end-of-treatment, ESA = erythropoiesis stimulating agent, Hgb = hemoglobin, LS = least squares, MITT = modified intent-to-treat.

[a] 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. Residuals from the model were examined and no transformation of the data is required.

The primary endpoint in the supportive trial, NIH-1, was the percent change from baseline in the prescribed ESA dose required to maintain Hgb in the target range at EofT evaluated for the MITT population by treatment group, based on an ANCOVA model with baseline Hgb as the covariate. In this study, the majority of the subjects were male (61.2%), White (61.2%), and not Hispanic or Latino (60.2%), with a mean age of 59.0 years (range of 25 to 93 years) and a mean post-dialysis body weight of 84.4 kg. The mean times at baseline since the last IV iron therapy and the last oral iron therapy were 9.85 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. The mean prescribed ESA dose in equivalent units of epoetin was 9345.9 U/week. As shown in **Table 3**, the applicant reports that at the EoT, the SFP cohort had statistically significant treatment differences in prescribed ESA dose from placebo with LS mean values of -35% (95% CI=-69.1, -0.8; p=0.045).

Table 3. Percent Change from Baseline Prescribed ESA Dose: MITT Population (Applicant's analysis)

	SFP (N=52)			Placebo (N=51)		
	Weekly Dose Value	Change from Baseline	Percent Change from Baseline	Weekly Dose Value	Change from Baseline	Percent Change from Baseline
Baseline prescribed ESA dose - equivalent units of epoetin (U/week)[a]						
n	52			51		
Mean (SD)	9483.2 (5413.86)			9205.9 (5500.05)		
End-of-Treatment prescribed ESA dose - equivalent units of epoetin (U/week)[a]						
n	52	52	52	51	51	51
Mean (SD)	9871.2 (7523.23)	387.9 (5556.24)	7.3 (67.66)	12628.8 (13967.36)	3422.9 (11641.90)	37.3 (106.09)
ANCOVA with Covariate of Baseline Hgb						
LS Mean (SE)[b]			4.9 (12.07)			39.8 (12.18)
95% CI of LS Mean			(-19.1, 28.8)			(15.7, 64.0)
LS Mean Difference from Placebo(SE)[b]			-35.0 (17.20)			
95% CI of LS Mean Difference from Placebo			(-69.1, -0.8)			
P-value[b]			0.045			

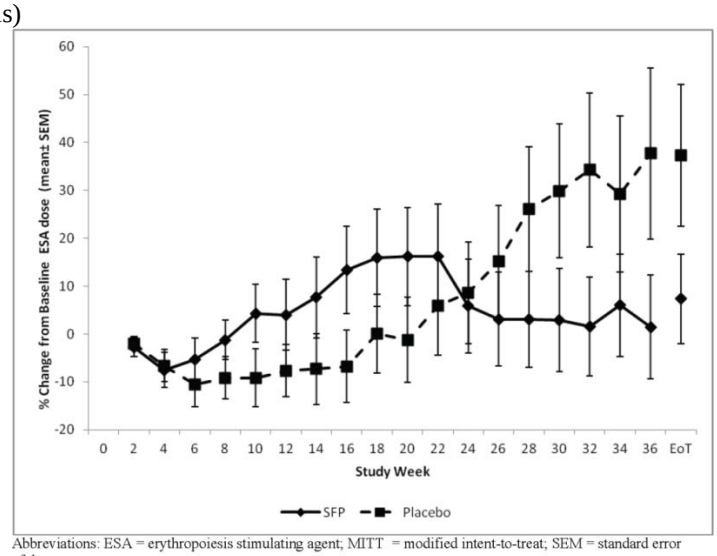
Abbreviations: ANCOVA = analysis of covariance; CI= confidence interval; ESA = erythropoiesis stimulating agent; Hgb= hemoglobin; LS= least squares; MITT = modified intent-to-treat

[a] Darbepoetin values were converted to equivalent units of epoetin using Table 4 of the Statistical Analysis Plan.

[b] 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 stratum.

However, as shown in **Figure 1**, these results are confounded by the fact that the placebo cohort required less ESA during the first 24 weeks of the study compared to the SFP cohort.

Figure 1. Percent Change from Baseline in Prescribed ESA Dose By Study Week: MITT Population (Applicant's analysis)



Abbreviations: ESA = erythropoiesis stimulating agent; MITT = modified intent-to-treat; SEM = standard error of the mean

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

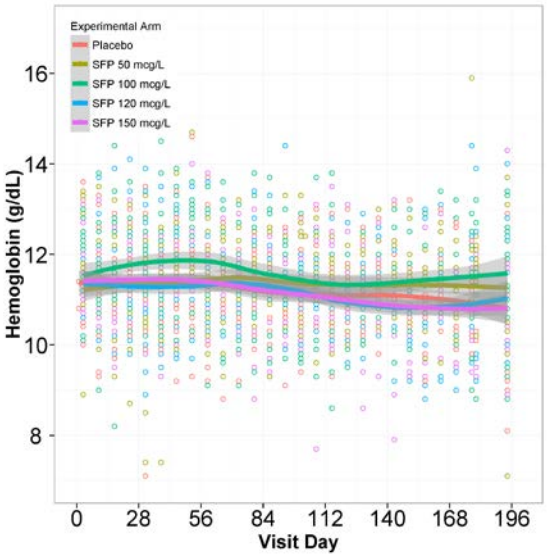
Yes. The applicant collected sufficient serum and dialysate samples from Study SFP-2, SFP-8, and SFP-9.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Exposure response relationships were not identified for SFP efficacy. Dose-response relationships were evaluated for SFP using data obtained from Study SFP-2. For Study SFP-2, dose-response analyses were conducted to determine if an increase in dose resulted in a corresponding change in Hgb. No exposure-or dose-response relationships were observed between dose and change in Hgb over time. As shown in **Figure 2**, the Hgb levels were higher for the SFP 100 µg Fe/L dose cohorts compared to the rest of the dosing cohorts.

Figure 2. Change in hemoglobin by dose with a loess smother through the data for Study SFP-2



2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Exposure-response relationships were not identified for safety. No dose-ranging data were obtained from the patients enrolled in the pivotal trials SFP-4 and SFP-5. However, during the Phase 2 clinical dose-ranging trial (SFP-2), moderate to severe adverse events were observed in all patients as shown in **Table 4** by dosing cohort. These events did not appear to be dose-related.

Table 4. Number of Moderate to Severe Adverse Events by Dosing Cohort in Study SFP-2

Dosing cohort	Safety population	% (n) of subjects with moderate to severe adverse events
Placebo	26	61.5 (16)
50 µFe/L	26	38.5 (10)
100 µFe/L	22	44.8 (13)
120 µFe/L	22	40.9 (9)
150 µFe/L	28	39.3 (11)

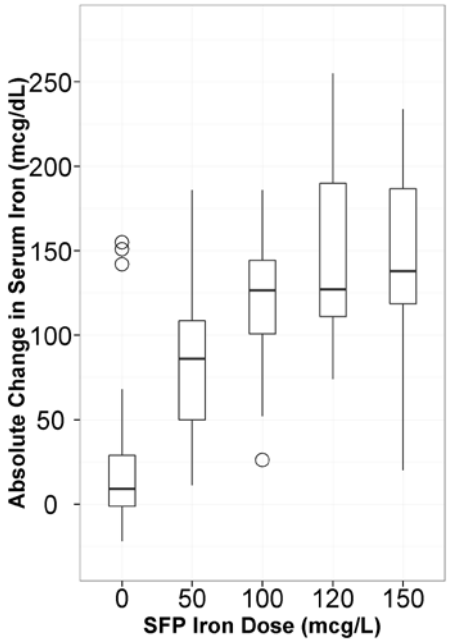
2.2.4.3 Does this drug prolong the QT or QTc interval?

The Interdisciplinary Review Team (IRT) for QT Studies evaluated the QTc data from SFP-2 and concluded that SFP did not cause large effects on QTc. IRT concluded that no further investigation on the effect of SFP on ECG intervals were required. The IRT review is available in DARRTS (IND 51,290, review of November 10, 2010 by M. Fiszman).

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

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. As shown in **Figure 3**, SFP 100 µg Fe/L or greater did not result in a markedly higher increase in serum iron. This supports the adequacy of the 110 µg Fe/L dose of SFP.

Figure 3. Absolute change in post-dialysis serum iron relative to pre-dialysis levels by SFP iron dose on week 1 visit 2.



2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

In study SFP-9, the serum iron profile (serum total iron, total iron-binding capacity [TIBC], and transferrin-bound iron [TBI]) of healthy subjects administered placebo, 2.5, 5, 7.5, or 10 mg Triferic as an intravenous infusion over 4 hours or 15 or 20 mg of Triferic intravenously over 12 hours were evaluated. The summary of the PK parameters for the total serum iron by dosing regimen is shown in **Table 5**. Multiple-doses of Triferic were not administered.

Table 5. Summary of the Total Serum Iron PK Parameters by Dosing Regimen (adapted from Applicant's table)

Parameter	4-Hour Infusion										12-Hour Infusion					
	0 mg		2.5 mg		5.0 mg		7.5 mg		10.0 mg		0 mg		15.0 mg		20.0 mg	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Tmax (hr)	8	-	6	-	6	-	6	-	6	-	4	-	6	-	6	-
Cmax (µg/dL)	8	196 (97.8)	6	278 (52.2)	6	316 (39.5)	6	453 (40.5)	6	376 (40.4)	4	175 (48.7)	6	299 (51.6)	6	361 (64.7)
Cmax/Dose (µg/dL/mg)	0	-	6	111 (20.9)	6	63.3 (7.9)	6	60.4 (5.4)	6	37.6 (4.04)	0	-	6	20 (3.44)	6	18 (3.23)
AUC_{0-4} (h*µg/dL)	8	655 (374)	6	897 (220)	6	991 (119)	6	1360 (189)	6	1050 (132)	4	625 (200)	6	796 (197)	6	866 (175)
AUC_{0-12} (h*µg/dL)	8	1880 (1070)	6	2530 (673)	6	2880 (385)	6	4120 (494)	6	3160 (381)	3	1670 (551)	6	3070 (625)	6	3530 (570)
AUC_{0-24} (h*µg/dL)	8	3310 (1860)	6	4150 (1220)	6	4660 (526)	6	6770 (769)	6	4330 (636)	3	2950 (1170)	6	5000 (1360)	6	5610 (1090)
AUC_{0-last} (h*µg/dL)	8	6500 (3680)	6	7740 (2650)	6	8640 (947)	6	11200 (1420)	6	6770 (1340)	4	5080 (2760)	6	7610 (2580)	6	7830 (1170)

Abbreviations: AUC_{0-4} = area under the curve from time 0 (predose) to 4 hours postdose, AUC_{0-12} = area under the curve from time 0 (predose) to 12 hours postdose, AUC_{0-24} = area under the curve from time 0 predose) to 24 hours postdose, AUC_{0-last} = area under the curve from time 0 (predose) through the last quantifiable concentration time, Cmax = maximum drug concentration, Tmax = observed time to reach maximum concentration.

As shown in **Figure 4**, the subjects that received placebo, the concentrations of serum iron observed over time displayed a circadian profile with consistent peaks and nadir. As such, the applicant conducted baseline correction for active and placebo treatments based on the observed concentrations at the -12, -6, and 0 hour pre-dose time points. PK parameter estimates with the baseline correction are shown in **Table 6**.

Figure 4. Change in total iron concentrations over time for healthy subjects administered placebo in Study SFP-9 (Applicant's Figure)

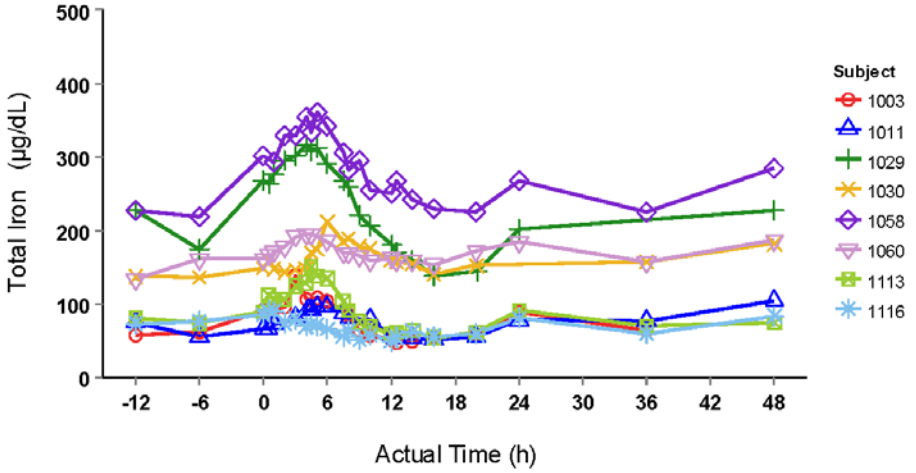


Table 6. Baseline-Corrected Total Serum Iron PK Parameters (adapted from Applicant's table)

Parameter	4-Hour Infusion					12-Hour Infusion		
	0 mg	2.5 mg	5.0 mg	7.5 mg	10.0 mg	0 mg	15.0 mg	20.0 mg
λz (1/hr)	-	0.544 (0.08)	0.668 (0.28)	0.711 (0.42)	0.917 (0.69)	-	0.475 (0.26)	0.337 (0.11)
T½ (hr)	-	1.3 (0.19)	1.19 (0.48)	1.29 (0.72)	1.04 (0.51)	-	1.87 (1.08)	2.21 (0.55)
CL (dL/hr)	-	4.06 (1.2)	5.11 (0.99)	4.59 (0.46)	5.56 (0.94)	-	6.72 (1.63)	6.61 (1.50)
Vz (dL)	-	7.65 (2.84)	8.43 (2.94)	8.59 (4.79)	8.33 (4.05)	-	16.6 (6.33)	20.8 (6.8)
Tmax (hr)	-	4.9	4.3	4.75	4.33	-	8.5	7.8
Cmax (µg/dL)	62.6 (32.4)	113 (44.5)	151 (33.9)	228 (19.7)	261 (30.3)	44.3 (34.8)	177 (38.2)	251 (51.7)
AUC_{0-4} (h•µg/dL)	126 (103)	235 (104)	329 (84.8)	471 (97.7)	590 (76.7)	107 (68.8)	305 (56)	426 (151)
AUC_{0-12} (h•µg/dL)	289 (235)	546 (312)	890 (258)	1420 (316)	1770 (222)	334 (412)	1590 (336)	2210 (402)
AUC_{0-last} (h•µg/dL)	340 (206)	579 (265)	903 (261)	1460 (340)	1820 (263)	277 (409)	2070 (639)	3000 (677)
$AUC_{0-\infty}$ (h•µg/dL)	-	675 (270)	1010 (190)	1650 (172)	1840 (263)	-	2340 (565)	3150 (657)

Abbreviations: AUC_{0-4} = area under the curve from time 0 (predose) to 4 hours postdose, AUC_{0-12} = area under the curve from time 0 (predose) to 12 hours postdose, $AUC_{0-\infty}$ = area under the curve from time 0 (predose) to infinity, AUC_{0-last} = area under the curve from time 0 (predose) through the last quantifiable concentration time, CL = clearance, Cmax = maximum drug concentration, λz = terminal phase rate constant, T½ = terminal phase half-life, Tmax = observed time to reach maximum concentration.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Due to PK assay problems, the PK of iron in dialysis patients was not determined. Thus, a comparison could not be conducted.

2.2.5.3 What are the characteristics of drug absorption?

Triferic is administered via the dialysate during hemodialysis.

2.2.5.4 What are the characteristics of drug distribution? (Include protein binding.)

Iron is not bound to serum albumin or globulins. Iron delivered via SFP is expected to bind to available human apotransferrin iron binding sites *in vivo*. The volume of distribution of SFP iron administered intravenously is shown in **Table 6**.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The applicant did not conduct a human ADME study.

2.2.5.6 What are the characteristics of drug metabolism?

Iron is not metabolized.

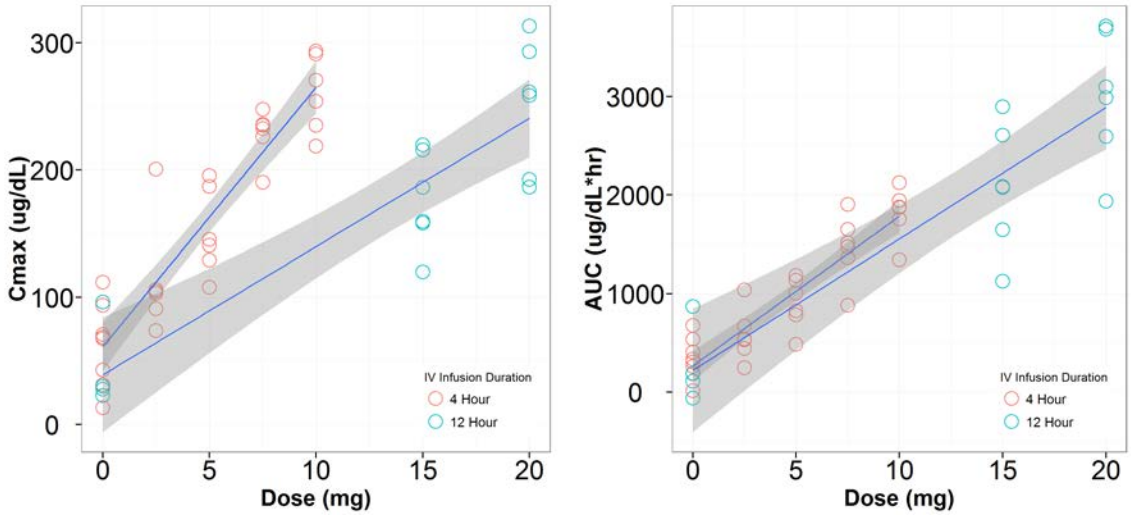
2.2.5.7 What are the characteristics of drug excretion?

No excretion studies were conducted by the applicant.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

As shown in **Figure 5**, the baseline corrected serum iron Cmax and AUC after the IV administration of Triferic over 4 or 12 hours increased in proportion to dose.

Figure 5. Dose-proportionality assessment of SFP using the baseline-corrected total serum iron data from a dose-escalation study in healthy subjects (Study SFP-9).



2.2.5.9 How do the PK parameters change with time following chronic dosing?

SFP is administered during dialysis, which can be conducted three to four times a week. Given that the half-life of serum iron after the administration of SFP is less than 3 hrs (see **Table 6**), these are multiple single doses. While not assessed, no changes in PK parameters are expected with time.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

See Question 2.2.5.1 for the serum iron PK parameter estimates in heathy subjects. Diurnal variation is a source of variability and correcting for it using the baseline values reduced the variability.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Neither PK sampling during the large clinical trials nor PK studies in specific populations were performed. Thus, the impact of intrinsic factors such as age, gender, race, weight, height, or organ dysfunction on serum iron after the administration of SFP was not be evaluated.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

Dosage regimen adjustments for SFP are not recommended for any specific population

2.3.2.1 Elderly

See responses to Questions 2.3.1 and 2.3.2.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

The applicant has not conducted clinical studies with SFP in pediatric patients. However, a pediatric development plan has been submitted for FDA review under the drug's original IND. The plan appears largely acceptable and the review team will be completing review of the plan prior to an action on the NDA.

2.3.2.3 Gender

See responses to Questions 2.3.1 and 2.3.2.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

See responses to Questions 2.3.1 and 2.3.2.

2.3.2.5 Renal impairment

The drug is intended for patients with chronic renal failure requiring hemodialysis. A renal impairment study is not needed.

2.3.2.6 Hepatic impairment

The applicant did not conduct a hepatic-impairment study. Patients with significant hepatic impairment that also require dialysis are more likely to receive kidney transplant than to be maintained on chronic hemodialysis and administered SFP.

2.3.2.7 What pregnancy and lactation use information is there in the application?

No pregnancy and lactation use information was provided in the application

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The applicant submitted Study SFP-8 which evaluated the impact of varying 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. In this study, enrolled subjects were assigned to 1 of 2 groups based on the type of dialyzer membrane used by each subject at screening: (b) (4) (Group 1; N = 6; cellulose triacetate membrane) or (b) (4) (Group 2; N = 6; polyamide membrane). Within each dialyzer membrane group, each subject was randomized to 1 of 6 treatment sequences shown in **Table 7**, to receive crossover study treatments during HD sessions so that every subject received dialysis using the (b) (4) membrane at least once.

Table 7. Treatment groups evaluated in Study SFP-9 (adapted from Applicant's Table)

Treatment	Description	SFP In Dialysate	Bicarbonate (mEq/L)	Dialyzer	Qb (mL/min)	Qd (mL/min)
A	Control	No	37 or 38	Standard (New)	(b) (4)	
B	Reference	Yes	37 or 38	Standard (New)		
C	Re-used Dialyzer	Yes	37 or 38	Standard (New)		
D	Low HCO3	Yes	31	Standard (New)		
E	Low Qb/Qd	Yes	37 or 38	Standard (New)		
F	PAES membrane	Yes	37 or 38	New		

Abbreviations: HD, hemodialysis; PAES, polyarylethersulfone; Qb, blood flow rate; Qd, dialysis flow rate

The cumulative net iron delivered by treatment and membrane type is shown in **Figure 6** as a boxplot and a tabular summary of the aforementioned data are shown in **Table 8**. The cumulative net iron delivered was calculated as shown in the equation below.

$$FeNet\ (\mu g) = (Qd\ L/min * td\ (min) * CFe\text{-}in\ \mu g/L) - VDt\ (L) * CFe\text{-}out\ \mu g/L)$$

Where

FeNet = Estimated net iron delivery

Qd = dialysate flow rate

td = Total dialysis time (or collection interval time, as appropriate)

CFe-in = Inflow concentration of SFP iron

VDt = Volume of expended dialysate during a collection interval

CFe-out = Concentration of SFP iron in pooled collection

The sponsor states that the positive values of cumulative iron delivery represent a net delivery of iron to systemic circulation and a negative value represent a net loss of iron from systemic circulation. The reviewer agrees with the sponsor, given that the cumulative net iron delivery is calculated by subtracting the amount of iron left in the dialysate after dialysis (VDt * CFe-out) from the amount of iron delivered to the body via the dialysate (Qd*td*CFe-in), and the extraction of iron from systemic circulation as well as blood loss resulting in the presence of iron from hemoglobin in the dialysate fluid may be reflected the net loss of iron. In addition, it is important to note that negative values may also be due, in part, to poor accuracy or precision in the volume of the dialysate collected and subtle changes in the dialysis flow rate which may result in a higher estimated amount of iron left in the dialysate and/or a lower amount of iron delivered to the body via the dialysate.

As shown in **Figure 6** and in **Table 8**, the net iron delivered was variable for each of the treatment groups. The reviewer finds that a lower amount of iron is delivered by low Qb/Qd compared to the reference.

Figure 6. Box-plots for the cumulative net iron delivered by treatment group (left panel) and by treatment group/dialyzer membrane (In the right panel, for each group of two, the left box is for polyamide, the right for triacetate).

Table 8. Cumulative Net Iron Delivery (mg) by Treatment and Membrane Type

Treatment	Dialyzer membrane	Summary Statistic (mg)						
		N	min	median	max	mean	sd	cv
Reference	Polyamide	6	(b) (4)					
	Triacetate	6						
	Both	12						
Re-used Dialyzer	Polyamide	6						
	Triacetate	6						
	Both	12						
Low HCO3	Polyamide	6						
	Triacetate	6						
	Both	12						

Table 8. Cumulative Net Iron Delivery (mg) by Treatment and Membrane Type

Treatment	Dialyzer membrane	Summary Statistic (mg)						
		N	min	median	max	mean	sd	cv
Low Qb/Qd	Polyamide	6						(b) (4)
	Triacetate	6						
	Both	12						
PAES membrane	Polyamide	5						
	Triacetate	6						
	Both	11						

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

No dosage regimen adjustments are recommended.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

In vitro metabolism studies were not performed. Iron is not metabolized. As SFP is used to maintain plasma iron within a normal range, SFP is not expected to perpetrate *in vivo* drug interactions.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

See Section 2.4.2.1

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

See Section 2.4.2.1

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No *in vitro* or *in vivo* studies evaluating the interaction of SFP and P-glycoprotein transport process were conducted. Based on the rationale given in response to Question 2.4.2.1 as well as a literature search by this reviewer, no interactions between iron and P-glycoprotein are expected.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No experiments were conducted in other metabolic or transporter systems. Based on the rationale given in the response to Question 2.4.2.1, no interactions are expected.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The label does not specify the co-administration of SFP with other drugs.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

IV iron, ESA, and heparin are likely to be administered to the target patient population during dialysis. However, no drug-drug interactions are expected. It is possible for the administration of IV iron to result in iron overload if the serum iron levels are not monitored.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no known mechanistic basis for PD drug-drug interactions.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None.

2.5 General Biopharmaceutics

SFP is formulated administration via dialysate during hemodialysis. As such, solubility, permeability and dissolution issues will not influence the exposure to SFP.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Given that SFP is expected to deliver iron during dialysis, the parameters measured in the clinical pharmacology and biopharmaceutics studies included dialysate iron, total serum iron, transferrin, transferrin bound iron (TBI), total iron binding capacity (TBIC).

2.6.2 Which metabolites have been selected for analysis and why?

As iron is elemental, it has no metabolites. No metabolites were identified for this drug

2.6.3 What bioanalytical methods are used to assess concentrations?

In Study SFP-8 and SFP-9, a bioanalytical method was developed and validated for the determination of serum total iron, TBI, and TIBC using a validated spectrophotometric assay. A summary of the analytical methods is provided in **Table 9**. For the determination of dialysate iron in Study SFP-8, a graphite furnace atomic absorption spectroscopic assay was developed with a LLOQ for dialysate iron of 5 µg/L and a range of 5 to 150 µg/L. Details of the analytical method are provided in **Table 9**.

Table 9. Summary of Bioanalytical methods for Total Iron from Clinical Studies

Method Validation	Corresponding Study	Matrix/ Analytes	Assay Performance description
(b) (4) 13-162	SFP-8	Serum/Total Iron	Lower limit of quantification: 20 µg/dL Linearity Range: 20 to 3500 µg/dL , QC Inter-day Precision Range (%CV): 2.2 to 10% QC Inter-day Accuracy Range (%RE): -6 to 6.8%
		Serum/Transferrin bound Iron	Lower limit of quantification: 20 µg/dL Linearity Range: 20 to 800 µg/dL , QC Inter-day Precision Range (%CV): 1.2 to 3.9% QC Inter-day Accuracy Range (%RE): 2.2 to 8.6%
(b) (4) 2619/0003	SFP-8	Dialysate/ Total Iron	Lower limit of quantification: 5 µg/L Linearity Range: 5 to 150 µg/L, QC Inter-day Precision Range (%CV): ≤ 9.37% QC Inter-day Accuracy Range (%RE): -2.68 to 2.14%
(b) (4) 13-163	SFP-9	Serum/Total Iron	Lower limit of quantification: 20 µg/dL Linearity Range: 20 to 3500 µg/dL , QC Inter-day Precision Range (%CV): 1.0 to 11.2% QC Inter-day Accuracy Range (%RE): -5.3 to 5.4%
		Serum/Transferrin bound Iron	Lower limit of quantification: 20 µg/dL Linearity Range: 20 to 800 µg/dL , QC Inter-day Precision Range (%CV): 0.6 to 5.4% QC Inter-day Accuracy Range (%RE): -3.4 to 13.2%

Serum iron values in the rest of the clinical studies were measured using either using a CLIA certified auto-analyzer method by [redacted] (b) (4) (Studies NIH-FP-01, SFP-3, SFP-4, SFP-5, SFP-6) or using the clinical laboratory at the investigative sites (Studies SFP-1 and SFP-2).

2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

See Section 2.6.3 above.

2.6.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Section 2.6.3 above.

2.6.6 What are the accuracy, precision, and selectivity at these limits?

See Section 2.6.3 above.

3 Detailed Labeling Recommendations

Only relevant clinical pharmacology sections are included. The Agency's suggested clinical pharmacology changes to the proposed labeling are shown in underline red text and removal of content shown by red strikethroughs. Of note, the Agency's labeling modifications have not been agreed upon by the Applicant as of the date of this review.

1.1 Limitation of Use

(b) (4)

[redacted]

12.3 Pharmacokinetics

The pharmacokinetics of serum iron (b) (4) was investigated in (b) (4) healthy volunteers (b) (4) administered (b) (4) -2.5, 5, 7.5 and 10 mg Triferic (b) (4) intravenously over 4 hours, or 15 mg and 20 mg Triferic® intravenously over 12 hours. After correcting for the basal iron levels, (b) (4) the AUC and C_{max} of baseline-corrected serum iron increased in a dose proportional manner. The half-life of serum iron was approximately 1.48 hours, the clearance ranged from 0.406 to 0.556 L/hour, the volume of distribution ranged from 0.765 to 8.59L after a 4 hour intravenous administration of Triferic®. (b) (4)

[redacted]

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix 2. OCP Filing Form

6 Pages Have Been Withheld As A Duplicate Copy Of The "OCP Filing Review Form" signed 05/23/2014 Which Is Located In This Clinical Pharmacology Review Section Of This NDA Approval Package.

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

/s/

OLANREWAJU OKUSANYA
12/11/2014

JEE E LEE
12/11/2014

GENE M WILLIAMS
12/11/2014
I concur with the recommendations.

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission			
NDA/BLA Number:	206317/S-0000	**SDN:**	1
Sponsor:	Rockwell Medical Inc	**Date of Submission**	24-March-2014
Brand Name:	Triferic®	**Generic Name:**	Soluble Ferric Pyrophosphate (SFP)
Drug Class:	Mixed-ligand iron compound		
Dosage Form:	Single use ampoules (27.2 mg Fe/5 mL)		
Dosing Regimen:	1 vial per 2.1 to 2.5 gallon of liquid bicarbonate		
Route of Administration:	Via Dialysis		
Indication:	Treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease (CKD 5HD)		
OCP Division:	DCP5	**OND Division:**	DHP
OCP Reviewer:	Olanrewaju O. Okusanya, Pharm.D, MS		
OCP Team Leader:	Julie M. Bullock, Pharm. D.		
PM Reviewer:			
PM Team Leader:			
GG Reviewer:			
GG Team Leader:			
Priority Classification:	☒ Standard ☐ Priority	**PDUFA Due Date**	24-Jan-2015
OCP Review Due Date:	27-Dec-2014	**OND Division Due Date:**	03-Jan-2015

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Critical Comments
Table of Contents present and sufficient to locate reports, tables, data, etc.	☒		
Tabular Listing of All Human Studies	☒		
Human PK Summary	☒		
Labeling	☒		
Bioanalytical and Analytical Methods	☒		Appendix 16.1.14 to Study SFP-8 for Dialysate Iron Content Appendix 16.1.14 to Study SFP-8 for total Iron and TBI in SFP-9
I. Clinical Pharmacology			
Mass balance:	☒	1	
Isozyme characterization:	☐		
Blood/plasma ratio:	☐		
Plasma protein binding:	☐		
Pharmacokinetics (e.g., Phase I) -	☐		
Healthy Volunteers:			
single dose:	☒	1	SFP-9
multiple dose:	☐		
Patients:			
single dose:	☐		
multiple dose:	☒	1	Dialysate Fe collected. No serum Fe assed due to assay problems
Dose proportionality -			
fasting / non-fasting single dose:	☒		SFP-9
fasting / non-fasting multiple dose:	☐		NA
Drug-drug interaction studies -			
In-vivo effects on primary drug:	☐		
In-vivo effects of primary drug:	☐		
Concomitant therapy:	☐		
In-vitro:	☐		
Subpopulation studies -			

ethnicity:	☐		
gender:	☐		
pediatrics:	☐		
geriatrics:	☐		
renal impairment:	☐		
hepatic impairment:	☐		
PD -			
Phase 2:	☒	2	
Phase 3:	☒	6	
PK/PD -			
Phase 1/2, proof of concept:	☒	2	SFP-1, SFP-2
Phase 3 clinical trial:	☒		
Population Analyses -			
Data rich:	☐		
Data sparse:	☐		
QT evaluation:	☐		
II. Biopharmaceutics			
Absolute bioavailability:	☐		NA
Relative bioavailability -			
solution as reference:	☐		NA
alternate formulation as reference:	☐		NA
Bioequivalence studies -			
traditional design:	☐		NA
replicate design:	☐		NA
Food-drug interaction studies:	☐		NA
Bio-waiver request based on BCS	☐		NA
BCS class	☐		NA
Alcohol induced dose-dumping	☐		NA
III. Other CPB Studies			
Genotype/phenotype studies	☐		
Chronopharmacokinetics	☐		
Pediatric development plan	☒		PSP submitted under NDA
Literature References	☒	63	
Total Number of Studies		9	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Study SFP-3 assessed safety between SFP_{FG} and SFG_{GMP}
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	iPSP Submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X		
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

Is the Clinical Pharmacology Section of the Application Fileable?

☒ **Yes**

☐ **No**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant:

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

Signatures:

Olanrewaju O. Okusanya, Pharm.D., M.S.
Reviewer
Division of Clinical Pharmacology 5

Julie M. Bullock, Pharm.D.
Team Leader
Division of Clinical Pharmacology 5

Clinical Pharmacology - NDA Filing Memo

NDA:	**206317/000 Original Submission IND: 51,290**
Compound:	**Soluble Ferric Pyrophosphate (Triferic®), Concentrate solution in water for delivery via bicarbonate-based hemodialysis solutions**
Sponsor:	**Rockwell Medical Inc.**
Filing Date:	
Reviewer:	**Olanrewaju O. Okusanya, Pharm.D., M.S.**

The sponsor proposes Triferic™ as an iron replacement product, delivered via hemodialysate, to compensate for the increased iron losses in Stage 5 chronic kidney disease patients receiving maintenance hemodialysis (CKD 5HD). Triferic™ Concentrate Solution for Hemodialysis is composed of Soluble Ferric Pyrophosphate (SFP), a mixed ligand iron compound in which iron (III) is covalently bound to pyrophosphate and citrate. The sponsor states that each 5 mL single use ampoule contains 27.2 mg elemental iron (5.44 mg iron/mL) in water for injection which when added to 2.5 gallons of liquid bicarbonate concentrate generates a hemodialysate with 110 µg or 2 µmoles of SFP-iron per liter of dialysate.

The sponsor is pursing the following indications:

- The treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with CKD 5H
- Reduce ESA and (b) (4) requirements in CKD 5 HD patients

The sponsor states that SFP is transferred from the dialysate to the blood compartment by diffusive transport across the dialyzer membrane over the entire three- to four hour HD treatment. The sponsor states that it is transferred across the dialyzer membrane to the patient at about 50% the rate of urea and other low MW solutes generating a slow, controlled infusion of SFP iron so as not to exceed the binding capacity of circulating transferrin.

Pharmacokinetics:
The PK of SFP were studied in healthy volunteers. The sponsor reported that serum iron concentrations in healthy volunteers demonstrated a diurnal variation; therefore baseline correction was conducted when reporting PK values. The sponsor reports the mean terminal phase half-life (t½) for the 4-hour SFP administered iron is approximately 1.2 hours and states that the rapid clearance likely reflects the removal of diferric transferrin via the transferrin receptor mediated pathway.

The sponsor also states that across all of the clinical studies, SFP at doses of 20 to 150 µg/L added to dialysate demonstrated a dose-proportional increase in incremental iron delivery pre to post HD up to a concentration of 110 µg/L and doses between 100 and 150 µg/L appear to saturate the delivery mechanism.

Pharmacodynamics:
The sponsor reports that SFP resulted in a net increase in the delivery of iron via the dialysate. The sponsor states that the SFP "dose" that will be transferred to a patient during a single 4-hour dialysis session will vary between patients and between dialysis sessions because it will be inversely related to the degree of transferrin saturation (TSat) at the start of the dialysis session and potentially range from a low of (b) (4)% ((b) (4) mg of SFP that contains (b) (4)% iron, equivalent to approximately (b) (4) mg of iron) to a maximum of (b) (4)% (b) (4) mg of SFP that contains (b) (4)% iron, equivalent to approximately (b) (4) mg of iron). The sponsor states that these iron amounts approximately match the ongoing loss of iron from residual blood in the dialyzer circuit at the termination of dialysis.

Safety:
The integrated safety of SFP was based on the following 2 study groupings:

- **CONT23**: This study grouping includes the 3 blinded, Phase 2/3, randomized, placebo-controlled studies (NIH-1 [subjects who enrolled 02 DEC 2010 and later], SFP-4-RC, and SFP-5-RC). This is the primary grouping being used to compare the safety profile of SFP to placebo.
- **ALL23**: This study grouping includes all subjects who received at least 1 dose of SFP (all formulations, all doses) in a Phase 2 or a Phase 3 blinded or OL study. Seven studies comprise this population (SFP-1, SFP-2, SFP-3, NIH-1, SFP-4, SFP-5 SFP-6); 3 of these studies have both a blinded and an OL treatment period (SFP-4-RC, SFP-4-OL, SFP-5-RC, SFP-5-OL, SFP-6-RC, SFP-6-OL). This group excludes subjects who did not receive SFP, and is used to present overall exposure to SFP. This grouping also includes the 6 NIH-1 study subjects who enrolled prior to 02 DEC 2010 and received SFP.

In the CONT23 study grouping, a total of 2029 TEAEs were reported in 276 subjects (79.8%) in the SFP group and a total of 2025 TEAEs were reported in 268 subjects (77.7%) in the placebo group. The 5 most common TEAEs, occurring in ≥9% of subjects in the SFP group, were procedural hypotension (23.4% for SFP and 22.3% for placebo), arteriovenous fistula site complication (10.1% for SFP and 12.2% for placebo), headache (9.8% for SFP and 7.0% for placebo), diarrhea (9.5% for SFP and 10.7% for placebo), and cough (9.0% for SFP and 7.8% for placebo). A summary of TEAEs occurring in ≥5% of subjects by preferred term (PT), sorted by decreasing frequency in the SFP group in the CONT23 study grouping is presented in **Table 1**.

Table 1. Summary of TEAEs Reported in ≥5% of SFP-treated Subjects by PT and Decreasing SFP Frequency: CONT23 Study Grouping

Preferred Term	SFP N=346	Placebo N=345
Total number of TEAEs	2029	2025
Number of subjects with ≥1 TEAE	276 (79.8)	268 (77.7)
Procedural hypotension	81 (23.4)	77 (22.3)
Arteriovenous fistula site complication	35 (10.1)	42 (12.2)
Headache	34 (9.8)	24 (7.0)
Diarrhoea	33 (9.5)	37 (10.7)
Cough	31 (9.0)	27 (7.8)
Nausea	30 (8.7)	36 (10.4)
Haemodialysis-induced symptom	29 (8.4)	19 (5.5)
Dizziness	26 (7.5)	26 (7.5)
Pain in extremity	24 (6.9)	24 (7.0)
Dyspnoea	23 (6.6)	18 (5.2)
Oedema peripheral	23 (6.6)	10 (2.9)
Vomiting	22 (6.4)	32 (9.3)
Fluid overload	21 (6.1)	27 (7.8)
Muscle spasms	18 (5.2)	20 (5.8)
Upper respiratory tract infection	18 (5.2)	19 (5.5)
Asthenia	18 (5.2)	11 (3.2)

One hundred and seventy three TESAEs occurred in 95 of 346 subjects (27.5%) in the SFP group and 200 TESAEs occurred in 98 of 345 subjects (28.4%) in the placebo group. The most common TESAEs occurring in the SFP group (occurring in ≥2% of SFP-treated subjects) were cardiac failure congestive (SFP: 2.3%; placebo: 2.6%), fluid overload (SFP: 2.3%; placebo: 4.6%), and pneumonia (SFP: 2.0%; placebo: 2.9%).

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/s/

OLANREWAJU OKUSANYA
05/21/2014

JULIE M BULLOCK
05/23/2014

Clinical Pharmacology Pediatric Submission Review

IND: 51,290	NDA: 206317	Submission Date: 03/24/14
SDN:	SDN: 1	
Product Name:	Soluble Ferric Pyrophosphate (SFP)	
Sponsor:	Rockwell Medical, Inc	
Submission Type:	☐ Proposed Pediatric Study Request (PPSR)	
	☐ Amendment to Written Request (WR)	
	☐ Pediatric Protocol Review	
	☒ Pediatric Study Plan	
Internal meeting date:	04/24/14	
PeRC meeting date:	04/30/14	
Pharmacometrics Reviewer/TL:		

This review is for a proposed Pediatric Study Plan (PSP) for soluble ferric pyrophosphate (SFP). The sponsor submitted a New Drug Application (NDA) for SFP for the chronic treatment of iron loss, maintenance of hemoglobin, and reduction of erythropoietin stimulating agents (ESA) use in adults who are hemodialysis-dependent due to chronic kidney disease.

BACKGROUND

The sponsor states that SFP is composed of Soluble Ferric Pyrophosphate (SFP), a mixed ligand iron compound in which iron (III) is covalently bound to pyrophosphate and citrate. Each 5 mL single use ampoule contains 27.2 mg elemental iron (5.44 mg iron/mL) in water for injection. It is intended as an iron replacement product, delivered via hemodialysate, to compensate for the increased iron losses in Stage 5 chronic kidney disease patients receiving maintenance hemodialysis (CKD 5HD).
In an NDA submitted 3/24/2014, the sponsor is pursing the following indications:

- The treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with CKD 5H
- Reduce ESA and (b) (4) requirements in CKD 5 HD patients

Adult Pharmacokinetics:

The PK of SFP were studied in healthy volunteers. The sponsor reported that serum iron concentrations in healthy volunteers demonstrated a diurnal variation; therefore baseline correction was conducted when reporting PK values. Baseline corrected concentrations of total serum iron parameters are presented in **Table 1**. The sponsor states that the rapid clearance likely reflects the removal of diferric transferrin via the transferrin receptor mediated pathway.

Table 1. Total Iron PK Parameters (Baseline Corrected Mean [SD]): SFP-9

Parameter	4-Hour Infusion					12-Hour Infusion		
	0 mg	2.5 mg	5.0 mg	7.5 mg	10.0 mg	0 mg	15.0 mg	20.0 mg
λz (1/hr)	-	0.544 (0.08)	0.668 (0.28)	0.711 (0.42)	0.917 (0.69)	-	0.475 (0.26)	0.337 (0.11)
T½ (hr)	-	1.3 (0.19)	1.19 (0.48)	1.29 (0.72)	1.04 (0.51)	-	1.87 (1.08)	2.21 (0.55)
Cl (dL/hr)	-	4.06 (1.2)	5.11 (0.99)	4.59 (0.46)	5.56 (0.94)	-	6.72 (1.63)	6.61 (1.50)
Tmax (hr)	-	4.9	4.3	4.75	4.33	-	8.5	7.8
Cmax (µg/dL)	62.6	113	151	228	261	44.3	177	251

	(32.4)	(44.5)	(33.9)	(19.7)	(30.3)	(34.8)	(38.2)	(51.7)
AUC_{0-4} (h*µg/dL)	126	235	329	471	590	107	305	426
	(103)	(104)	(84.8)	(97.7)	(76.7)	(68.8)	(56)	(151)
AUC_{0-12} (h*µg/dL)	289	546	890	1420	1770	334	1590	2210
	(235)	(312)	(258)	(316)	(222)	(412)	(336)	(402)
AUC_{0-last} (h*µg/dL)	340	579	903	1460	1820	277	2070	3000
	(206)	(265)	(261)	(340)	(263)	(409)	(639)	(677)
$AUC_{0-\infty}$ (h*µg/dL)	-	675	1010	1650	1840	-	2340	3150
		(270)	(190)	(172)	(263)		(565)	(657)

Abbreviations: AUC_{0-4} = area under the curve from time 0 (predose) to 4 hours postdose, AUC_{0-12} = area under the curve from time 0 (predose) to 12 hours postdose, $AUC_{0-\infty}$ = area under the curve from time 0 predose) to infinity, AUC_{0-last} = area under the curve from time 0 (predose) through the last quantifiable concentration time, Cl = clearance, Cmax = maximum drug concentration, λz = terminal phase rate constant, PK = pharmacokinetics, t½ = terminal phase half-life, Tmax = observed time to reach maximum concentration.

The sponsor also states that across all of the clinical studies, SFP at doses of 20 to 150 µg/L added to dialysate demonstrated a dose-proportional increase in incremental iron delivery pre to post HD up to a concentration of 110 µg/L. Doses between 100 and 150 µg/L appear to saturate the delivery mechanism.

Adult Pharmacodynamics:
The sponsor reports that SFP resulted in a net increase in the delivery of iron via the dialysate. The sponsor states that the SFP "dose" that will be transferred to a patient during a single 4-hour dialysis session will vary between patients and between dialysis sessions because it will be inversely related to the degree of transferrin saturation (TSat) at the start of the dialysis session and potentially range from a low of (b) (4)% ((b) (4)mg of SFP that contains (b) (4)% iron, equivalent to approximately (b) (4)mg of iron) to a maximum of (b) (4)% ((b) (4)mg of SFP that contains (b) (4)% iron, equivalent to approximately (b) (4)mg of iron). The sponsor states that these iron amounts approximately match the ongoing loss of iron from residual blood in the dialyzer circuit at the termination of dialysis.

Pediatric Pharmacokinetics:
No clinical studies in children have been conducted.

What is the relevant pediatric regulatory history?

- EOP2 meeting (June 30, 2010), the company was informed of the need to provide a pediatric plan with the recommendation that juvenile animal studies be performed, when appropriate, and included in the plan.

What has the sponsor provided in the submission?

- A PSP for SFP.

PEDIATRIC DEVELOPMENT PLAN
What types of studies has the sponsor proposed? Are any of the studies completed or on-going?

Study Type	Age Group	Type of Study	Comments	Status	Trial Start
Pediatric PK study	(b) (4)	Phase 1 PK study+ (b) (4)	(b) (4)	Deferral request planned	No later than Sept

		strata.	PK/PD endpoint		2015
Clinical Effectiveness and Safety Studies	(b) (4)			(b) (4)	
	(b) (4) <18 years	(b) (4)		Deferral request planned	No later than Sept 2018
		Safety and Efficacy Study			
Abbreviations: +PK = pharmacokinetics; PD = pharmacodynamics					

For the proposed studies submitted, what is the study design, objectives, and endpoints? For each of the studies; what dose and dosing regimen was proposed? Was a rationale provided?

Study 1: Pharmacokinetics of SFP iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis.

(b) (4)

Study 2: (b) (4)

(b) (4)

(b) (4)

[Reviewers' note: (b) (4)

What is the formulation that will be used in the pediatric trials? If it is an oral formulation; has adequate information been provided to administer to patients who cannot swallow tablets/capsules?

(b) (4)

What is the pediatric pharmacokinetic plan?

(b) (4)

In the proposed studies has the sponsor adequately addressed clinical pharmacology related safety issues (e.g., DDI's, organ impairment and dosing with food)?
Yes

If this is a Written Request (WR) amendment, what are the sponsors proposed changes?
Not applicable.

Clinical Pharmacology Comments:

Study 1: Pharmacokinetics of SFP iron delivered via dialysate in pediatric patients with chronic kidney disease on hemodialysis.

(b) (4)

Study 2: (b) (4)

(b) (4)

Action:
The Office of Clinical Pharmacology, Division of Clinical Pharmacology V, has reviewed this proposed PSP and has provided comments to be communicated to the sponsor.

Signatures:

Olanrewaju O. Okusanya, Pharm.D., MS Reviewer Division of Clinical Pharmacology 5	Julie Bullock, Pharm.D. Team Leader Division of Clinical Pharmacology 5

Cc: DHP: CSO - **A Chi;** MTL - **K Robie-Suh**; MO – **M Lu**
DCP-5: Reviewer – **O Okusanya;** TL – **JBullock** Deputy DD - **B Booth;** DD - **A Rahman**

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/s/

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04/24/2014

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04/28/2014