CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA #:	NDA 206317
Supplement #:	
Drug Name:	Triferic® (Soluble Ferric Pyrophosphate) Concentrate Solution for Administration via Hemodialysis Dialysate;
Indication(s):	Iron replacement therapy for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with hemodialysis-dependent stage 5 chronic kidney disease.
Applicant:	Rockwell Medical, Inc.
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Keywords:
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EXECUTIVE SUMMARY

Triferic ("soluble ferric pyrophosphate"; SFP) is submitted for approval as a parenteral iron agent for use in the chronic treatment of iron loss, maintenance of hemoglobin (Hgb), and reduction of erythropoiesis stimulating agent (ESA) use in adults with hemodialysis-dependent chronic kidney disease (HDD-CKD).

The primary efficacy endpoint was the change in mean Hgb from baseline to the end of treatment (EoT) period (last one-sixth of the randomized treatment period). In Study SFP-4-RC, the mean Hgb decreased 0.03 g/dL in the SFP group as compared to 0.38 g/dL in the placebo group in the intent-to-treat (ITT) population. In Study SFP-5-RC, the mean Hgb decreased 0.09 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 analysis of covariance (ANCOVA) model with baseline Hgb as the covariate. The treatment difference in Hgb calculated as least square (LS) mean difference was 0.35 g/dL between the SFP and the placebo groups in both studies and was statistically significant with a p value of 0.01. The results of sensitivity analyses and key secondary endpoints (mean change from baseline in ferritin, reticulocyte Hgb content (CHr), and transferrin saturation (TSAT)) appear to be supportive of the results from the primary efficacy analysis in both studies. Due to the concern of early treatment discontinuation, differential reasons of early discontinuation and the results represent various time values, whether or not Triferic can sufficiently provide maintenance of Hgb level cannot be confirmed.

The submission also includes a Phase 2 study (NIH-FP-01) to support a labeling statement for reduction of erythropoiesis stimulating agent (ESA) in these patients. One hundred and eight iron-replete patients with HDD-CKD patients were randomized to the study. 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 EoT. The results showed that the subjects receiving SFP had a mean increase of 5% in prescribed ESA dose at the EoT as compared to a mean increase of 37.3% in the placebo group (nominal p=0.052). However, 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 (nominal p=0.111). Both results had nominal P values of greater than 0.05. Based on the study results, this statistical review cannot confirm that Triferic reduces the prescribed dose of ESA required to maintain desired Hgb levels because the study was exploratory in nature, no formal sample size or power calculations planned and difficulties in the interpretation of the efficacy of Triferic over the placebo at the EoT due to the cross-over of the prescribed ESA dose levels between treatment groups.

In summary, this statistical review confirms the improvement of the mean change from baseline in Hgb level in favor of the Triferic treated group. However, the data did not support the treatment of iron loss or reduction of ESA use. Whether the positive results of mean change from baseline in Hgb level is beneficial for the HDD-CKD patient population and whether the results have a favorable benefit to risk ratio to support an approval of Triferic will be deferred to clinical judgment.

Of note, this application was discussed at the Oncologic Drugs Advisory Committee (ODAC) meeting on Nov 6th, 2014. The committee voted 8 to 3 in favor of Triferic.

1 INTRODUCTION

1.1 Background

The sponsor has developed Triferic for use in the chronic treatment of iron loss, maintenance of Hgb, and reduction of ESA use in adults who are HDD-CKD. As rationale for product development the sponsor states that the administration of iron via dialysate approach "is intended to provide a slow, measured, continuous transfer of iron to the patient in contrast to the more intermittent bolus delivery used with IV macromolecular iron complexes." The sponsor states the following in the Indications section of the proposed labeling:

> "Triferic® is a sterile concentrate solution in water for reconstitution in the bicarbonate concentrate component of the hemodialysis solutions. Triferic® provides bioavailable iron 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).
>
> Triferic® has been shown to reduce the prescribed dose of erythropoiesis stimulating agent (ESA) required to maintain desired hemoglobin levels. An average dose reduction of 35% in ESA requirement was observed compared to placebo in a single well-controlled study. Doses of ESA should be titrated accordingly."

1.2 Statistical Analysis Plan Critical Amendments

In SFP-4-RC, first subject was enrolled in the randomized treatment phase (Please see Figure 1 in section 2.2.1.1) on April 25, 2011 and last subject completed on May 24, 2013. The statistical analysis plan (SAP) was finalized on May 14, 2013. In SFP-5-RC, first subject was enrolled in the randomized treatment phase on June 15, 2011 and last subject completed on July 19, 2013. The statistical analysis plan was finalized on May 14, 2013.

Some important protocol /SAP amendments for both studies are summarized below:

- The design of randomized treatment phase of the study was changed from double-blinded to single-blinded (only the study subjects were blinded to treatment assignment).
- The description of the interim analysis for sample size confirmation was updated to confirm the absence of unblinded interim analyses of efficacy.
- The protocol-mandated change in anemia management thresholds were changed from Hgb <90 g/L or >125 g/L to Hgb <90 g/L or >120 g/L. Also, the confirmation of high/low Hgb thresholds 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."

- Primary analysis population was changed from ITT (intent-to-treat) to MITT (modified intent-to-treat, will be defined later) because some subjects did not receive any study drug after randomization.

- The analysis of the primary efficacy endpoint was updated from an ANCOVA model adjusting for stratification of both baseline Hgb and prescribed ESA dose to an ANCOVA model adjusting for stratification of baseline prescribed ESA dose, with baseline Hgb as a covariate.

- Analyzing the secondary efficacy endpoints in a sequential manner was later felt unnecessary and was removed.

- The endpoints "the mean change and mean percentage change in pre-dialysis CHr, serum iron, unsaturated iron binding capacity (UIBC), transferrin, and $TSAT_{UIBC}$(serum iron (μg/dL)/$TIBC_{UIBC}$ (μg/dL) x 100; and TIBC =serum iron + UIBC (unsaturated iron binding capacity)) from baseline every 4 weeks and at EoT" and "the mean change from pre-dialysis to post-dialysis in serum iron, UIBC and $TSAT_{transferrin}$ (serum iron divided by TIBCtransferrin) over the course of the randomized treatment period" were added as secondary endpoints.

NIH-FP:
First subject was enrolled on January 31, 2011 and last subject completed randomized phase on January 10, 2013. The statistical analysis plan was finalized on January 28, 2013. Some important protocol /SAP amendments are summarized in the following.

- The target range for maintaining Hgb was changed to 95 - 115 g/L in study design taking into consideration the newer guidance regarding acceptable Hgb levels.

- The primary analysis of primary efficacy endpoint was changed to adjust for baseline Hgb, rather than change from baseline in Hgb, to avoid adjusting for treatment related variables.

- The alternative analyses of ESA changes over 4-week intervals was changed to descriptive only.

- Other alternative analyses of primary endpoint was removed to reduce number of comparisons /multiple testing.

- Applied modifications to statistical analysis to account for simplification of secondary endpoints and simplifying analyses in general.

- A planned confirmatory analysis of the primary endpoint, an ANCOVA model would be applied to the percent change from baseline in the mean weekly ESA dose with the treatment group as the main effect and the change from baseline Hgb as a covariate, was removed because the change from baseline Hgb is an outcome and treatment related, thus, should not be included as a covariate in an ANCOVA model.

- The summary of percent change in ESA dose was changed from four-week to two-week to be consistent with the Hgb changes.

1.3 Clinical Studies

To support the proposed indication for the treatment of iron loss or iron deficiency to maintain hemoglobin in adult patients with HDD-CKD, the sponsor has submitted 2 pivotal randomized, single-blind, placebo-controlled, parallel group studies of essentially the same design (SFP-4-RC and SFP-5-RC), each with an open-label extension following the randomized treatment period. To support labeling to reduce the prescribed dose of ESA required maintaining desired Hgb level, the sponsor submitted one Phase 2 trial (NIH-FP-01). The major study design characteristics of these studies are summarized in Table 1.

Table 1 Overview of the Studies

Study Name	Study Description	Treatment Groups	No. of Subjects
SFP-4-RC	A multicenter, randomized (1:1), single-blinded (only the study patients were blinded to treatment assignment), placebo-controlled, phase III study to evaluate the efficacy and safety of SFP in adult patients with hemodialysis-dependent CKD (HDD-CKD).	**Treatment A**: SFP in dialysate at 2 µM (11 µg iron/dL of dialysate) **Treatment B:** Placebo (standard dialysate without SFP)	Randomized 305 subjects from 43 sites in U.S. SFP: 152 (67.1% Male) Placebo: 153 (68.6% Male)
SFP-5-RC	A multicenter, randomized (1:1), single-blinded (only the study patients were blinded to treatment assignment), placebo-controlled, phase III study to evaluate the efficacy and safety of SFP in adult patients with hemodialysis-dependent CKD (HDD-CKD).	**Treatment A**: SFP in dialysate at 2 µM (11 µg iron/dL of dialysate) **Treatment B:** Placebo (standard dialysate without SFP)	Randomized 294 subjects from 41 sites in U.S. and 2 sites in Canada. SFP: 147 (55.8% Male) Placebo: 147 (63.3% Male)
NIH-FP-01	A multicenter, randomized, placebo-controlled, double-blinded, phase II trial to evaluate the safety and efficacy of SFP via hemodialysate in patients with HDD-CKD.	**Treatment A**: SFP in dialysate at 2 µM (11 µg iron/dL of dialysate) **Treatment B:** Placebo (standard dialysate without SFP)	Randomized 108 subjects. SFP: 54 (57.4% Male) Placebo: 54 (66.7% Male)

1.4 Data Sources

Reviewed data were provided electronically with the standard analysis data formats. SAS programs used to create key efficacy and safety outputs for the pivotal studies SFP-4-RC, SFP-5-RC and NIH-FP-01 were submitted electronically with this application.

The path to the CDER Electronic Document Room (EDR) to store the data is:
\\Cdsesub1\evsprod\NDA206317\0000\m5\datasets

2 STATISTICAL EVALUATION

2.1 Data and Analysis Quality

Data from the pivotal studies SFP-4-RC, SFP-5-RC and the phase 2 NIH-FP-01study were provided with SDTM and ADaM. Documentations on datasets and programming for the key study endpoints were included with sufficient details for verifications.

2.2 Evaluation of Efficacy

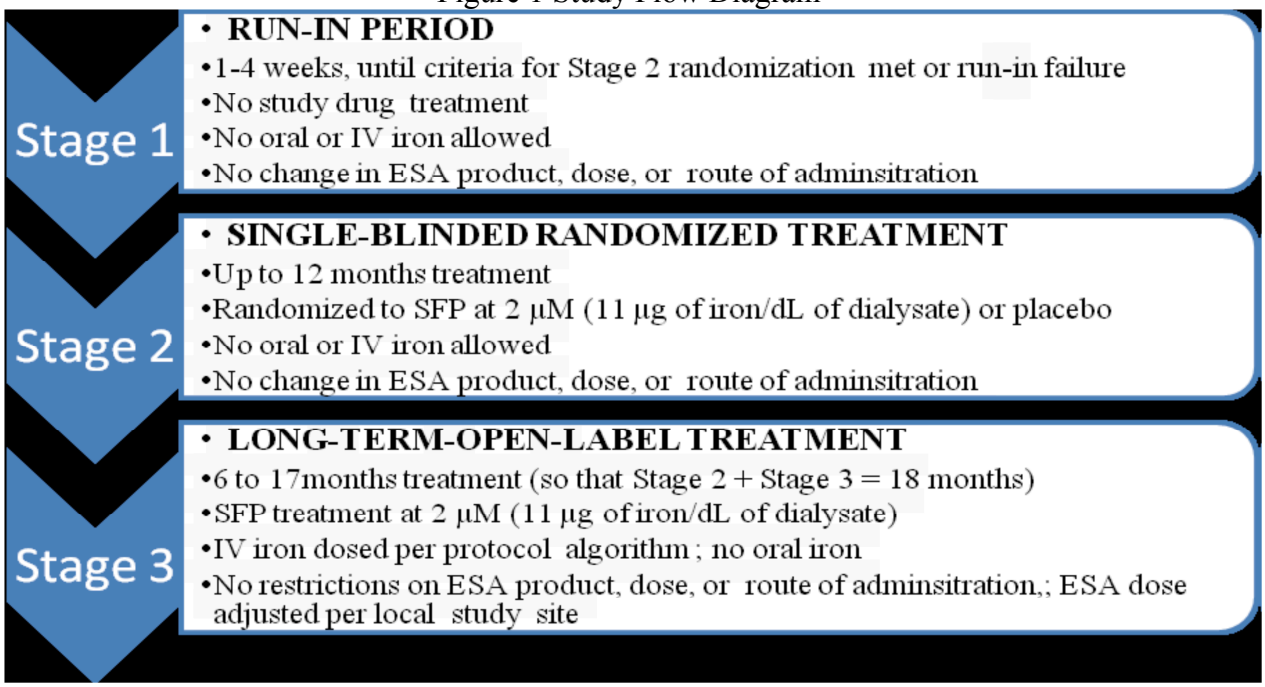
2.2.1 SFP-4-RC

2.2.1.1 Study Design

SFP-4-RC was a multicenter, randomized (1:1), single-blinded (only the study patients were blinded to treatment assignment), placebo-controlled, Phase 3 study to evaluate the efficacy and safety of SFP in adult patients with HDD-CKD.

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

Figure 1 Study Flow Diagram



Because the statistical analyses are focused on the data from the randomized treatment phase, only randomized treatment phase will be discussed in this review.

The protocol provided the following restrictions for iron and ESA treatment during the study in order to minimize the potential confounding effect of concomitant iron therapy and ESA on Hgb 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 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 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 every-other-week pre-dialysis Hgb, serum ferritin, CHr, and serum iron panel (serum iron, UIBC, transferrin, and calculated TIBC and TSAT), and every-four-week post-dialysis serum iron panel.

In the study, the protocol-mandated change in anemia management criteria that triggered subjects to be removed from randomized treatment 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)

In addition, patients were to be withdrawn from the study from the randomization for the following reasons:

- 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 changes 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 an 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).

Study Treatment:
Patients who meet the Randomized phase 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).

Triferic is supplied as single use 5mL ampules each containing 27.2 mg elemental iron(5.44 mg iron/mL) in water for injection. For use in hemodialysis (HD) a 5 mL SFP ampule is added to 2.1-2.5 gallons of liquid bicarbonate concentrate. The resulting mix is then added to the remainder of the dialysis solution components diluting the iron further. The sponsor indicates that addition of a 5 mL SFP ampule to 2.5 gallons of liquid bicarbonate concentrate generates a hemodialysate with a final concentration of 110 micrograms or 2 micromoles of SFP iron per liter of dialysate. Triferic is intended to be included in the hemodialysate at each hemodialysis procedure for as long as patients are receiving maintenance hemodialysis therapy for CKD.

Patients were stratified at randomization by baseline Hgb value and baseline ESA dose (details are presented in the randomization section].

The study duration for Stages 2 (randomized phase) and Stage 3 (long term open-label phase) combined was intended to be 18 months, regardless of whether the patient was randomized to SFP or placebo in Stage 2.

Randomization:
Subjects in the Stage 1 run-in period who met the criteria for randomization into Stage 2, Randomized phase, were randomized in a 1:1 ratio to either placebo (standard dialysate without SFP) or SFP in dialysate at 2 μM (11 μg iron/dL of dialysate). Randomization was stratified by the pre-randomization Hgb (Hgb > 11 g/dL vs. Hgb ≤ 11 g/dL), and by the baseline prescribed ESA dose (the weekly prescribed dose: ≤ 13,000 units/week epoetin alfa [or ≤ 40 μg/week darbepoetin alfa], ESAStratum I; vs. > 13,000 units/week epoetin alfa [or > 40 μg/week darbepoetin alfa], ESA Stratum II). In Randomized phase of the study, only the subjects were blinded to the treatment group assignment.

Primary Endpoint:
- Mean change from baseline in Hgb assessments to the EoT. EoT is defined as 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).

2.2.1.2 Statistical Methodologies

Sample size determination:
The study design was based on the assumption that a treatment difference in mean change from baseline between treatment groups is 0.5 g/dL and has a standard deviation of 1.25 g/dL, e.g., a variance of 1.56 g/dL. The necessary sample size for 90 percent power based on these assumptions was 132 subjects per group, which was rounded up to 150 subjects per group to

account for loss to follow-up.

Interim Analysis:
A blinded interim analysis was performed after approximately 50% of the target of 300 subjects was randomized to Randomized phase. If required, sample size might be increased to assure adequate power for the primary efficacy endpoint. The review was conducted using the procedure for sample size re-estimation described by Kieser and Friede (1) based on a 2-sample t-test to detect the original delta value (≥ 0.5 g/dL in the Hgb change from baseline) targeted for 90% power with an alpha level of 5% (2-sided); the interim observed, blinded, pooled standard deviation for change from baseline Hgb was used for this calculation. This type of blinded interim analysis would not inflate the Type I error rate for the final statistical test. (2)

This sample size re-estimation analysis was performed by an independent statistician with no access to the database or the randomization code. The only data provided for this analysis were the Hgb levels for individual subjects in the trial. Neither the randomization code nor the treatment group assignments were provided. The only analysis was performed on pooled, aggregate data, without knowledge of the treatment group assignment.

Using the 12-week follow-up based on SFP-4-RC study (55 subjects), sample sizes of 73 and 68 subjects per group was indicated by the unadjusted and adjusted pooled variance estimates. These variance estimates were 0.87 and 0.81, respectively, roughly 60 percent of the assumed value of 1.56. Based on the calculation, the proposed sample size of 132 subjects per group appeared adequate to achieve 90 percent power under the assumed delta value (i.e. $\delta = 0.5$).

Reviewer's comment:
The interim analysis was performed, but the results did not meet the sample size re-estimation criteria, so sample size had not been changed.

Efficacy Analysis Populations:
The following are definitions of analyzed populations used in this review:

- Intent-to-treat (ITT) population: All subjects who were randomized to a treatment group in Randomized phase.
- Modified-ITT (MITT) population: Randomized subjects who received at least 1 dose of study drug and also had at least 1 post-baseline Hgb value.

The numbers of subjects in analyzed populations are shown below.

Table 2 Analysis Populations

	SFP-4-RC	
Subject Disposition	**SFP**	**Placebo**
ITT	152	153
MITT	148 (97.4)	151 (98.7)

Reviewer Comments*: The sponsor chose to use MITT population for the primary and secondary efficacy analyses. FDA has recommended the sponsor to use ITT population for the primary and secondary efficacy analyses. The primary efficacy result for both the ITT and MITT population are included in this document.*

Statistical Analyses
All statistical comparisons were performed using two-sided tests at α=0.05 significance level.

Hypothesis Testing:

- H_o: The mean change in Hgb from baseline to EoT is not different between the SFP and the placebo groups;
- H_a: The mean change in Hgb from baseline to EoT is different between the SFP and the placebo groups.

Statistical Analysis for Primary Efficacy Endpoint:
An ANCOVA was used to evaluate H_o, where the mean change in Hgb from baseline to EoT was the response variable, the treatment group (SFP or placebo) was the factor, and baseline Hgb was the covariate. The model also included an indicator variable for the baseline ESA dose stratum.

A test of the treatment effect (H_o vs. H_a) was performed at the two-tailed 5% significance level comparing the least-squares mean values for the two treatments.

For the ANCOVA model, the LS means, standard errors (SE), and 95% CIs for mean change from baseline in Hgb was presented by treatment. In addition, the LS mean difference between treatments, SE, and 95% CIs was displayed. The p-value for treatment differences was reported.

Statistical Analysis for Secondary Efficacy Endpoints:
For secondary endpoints such as CHr, ferritin, and $TSAT_{UIBC}$, descriptive statistics for the mean, mean change from baseline was calculated by treatment group. For each parameter, the change from baseline per subject was calculated as the post-baseline value minus the baseline value. The baseline value per subject was the last pre-dialysis value obtained prior to the time of first dose of study drug. For this analysis, the value at any given post-baseline nominal time point per subject was the last pre-dialysis value obtained within the applicable study day window. The EoT value was the average of all values obtained during the last one-sixth of the randomized treatment period per subject.

Multiple Comparison/Multiplicity:
Statistical tests were not adjusted for multiple comparisons. All the secondary endpoints analyses were considered exploratory, not conclusive.

Missing Data Handling Strategies:
For primary efficacy analysis, for subjects who prematurely withdraw from study treatment, the EoT value for a parameter would be the average of all values obtained for that parameter over

the last one-sixth of the randomized treatment period. This would include a minimum of at least the last two post-baseline values that occur during the treatment period, unless the subject had only one post-baseline value during the treatment period (in which case the single post-baseline value will be used). If the subject had no post-baseline value, then the baseline value will be used as the EoT value.

Reviewer Comments*: One-sixth of the randomized treatment period was proportional to the 8-week period used for subjects who complete 48 weeks of treatment (8/48 weeks).*

For secondary efficacy analyses, if no values for a given parameter occurred within the study day window for a given subject at a given post-baseline nominal time point, then the last post-baseline observation prior to that time point would be carried forward (LOCF) and used as the value for that time point. If there was no LOCF value or post-baseline available, then the subject would not be included in the summary.

2.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Study SFP-4-RC randomized 305 patients at Randomized phase from 43 sites in U.S. The majority of the subjects were male (67.9%) and a majority were white (55.1%). The mean age was 58.3 years (range of 23 to 89 years). In general, the distribution of age, gender and race appear to be comparable, however more patients under 65 years old were in SFP group as compared to the placebo group.

Table 3 Demographics, ITT

Demographics	**SFP-4**	
	SFP (N=152)	**Placebo (N=153)**
Age (years)		
Mean (SD)	56.6 (12.6)	59.9 (13.0)
<65 years	111 (73.0)	97 (63.4)
65-74 years	34 (22.4)	35 (22.9)
≥75 years	7 (4.6)	21 (13.7)
Gender, n (%)		
Male	102 (67.1)	105 (68.6)
Female	50 (32.9)	48 (31.4)
Race, n (%)		
Asian	8 (5.3)	5 (3.3)
African American	50 (32.9)	48 (31.4)
Caucasian	84 (55.3)	84 (54.9)
Other	10 (6.4)	16 (10.4)

Baseline Characteristics:
Baseline Hemoglobin and iron parameters
The baseline mean pre-dialysis hgb level was comparable between the SFP and placebo groups in both studies (see Table below). The baseline mean TSAT, serum ferritin and other iron parameters were also similar between the two groups.

Table 4 Baseline Hemoglobin and Iron Parameters, ITT

Hgb and iron parameters	SFP-4	
	SFP (N = 152) Mean (SD)	**Placebo (N = 153) Mean (SD)**
Hemoglobin (g/dL)	10.96 (0.59)	10.91 (0.63)
Iron parameters (n)	149	151
TSAT (%)	28.1 (8.1)	27.1 (7.8)
Ferritin (µg/L)	507.7 (194.8)	511.3 (209.7)
TIBC (µmol/L)	42.9 (7.4)	42.2 (7.4)
UIBC (µmol/L)	30.9 (6.8)	30.8 (6.5)
Serum iron (µmol/L)	12.0 (3.9)	11.4 (3.9)
Transferrin (g/L)	1.9 (0.3)	1.9 (0.4)
Reticulocyte hemoglobin (pg)	32.4 (2.0)	32.6 (2.0)

Renal failure and other medical history:
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). In general, there were no significant differences between the SFP and the placebo groups regarding medical history.

History of iron use, ESA and transfusion:
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 Randomized phase 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.

Table 5 Baseline Hemoglobin and Iron Parameters, ITT

	SFP-4	
	SFP (N=152)	**Placebo (N=153)**
Any IV Iron Within the 2 Months Prior to Study	114 (75.0)	115 (75.2)
Total iron administered within 2 months prior to study (mg)	328.4 (241.7)	328.6 (239.7)
ESA Weekly Dose		
ESA Stratum I	124 (81.6)	124 (81.0)
ESA Stratum II	28 (18.4)	29 (19.0)
History of RBC or whole blood transfusions [n (%)]		
Yes	41 (27.0)	35 (22.9)
No	111 (73.0)	118 (77.1)

Study Treatment, Duration and Compliance:
There were 299 subjects who took at least one dose of study drug after baseline (148 in SFP and 151 in the placebo group). Only about 20% of subjects in both treatment groups had more than 44 weeks of treatment. The mean duration of exposure to study drug was 157.7 days (SD=115.42) and 164.6 days (SD=111.80) in the SFP and the placebo groups, respectively. The treatment duration was comparable between the two groups.

Table 6 Treatment Duration in Randomized Phase, ITT

	SFP (N=152)	**Placebo (N=153)**
Treatment Duration (days) exposure		
Mean (SD)	157.7 (115.42)	164.6 (111.80)
Median	125	143
Min, Max	1, 332	1, 333
Duration of exposure (n (%))		

≥1 day	148 (100.0)	151 (100.0)
≥1 week	147 (99.3)	149 (98.7)
≥2 weeks	140 (94.6)	147 (97.4)
≥4 weeks	130 (87.8)	137 (90.7)
≥8 weeks	109 (73.6)	118 (78.1)
≥12 weeks	90 (60.8)	103 (68.2)
≥16 weeks	84 (56.8)	87 (57.6)
≥20 weeks	68 (45.9)	78 (51.7)
≥24 weeks	62 (41.9)	65 (43.0)
≥28 weeks	55 (37.2)	57 (37.7)
≥32 weeks	46 (31.1)	48 (31.8)
≥36 weeks	41 (27.7)	40 (26.5)
≥40 weeks	36 (24.3)	35 (23.2)
44 -47 weeks	30 (20.3)	32 (21.2)

Subject Disposition:
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 randomized phase, 8 (2.6%) subjects died, and 151 (49.5%) subjects who required protocol-mandated change in anemia management were withdrawn from randomized phase 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 rin the SFP group as compared to the placebo group due to withdrawn consent (6.6% vs. 2%, respectively). There 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).

Table 7 Subject Disposition

	SFP-4-RC	
Subject Disposition	**SFP (N=152)**	**Placebo (N=153)**
Received at least one dose of study drug	149 (98.0)	151 (98.7)
Completed 48 weeks treatment	27 (17.8)	27 (17.6)
Died	5 (3.3)	3 (2.0)
Protocol-mandated change in anemia management prior to 48 weeks	69 (45.4)	82 (53.6)
ESA dose change	65 (42.8)	69 (45.1)
IV iron administration	4 (2.6)	14 (9.2)
Non-protocol-mandated change in anemia management	17 (11.2)	20 (13.1)
ESA dose change	13 (8.6)	17 (11.1)
IV iron administration	6 (3.9)	5 (3.3)
Withdrew consent	10 (6.6)	3 (2.0)
Adverse event	5 (3.3)	5 (3.3)
RBC or whole blood transfusion	1 (0.7)	7 (4.6)
Protocol violation	3 (2.0)	1 (0.7)
Principal Investigator decision	3 (2.0)	1 (0.7)
Sponsor's request	2 (1.3)	0 (0.0)
Study drug suspended for >12 weeks	0	0
Lost to follow-up	1 (0.7)	0 (0.0)
Other	9 (5.9)	4 (2.6)

Reviewer's comments*: Twelve randomized subjects were stratified incorrectly (8 subjects who met the criterion for Stratum I were assigned to Stratum II and 4 subjects who met the criterion for Stratum II were assigned to Stratum I). Subjects who were stratified incorrectly were analyzed according to the stratum to which they were assigned.*

2.2.1.4 Efficacy Results

Primary Efficacy Endpoint – Primary Analysis

The ANCOVA analysis of the mean change in Hgb from baseline to EoT in Randomized phase for the ITT population is presented in the following table. At EoT, the subjects receiving SFP had a LS mean increase of 0.06 g/dL in Hgb while the placebo group had a LS mean decrease of 0.30 g/dL in Hgb level. The treatment difference in LS mean change from baseline in Hgb level of 0.35 g/dL was shown to be statistically significant (p = 0.010).

Table 8 Change from Baseline in Hemoglobin Level at EoT, ITT

	SFP-4-RC	
	SFP (N=152)	Placebo (N=153)
Baseline Hgb (g/dL)		
N	152	153
Mean (SD)	10.96 (0.592)	10.91 (0.632)
End-of-Treatment Hgb (g/dL)		
n	152	153
Mean (SD)	10.93 (1.239)	10.53 (1.353)
Change from Baseline Hgb (g/dL)		
n	152	153
Mean (SD)	-0.03 (1.147)	-0.38 (1.240)
ANCOVA with Covariate of Baseline Hgb (g/dL)		
LS Mean change from baseline (SE)	0.06 (0.111)	-0.3 (0.111)
95% CI of LS Mean	(-0.16, 0.28)	(-0.52, -0.08)
LS Mean difference from Placebo (SE)	0.35 (0.136)	
95% CI	(0.09, 0.62)	
P-value	0.010	

Reviewer's comment:

Because many subjects had protocol mandated early withdrawal, the reviewer had the following observation:

1) Differential reasons for protocol mandated early withdrawal::

- *In general, more subjects from placebo group withdrew early due to protocol mandated change (SFP – 45% vs. Placebo – 54%).*
- *More subjects in SFP group withdrew early due to Hgb>12g/dL (SFP vs. placbo: 27% vs 21%).*

- *More subjects in Placebo group withdrew early due to Hgb<9 g/dL (SFP vs. placebo: 11% vs. 18%).*
- *More subjects withdrew early due to final serum ferritin level <100 µg/L in the placebo group as compared to the SFP group (11.1% vs. 3.3%, respectively).*

Table 9 Reasons for Protocol Mandated Early Withdrawal

	SFP (N=152) N (%)	Placebo (N=153) N (%)	Total (N=305) N (%)
SFP-4-RC			
Overall	69 (45.4)	82 (53.6)	151 (49.6)
Hgb >12 g/dL	41 (27.0)	32 (20.9)	73 (23.9)
Hgb< 9 g/dL	17 (11.2)	27 (17.6)	44 (14.4)
Ferritin < 100 µg/L	5 (3.3)	17 (11.1)	22 (7.2)

2) *As a results of this extensive protocol mandated early withdrawal, many subjects did not complete 48 weeks of treatment:*

- *For SFP-4-RC, only a total of 54 (17.7%) of the 305 subjects completed 48 weeks of treatment; a total of 135 (44.3%) completed half (24 weeks) of the 48 weeks. At the pre-NDA meeting on September 9th, 2013, this issue raised concerns for intended long-term use of SFP in patients undergoing hemodialysis.*
- *151 out of 305 subjects from SFP-4-RC discontinued the study before the planned 48 weeks due to protocol mandated change. By protocol, these subjects have completed the study despite the fact that they did not reach week 48. These large number of subjects who dropout early but "completed" the study may create bias in estimated results*

Primary Efficacy Endpoint – Sensitivity Analysis

The mean change in Hgb from baseline to EoT in the MITT population is presented in the table below as a sensitivity analysis. At EoT, the subjects receiving SFP had a LS mean increase of 0.06 g/dL in Hgb while the placebo group had a LS mean decrease of 0.30 g/dL in Hgb. The SFP group had a treatment difference in Hgb from placebo with an LS mean value of 0.36 g/dL. This result is consistent with the primary efficacy result.

Table 10 Change from Baseline in Hemoglobin Level at EoT, MITT

	SFP-4-RC	
	SFP (N=148)	Placebo (N=151)
Baseline Hgb (g/dL)		
N	148	151
Mean (SD)	10.96	10.90

	(0.591)	(0.636)
End-of-Treatment Hgb (g/dL)		
N	147	150
Mean (SD)	10.91 (1.253)	10.52 (1.365)
Change from Baseline Hgb (g/dL)		
N	147	150
Mean (SD)	-0.04 (1.167)	-0.39 (1.252)
ANCOVA with Covariate of Baseline Hgb (g/dL)		
LS Mean change from baseline (SE)	0.06 (0.115)	-0.3 (0.114)
95% CI of LS Mean	(-0.17, 0.28)	(-0.53, -0.08)
LS Mean difference from Placebo (SE)	0.36 (0.140)	
95% CI	(0.08, 0.63)	
Nominal P-value	0.011	

Another sensitivity analysis was also conducted to assess the mean change in Hgb from baseline to all post-baseline values in the MITT population using a Mixed Effect Repeat Measurement (MMRM) model (see the following table). The SFP group had a treatment difference in Hgb from placebo with an LS mean value of 0.2 g/dL, which appears to have smaller magnitude as compared with the result from the primary efficacy analysis (i.e. 0.36 g/dL).

Table 11 Change from Baseline in Hemoglobin Level Using All Post-Baseline Values, MMRM

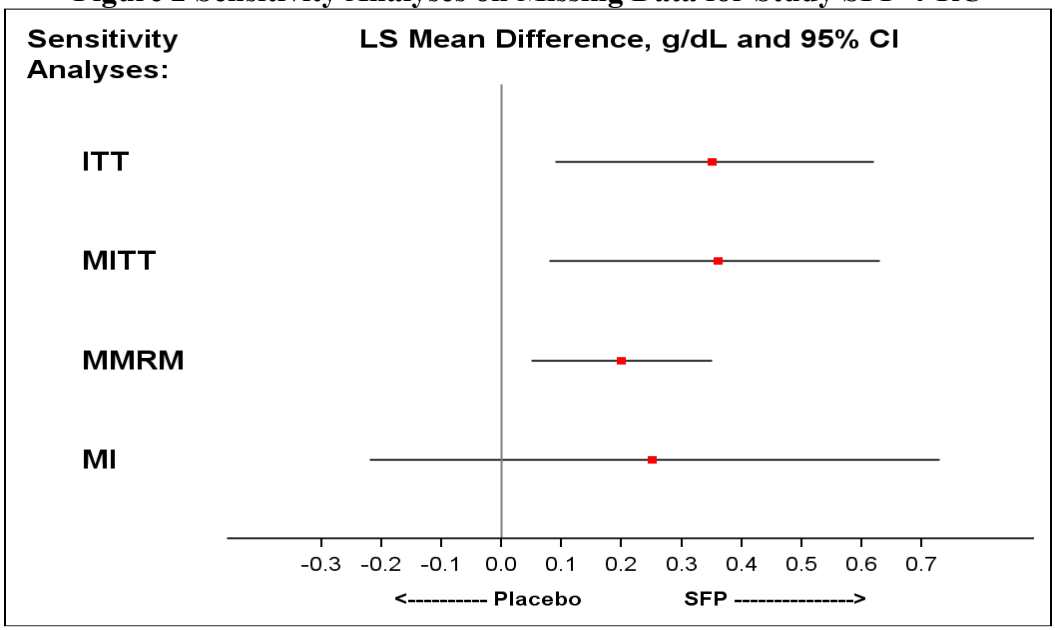
	SFP-4-RC	
	SFP (N=148)	Placebo (N=151)
Baseline Hgb (g/dL)		
N	148	151
Mean (SD)	10.96 (0.591)	10.90 (0.636)
Overall Hgb (g/dL)		
N	147	150
Mean (SD)	10.75	10.64

	(0.875)	(0.936)
MMRM with Covariate of Baseline Hgb using CS covariance structure (g/dL)		
LS Mean (SE)	10.8 (0.071)	10.6 (0.072)
95% CI of LS Mean	(10.66, 10.94)	(10.46, 10.74)
LS Mean difference from Placebo (SE)	0.2 (0.076)	
95% CI	(0.05, 0.35)	
Nominal P-value	0.008	

Reviewer's comment:

The difference in mean change from baseline between SFP and placebo groups and the associated 95% CI for these analyses are shown in the following forest plot. The difference in means, in the MITT population, had similar magnitude and 95% CI as the ITT population. There were six subjects who were in the ITT population but excluded from MITT. The third plot shows the effect estimated by a MMRM model using all data points after baseline instead of only data points at end of treatment. The difference in means between the two treatments appears to be reduced by using early data. The last plot shows the variability in estimating the mean difference associated with imputing a large amount of data using multiple imputation technique. Since so much data were imputed, a large standard deviation was observed and this estimate might not be reliable.

Figure 2 Sensitivity Analyses on Missing Data for Study SFP-4-RC



Note: Due to many patients did not complete 48 weeks of treatment, there are not enough data to perform valid multiple imputation (MI) up to 48 weeks. The MI results performed by this reviewer only include data up to week 36.

Secondary Efficacy Endpoints:

For ferritin, CHr , $TSAT_{UIBC}$, descriptive statistics for the mean change from baseline to EoT by treatment group are listed in the table below.

Table 12 Mean Change from Baseline for Key Secondary Efficacy Endpoints, ITT

	SFP-4-RC	
Change from Baseline	SFP (N=152)	Placebo (N=153)
Ferritin (µg/L)		
Mean (SD)	-70.8 (132.41)	-141.2 (187.74)
Reticulocyte Hgb content (CHr) (pg)		
Mean (SD)	-0.2 (1.19)	-0.9 (1.41)
$TSAT_{UIBC}$ (%)		

Mean (SD)	-1.0 (9.07)	-2.9 (7.65)

Reviewer's comment:

The results of ferritin level, CHr and $TSAT_{UIBC}$ also appear to have smaller numerical reduction in the SFP group compared to the placebo group. However, these secondary endpoint analyses are considered as exploratory, thus it is difficult to draw valid statistical inference from these results.

2.2.2 SFP-5-RC

2.2.2.1 Study Design

Study SFP-5-RC was 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 HDD-CKD. It was identical to study SFP-4-RC.

For study flow diagram, please refer to Figure 1 in section 2.2.1.1.

For an overview of the study design, please refer to section 2.2.1.1

Study treatment
Please refer to the study treatment section in section 2.2.1.1 for detailed description.

Randomization:
Please refer to the randomization section in section 2.2.1.1 for detailed description.

Primary Endpoint:
Please refer to the primary endpoint section in section 2.2.1.1 for detailed description.

Secondary Endpoints:
Please refer to the secondary endpoints section in section 2.2.1.1 for detailed description.

2.2.2.1 Statistical Methodologies

Sample size determination:
Please refer to the sample size determination section in section 2.2.1.2 for detailed description.

Interim Analysis:
Please refer to the interim analysis section in section 2.2.1.2 for detailed description.

Using the 12-week follow-up based on SFP-5-RC (57 subjects), sample sizes of 86 and 80 subjects per group were indicated by the unadjusted and adjusted pooled variance estimates. These variance estimates were 1.02 and 0.96, respectively, roughly 70 percent of the assumed value of 1.56. Based on this calculation, the proposed sample size of 132 subjects per group appeared adequate to achieve 90 percent power under the assumed $\delta = 0.5$.

Reviewer's comment:
The interim analysis was performed, but the results did not meet the sample size re-estimation criteria, so sample size had not been changed.

Efficacy Analysis Population:
Please refer to the efficacy analysis population section in section 2.2.1.2 for detailed description of analyzed populations used in the review.

Table 13 Analysis Populations

	SFP-5-RC	
Subject Disposition	**SFP**	**Placebo**
Randomized	147	147
MITT	142 (96.6)	144 (98.0)

Reviewer Comments:
The sponsor chose to use MITT population for the primary and secondary efficacy analyses. FDA has recommended the sponsor to use ITT population for the primary and secondary efficacy analyses. The primary efficacy result for both the ITT and MITT population are included in this document.

Statistical Analyses
All statistical comparisons were performed using two-sided tests at $\alpha=0.05$ significance level.

Hypothesis Testing:
- H_o: The mean change in Hgb from baseline to EoT is not different between the SFP and the placebo groups;
- H_a: The mean change in Hgb from baseline to EoT is different between the SFP and the placebo groups.

Statistical Analysis for Primary Efficacy Endpoint:
Please refer to the statistical analysis for primary efficacy endpoint section in section 2.2.1.2 for detailed description.

Statistical Analysis for Secondary Efficacy Endpoints:
Please refer to the statistical analysis for secondary efficacy endpoints section in section 2.2.1.2 for detailed description.

Multiple Comparison/Multiplicity:
Please refer to the multiple comparison/multiplicity section in section 2.2.1.2 for detailed description.

Missing Data Handling Strategies:
Please refer to the missing data handling strategies section in section 2.2.1.2 for detailed description.

2.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

The Study SFP-5-RC randomized 294 patients from 41 sites in U.S. and 2 sites in Canada. In this study, the majority of the subjects were male (59.5%). Most subjects were Caucasian (53.1%), and 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 and slightly more males and more Caucasians in the placebo group than in the SFP group.

Table 14 Demographics, ITT

Demographics	**SFP-5-RC**	
	SFP (N=147)	**Placebo (N=147)**
Age (years)		
Mean (SD)	58.1 (12.7)	59.0 (14.4)
<65 years	102 (69.4)	95 (64.6)
65-74 years	31 (21.1)	28 (19.0)
≥75 years	14 (9.5)	24 (16.3)
Gender, n (%)		
Male	82 (55.8)	93 (63.3)
Female	65 (44.2)	54 (36.7)
Race, n (%)		
Asian	8 (5.4)	4 (2.7)
African American	64 (43.5)	54 (36.7)
Caucasian	73 (49.7)	83 (56.5)
Other	2 (1.4)	6 (4.1)

Baseline Characteristics

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

Table 15 Baseline Hemoglobin and Iron Parameters, ITT

Hgb and iron parameters	SFP-5-RC	
	SFP (N = 147) Mean (SD)	**Placebo (N =147) Mean (SD)**
Hemoglobin (g/dL)	10.96 (0.61)	10.94 (0.62)
Iron parameters (n)	143	145
TSAT (%)	27.9 (8.2)	28.2 (8.6)
Ferritin (µg/L)	513.8 (200.7)	478.8 (201.2)
TIBC (µmol/L)	41.8 (6.2)	42.6 (6.9)
UIBC (µmol/L)	30.2 (5.8)	30.7 (6.5)
Serum iron (µmol/L)	11.6 (3.8)	11.9 (4.0)
Transferrin (g/L)	1.9 (0.3)	1.9 (0.3)
Reticulocyte hemoglobin (pg)	32.6 (2.2)	32.5 (1.9)

Renal failure and other medical history:
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). In both populations, the other baseline medical history was also similar for the SFP and placebo groups.

History of iron use, ESA and transfusion:
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 Randomized phase 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 (76.9%) and placebo (77.6%) 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 16 Baseline Hemoglobin and Iron Parameters, ITT

	SFP-5-RC	
	SFP (N=147)	**Placebo (N=147)**
Any IV Iron Within the 2 Months Prior to Study	120 (81.6)	125 (85.0)
Total iron administered within 2 months prior to study (mg)	381.8 (220.2)	384.1 (294.5)
ESA Weekly Dose		
ESA Stratum I	113 (76.9)	114 (77.6)
ESA Stratum II	34 (23.1)	33 (22.4)
History of RBC or whole blood transfusions [n (%)]		
Yes	38 (25.9)	38 (25.9)
No	109 (74.1)	109 (74.1)

Study Treatment, Duration and Compliance:
There were 286 subjects who took at least one dose of study drug after baseline (142 in SFP and 144 in the placebo group). Only 22.5% of subjects in SFP group and 16.7% of subjects in the placebo group had more than 44 weeks of treatment. The mean duration of exposure to study drug was 161.2 days (SD=111.10) and 157.9 days (SD=109.76) in the SFP and the placebo groups, respectively. The treatment duration was comparable between the two groups.

Table 17 Treatment Duration in Randomized Phase, ITT

	SFP-5-RC	
	SFP (N = 147)	**Placebo (N = 147)**
Treatment Duration (days) exposure		
Mean (SD)	161.2 (111.10)	157.9 (109.76)
Median	132	135
Min, Max	1, 332	3, 332
Duration of exposure (n (%))		
≥1 day	142 (100.0)	144 (100.0)
≥1 week	141 (99.3)	143 (99.3)
≥2 weeks	140 (98.6)	140 (97.2)
≥4 weeks	133 (93.7)	126 (87.5)

≥8 weeks	117 (82.4)	114 (79.2)
≥12 weeks	89 (62.7)	96 (66.7)
≥16 weeks	77 (54.2)	78 (54.2)
≥20 weeks	67 (47.2)	71 (49.3)
≥24 weeks	60 (42.3)	63 (43.8)
≥28 weeks	51 (35.9)	50 (34.7)
≥32 weeks	42 (29.6)	44 (30.6)
≥36 weeks	37 (26.1)	36 (25.0)
≥40 weeks	34 (23.9)	31 (21.5)
44 -47 weeks	32 (22.5)	24 (16.7)

Subject Disposition
A total of 294 patients with HDD-CKD were randomized into Randomized phase 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 Randomized phase, 10 (3.4%) subjects died, and 158 (53.7%) subjects who required protocol-mandated change in anemia management were withdrawn from Randomized phase 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-5 study.

Table 18 Subject Disposition

	SFP-5-RC	
Subject Disposition	**SFP (N=147)**	**Placebo (N=147)**
Received at least one dose of study drug	143 (97.3)	145 (98.6)
Completed 48 weeks treatment	28 (19.0)	22 (15.0)

Died	7 (4.8)	3 (2.0)
Protocol-mandated change in anemia management prior to 48 weeks	68 (46.3)	90 (61.2)
ESA dose change	65 (44.2)	69 (46.9)
IV iron administration	3 (2.0)	21 (14.3)
Non-protocol-mandated change in anemia management	14 (9.5)	6 (4.1)
ESA dose change	10 (6.8)	5 (3.4)
IV iron administration	4 (2.7)	1 (0.7)
Withdrew consent	1 (0.7)	5 (3.4)
Adverse event	7 (4.8)	2 (1.4)
RBC or whole blood transfusion	5 (3.4)	5 (3.4)
Protocol violation	7 (4.8)	4 (2.7)
Principal Investigator decision	3 (2.0)	1 (0.7)
Sponsor's request	0 (0.0)	2 (1.4)
Study drug suspended for >12 weeks	0 (0.0)	1 (0.7)
Lost to follow-up	0	0
Other	9 (6.1)	6 (4.1)

***Reviewer's comment*:** *Twenty-three randomized subjects were stratified incorrectly (17 subjects who met the criterion for Stratum I were assigned to Stratum II and 6 subjects who met the criterion for Stratum II were assigned to Stratum I). Subjects who were stratified incorrectly were analyzed according to the stratum to which they were assigned.*

2.2.2.3 Efficacy Results

Primary Efficacy Endpoint – Primary Analysis

The ANCOVA analysis of the mean change in Hgb from baseline to EoT for the ITT population is presented in the following table. At EoT, the subjects receiving SFP had a LS mean decrease of 0.04 g/dL in Hgb while the placebo group had a LS mean decrease of 0.39 g/dL in Hgb level. The treatment difference in LS mean change from baseline in Hgb level of 0.35 g/dL was shown to be statistically significant (p = 0.010).

Table 19 Change from Baseline in Hemoglobin Level at EoT, ITT

	SFP-5-RC	
	SFP (N=147)	Placebo (N=147)
Baseline Hgb (g/dL)		
N	147	147
Mean (SD)	10.96 (0.605)	10.94 (0.622)

End-of-Treatment Hgb (g/dL)		
n	147	147
Mean (SD)	10.87 (1.355)	10.50 (1.319)
Change from Baseline Hgb (g/dL)		
n	147	147
Mean (SD)	-0.08 (1.152)	-0.44 (1.157)
ANCOVA with Covariate of Baseline Hgb (g/dL)		
LS Mean change from baseline (SE)	-0.04 (0.105)	-0.39 (0.105)
95% CI of LS Mean	(-0.25, 0.16)	(-0.60, -0.19)
LS Mean difference from Placebo (SE)	0.35 (0.135)	
95% CI	(0.08, 0.61)	
P-value	0.010	

Reviewer's comment:

Because many subjects had protocol mandated early withdrawal, the reviewer had the following observation:

1) *Differential reasons for protocol mandated early withdrawal:*
    - *In general, more subjects from placebo group withdrew early due to protocol mandated change (SFP – 46% vs. Placebo – 61%).*
    - *More subjects in SFP group withdrew early due to Hgb>12 g/dL (SFP vs. placebo: 22% vs 14%).*
    - *More subjects in Placebo group withdrew early due to Hgb<9 g/dL (SFP vs. placebo: 15% vs. 23%).*
    - *More subjects withdrew early due to serum ferritin level <100 µg/L in the placebo group as compared to the SFP group (15.6% vs. 2.7%, respectively).*

Table 20 Reasons for Protocol Mandated Early Withdrawal

	SFP (N=147) N (%)	Placebo (N=147) N (%)	Total (N=294) N (%)
SFP-5-RC			
Overall	68 (46.3)	90 (61.2)	158 (53.7)
Hgb >12 g/dL	32 (21.8)	21 (14.3)	53 (18.0)
Hgb< 9 g/dL	22 (15.0)	34 (23.1)	56 (19.0)
Ferritin < 100 μg /L	4 (2.7)	23 (15.6)	27 (9.2)

2) As results of this extensive protocol mandated early withdrawal, many subjects did not complete 48 weeks of treatment:

- *For SFP-5-RC, a total of 47 (16.0%) of the 294 subjects completed 48 weeks of treatment; a total of 125 (42.5%) completed half (24 weeks). At the pre-NDA meeting on September 9th, 2013, this issue raised concerns for intended long-term use of SFP in patients undergoing hemodialysis.*

- *158 out of 294 subjects from SFP-5-RC discontinued the study before the planned 48 weeks due to protocol mandated change. By protocol, these subjects have completed the study despite the fact that they did not reach week 48. These large number of subjects who dropout early but "completed" the study may create bias in estimated results*

Primary Efficacy Endpoint – Sensitivity Analysis

The mean change in Hgb from baseline to EoT in the MITT population is presented in the table below as a sensitivity analysis. At EoT, the subjects receiving SFP had a LS mean decrease of 0.05 g/dL in Hgb while the placebo group had a LS mean decrease of 0.40 g/dL in Hgb. The SFP group had a treatment difference in Hgb from placebo with an LS mean value of 0.36 g/dL that appear to be consistent with the primary efficacy result.

Table 21 Change from Baseline in Hemoglobin Level at EoT, MITT

	SFP-5-RC	
	SFP (N=142)	Placebo (N=144)
Baseline Hgb (g/dL)		
N	142	144
Mean (SD)	10.96 (0.609)	10.93 (0.625)
End-of-Treatment Hgb (g/dL)		

N	141	143
Mean (SD)	10.87 (1.381)	10.49 (1.333)
Change from Baseline Hgb (g/dL)		
N	141	143
Mean (SD)	-0.09 (1.176)	-0.45 (1.171)
ANCOVA with Covariate of Baseline Hgb (g/dL)		
LS Mean change from baseline (SE)	-0.05 (0.108)	-0.40 (0.109)
95% CI of LS Mean	(-0.26, 0.17)	(-0.62, -0.19)
LS Mean difference from Placebo (SE)	0.36 (0.139)	
95% CI	(0.08, 0.63)	
Nominal P-value	0.011	

Another sensitivity analysis assessed the mean change in Hgb from baseline to EoT using all post-baseline values in the MITT population using a Mixed Effect Repeat Measurement (MMRM) model (see the following table). The SFP group had a treatment difference in Hgb from placebo with an LS mean value of 0.24 g/dL, which had smaller magnitude as compared with the result from the primary efficacy analysis (i.e. 0.36 g/dL).

Table 22 Change from Baseline in Hemoglobin Level Using All Post-Baseline Values, MMRM

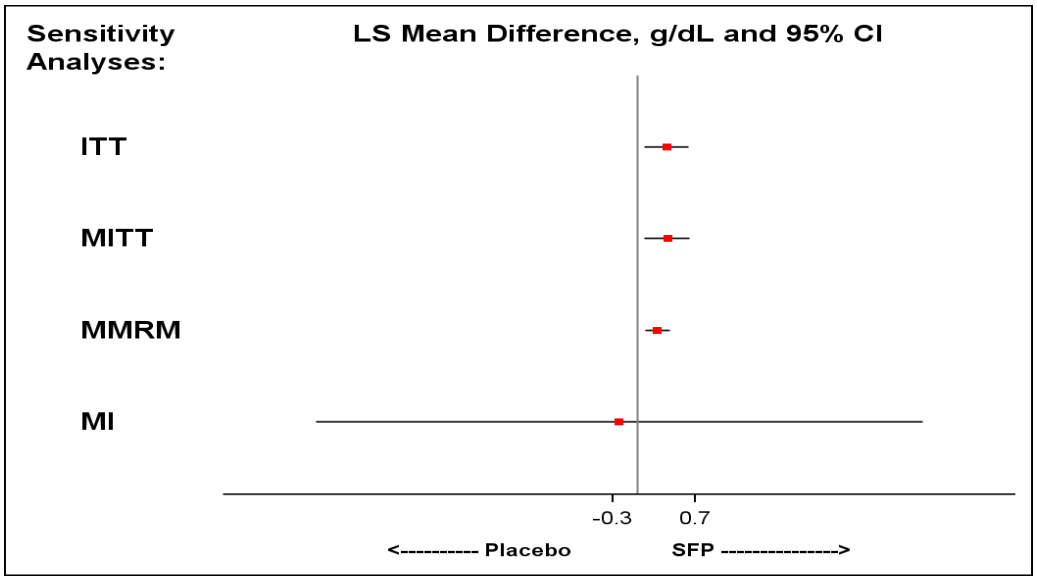
	SFP-5-RC	
	SFP (N=142)	Placebo (N=144)
Baseline Hgb (g/dL)		
N	142	144
Mean (SD)	10.96 (0.609)	10.93 (0.625)
Overall Hgb (g/dL)		
N	141	143

Mean (SD)	10.81 (0.949)	10.57 (0.927)
MMRM with Covariate of Baseline Hgb using CS covariance structure (g/dL)		
LS Mean (SE)	10.81 (0.072)	10.57 (0.073)
95% CI of LS Mean	(10.67,10.95)	(10.43,10.71)
LS Mean difference from Placebo (SE)	0.24 (0.077)	
95% CI	(0.09, 0.39)	
Nominal P-value	0.002	

Reviewer's comment:

The difference in means in change from baseline between SFP and placebo groups and the associated 95% CI for these analyses are shown in the forest plot below. The pattern seen here is similar to the pattern seen in study SFP-4-RC. The difference in means, in the MITT population, had similar magnitude and 95% CI as the ITT population. The third plot shows the effect estimated by a MMRM model using all data points after baseline instead of only data points at end of treatment. The difference in means between the two treatments appears to be reduced by using early data. The last plot shows the variability in estimating the mean difference associated with imputing a large amount of data using multiple imputation technique. Since so much data were imputed, a large standard deviation was observed and this estimate might not be reliable.

Figure 3 Sensitivity Analyses on Missing Data for Study SFP-5-RC



Note: Due to many patients did not complete 48 weeks of treatment, there are not enough data to perform valid multiple imputation (MI) up to 48 weeks. The MI results performed by this reviewer only include data up to week 32.

Key Secondary Efficacy Endpoints

For ferritin, CHr, $TSAT_{UIBC}$ [serum iron (µg/dL)/$TIBC_{UIBC}$ (µg/dL) x 100; and TIBC =serum iron + UIBC (unsaturated iron binding capacity)], descriptive statistics for the mean change from baseline to EoT by treatment group are listed in the table below.

Table 23 Mean Change from Baseline for Key Secondary Efficacy Endpoints, ITT

	SFP-5-RC	
Change from Baseline	SFP (N=147)	Placebo (N=147)
Ferritin (µg/L)		
Mean (SD)	-65.3 (162.45)	-120.9 (268.19)
Reticulocyte Hgb content (CHr) (pg)		
Mean (SD)	-0.6 (1.44)	-0.9 (1.47)
$TSAT_{UIBC}$(%)		

Mean (SD)	-0.9 (7.54)	-3.6 (7.29)

Reviewer's comment:

The results of ferritin level, CHr and $TSAT_{UIBC}$ appear to have smaller numerical reduction in the SFP group compared to the placebo group. However, these secondary endpoint analyses are considered as exploratory, thus it is difficult to draw valid statistical inference from these results.

2.2.3 NIH-FP-01

Study NIH-FP-01 was submitted to support labeling "To reduce the prescribed dose of ESA required maintaining desired Hgb levels."

2.2.3.1 Study Design

This was a multicenter, randomized, placebo-controlled, double-blinded, phase II trial to evaluate the safety and efficacy of SFP via hemodialysate in patients with HDD-CKD. The protocol stated that this study was exploratory in nature and statistical tests were considered to be descriptive rather than conclusive.

Reviewer's comment: *This is a single trial; the result from this trial is not duplicated. In general, FDA requires at least two well conducted pivotal trials to support any approvals or label claims.*

Primary Efficacy Objective:
To determine the efficacy of SFP in maintaining iron sufficiency and thereby sparing the need for ESAs required maintaining Hgb levels.

Randomization
Randomization was stratified by baseline ESA dose (the weekly dose as of the time of randomization, ≤ 13,000 units/week epoetin [or ≤ 40 μg/week darbepoetin], Stratum I; vs. > 13,000 units/week epoetin [or > 40 μg/week darbepoetin], Stratum II). Within each stratum, subjects were randomized in a 1:1 ratio to SFP or placebo using an appropriate block size.

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 μM (11 μg /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 algorithm, with the goal of maintaining Hgb in the target range of 9.5 to 11.5 g/dL.

Sample size determination
Because the trial was considered to be exploratory, there was no sample size calculation. The sample size of approximately 50 patients per treatment group was considered adequate for the intended purposes of this trial.

Reviewer's comment: *This study is considered exploratory, hence, there is no formal sample size or power calculation planned. It would be difficult to draw any valid statistical inference from the result.*

Interim Analysis
No interim analysis was planned.

Primary Efficacy Endpoints

- The percent change from baseline in prescribed ESA dose required to maintain Hgb in the target range, adjusted for baseline Hgb.

Statistical Methodologies
Since this clinical trial was considered exploratory, the statistical tests were considered to be descriptive rather than conclusive and were not adjusted for multiple comparisons. All tests were two-sided.

Efficacy Analysis Set

- The ITT population was defined as all subjects who were randomized after 02 December 2010 to a treatment group in the randomized, double-blinded, placebo controlled treatment period.

- The MITT population was defined as all subjects randomized after 02 December 2010 who received at least one dose of study drug and have any ESA dose information available during the treatment period. The MITT population was used as the basis for the primary efficacy analysis. All primary and secondary efficacy endpoints were analyzed using the MITT population.

Reviewer Comments*: The sponsor chose to use the MITT population for the primary endpoint analysis. Results in the ITT analysis population are included in this review.*

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

Table 24 Analyzed Populations

	SFP	Placebo
ITT	54	54
MITT population	52	51

Hypothesis Testing:

- Ho: The percent change from baseline in ESA dose at end-of-treatment, adjusted for baseline Hgb, is not different between the SFP and the placebo groups;

- Ha: The percent change from baseline in ESA dose at end-of-treatment, adjusted for baseline Hgb, is different between the SFP and the placebo groups.

Statistical Analysis for Primary Efficacy Endpoint:
The baseline prescribed ESA dose (expressed as U/week epoetin) per subject was defined as the average weekly dose of ESA prescribed for administration over the two-week period of time immediately prior to randomization. The EoT prescribed ESA dose (expressed as U/week epoetin) per subject was defined as the average weekly dose of ESA prescribed for administration over the last two weeks of the treatment period.

A one-way ANCOVA model was used for the treatment comparison, where the percent change from baseline in ESA was the response variable, the treatment group (SFP or placebo) was the factor, and baseline Hgb was the covariate. The model included an indicator variable for the baseline ESA dose stratum. Percent change from baseline in ESA was defined as follows:

$$\text{Percent change from baseline ESA} = 100 * \frac{\text{(end-of-treatment or post-baseline weekly dose} - \text{baseline weekly dose)}}{\text{baseline weekly dose}}$$

For the ANCOVA model, LS means and SE for percent change from baseline in ESA prescribed dose was presented by treatment. In addition, the LS mean difference between treatments, SE, and 95% CIs was also presented. The p-value for the treatment difference was reported.

Several sensitivity analyses were performed to validate the robustness of the primary efficacy result. They are described below:

- The primary efficacy endpoint was also analyzed as the percent change from baseline in the administered ESA dose (i.e. actual ESA dose). The definition of the percent change from baseline in the actual ESA dose is similar to what have been described for the

analysis of the change from baseline in the prescribed ESA dose earlier.

- Percent change from baseline in the prescribed and actual ESA dose were analyzed in the MITT population.

- A MMRM model also used to test the treatment effect for both percent change from baseline in the prescribed and actual ESA dose using the ITT population.

Missing Data Handling Strategies

For analyses using prescribed ESA doses, all ESA doses prescribed for administration within a given time interval was used to calculate the mean value for each time point. Data for subjects who were discontinued prematurely from the study would be incorporated in the analysis by using the average weekly ESA dose prescribed for administration during the last two weeks prior to discontinuation. If a subject failed to complete at least two weeks on study, the ESA dose and frequency prescribed for administration during the treatment period prior to the date of withdrawal would be used to calculate the average prescribed dose per week. For analyses using administered ESA doses, all ESA doses administered within a given time interval was used to calculate the mean value for each time point.

Missing ESA doses was not imputed or carried forward from previous visits in the derivation of mean values of administered ESA doses.

Patient Disposition, Demographic and Baseline Characteristics

Note: patient disposition, demographic and baseline characteristics will be summarized below using MITT population. Five subjects (2 in SFP, 3 in placebo) were in ITT but were not in MITT population.

In this study, the majority of the subjects were male (61.2%) and most were white (61.2%). 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 25 Demographics, MITT

	SFP (N=52)	Placebo (N=51)	Total (N=103)
Age (years)			
Mean (SD)	59.3 (12.61)	58.7 (13.65)	59.0 (13.07)
Median	59.0	58.0	59.0

Min, Max	37, 93	25, 86	25, 93
Gender, n (%)			
Male	29 (55.8)	34 (66.7)	63 (61.2)
Female	23 (44.2)	17 (33.3)	40 (38.8)
Race, n (%)			
Asian	1 (1.9)	0	1 (1.0)
Black or African American	20 (38.5)	19 (37.3)	39 (37.9)
White	31 (59.6)	32 (62.7)	63 (61.2)

Baseline Characteristics:

Baseline hemoglobin and iron parameters
The baseline mean pre-dialysis Hgb 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 26 Baseline Hemoglobin and Iron Parameters, MITT

	SFP N=52 Mean (SD)	**Placebo N=51 Mean (SD)**
Hemoglobin (g/dL)	10.96 (0.72)	11.11 (0.69)
Iron parameters		
TSAT (%)	26.7 (7.07)	28.4 (7.54)
TIBC (µmol/L)	45.72 (6.68)	46.1 (7.83)
UIBC (µmol/L)	40.77 (5.51)	41.21 (6.81)
Serum iron (µmol/L)	11.96 (3.03)	13.01 (4.10)
Reticulocyte hemoglobin content (pg)	32.76 (1.84)	32.49 (2.17)

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 27 Treatment Duration in Randomized Phase, MITT

	SFP (N=52)	**Placebo (N=51)**
Treatment Duration (days)		
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)

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%).

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 28 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)

Stratum I: ≤13,000 equivalent units/week epoetin; Stratum II: >13,000 equivalent units/week epoetin.

Efficacy Results

Primary Efficacy Endpoint

The percent change in prescribed ESA dose from baseline to EoT in the ITT population is presented in the following table. At baseline the SFP and the placebo groups were comparable with respect to prescribed ESA dose. At EoT, the subjects who had prescribed SFP had a LS mean 5% increase in ESA while the placebo group had a LS mean 37.3% increase in ESA dose, after adjusting for baseline Hgb. The SFP group had treatment difference in prescribed ESA dose from placebo with an LS mean value of -32.3% that a corresponding nominal p-value of 0.052.

Table 29 Percent Change from Baseline in Prescribed ESA Dose, ITT

	SFP N=54		Placebo N=54	
	Epoetin U/wk (SD)	%Change from Baseline LS mean	Epoetin U/wk (SD)	%Change from Baseline LS mean
Prescribed ESA Dose U/wk (SD) Baseline	9295.0 (5415.3)		9316.7 (5444.12)	

Prescribed ESA Dose U/wk (SD) EoT	9668.5 (7465.49)	5 .0 (11.60)	12549.4 (13602.99)	37.3 (11.60)
LS Mean Difference from Placebo (SE) 95% CI	-32.3 (16.45) (-64.9, -0.3)			
Nominal P-Value	0.052			

Sensitivity Analyses
Several sensitivity analyses are done to explore the robustness of the primary efficacy result. The findings are listed below.

Actual ESA Dose:
The percent change in actual ESA dose usage from baseline to EoT in the ITT population is presented below. At baseline the SFP and the placebo groups were comparable with respect to the actual ESA dose usage. At EoT, the subjects who had actual SFP had a LS mean 11.1% increase in ESA while the placebo group had a LS mean 40.7% increase in ESA dose, after adjusting for baseline Hgb. The SFP group had treatment difference in actual ESA dose from placebo with an LS mean value of -29.6% that a corresponding nominal p-value of 0.111. This result agrees with the findings from the prescribed ESA dose.

Table 30 Percent Change from Baseline in Actual ESA Dose, ITT

	SFP N=54		**Placebo N=54**	
	Epoetin U/wk (SD)	%Change from Baseline LS mean	Epoetin U/wk (SD)	%Change from Baseline LS mean
Actual ESA Dose U/wk (SD) Baseline	9000.5 (5493.11)		8960.5 (5476.49)	
Acutal ESA Dose U/wk (SD) EoT	9224.3 (7014.03)	11.1 (12.97)	12151.4 (13600.56)	40.7 (12.97)

LS Mean Difference from Placebo (SE) 95% CI	-29.6 (18.39) (-66.1, 6.9)
Nominal P-Value	0.111

MITT population:
The percent change in prescribed ESA dose usage from baseline to EoT in the MITT population is presented. At EoT, the subjects who had prescribed SFP had a LS mean 4.9% increase in ESA while the placebo group had a LS mean 39.8% increase in ESA dose, after adjusting for baseline Hgb. The SFP group had treatment difference in prescribed ESA dose from placebo with an LS mean value of -35% that lead to a nominal p-value of 0.045.

Table 31 Percent Change from Baseline in Prescribed ESA Dose, MITT

	SFP (N=52)	Placebo (N=51)
Baseline Prescribed ESA Dose (U/week)		
N	52	51
Mean (SD)	9483.2 (5413.86)	9205.9 (5500.05)
End-of-Treatment		
N	52	51
Mean (SD)	9871.2 (7523.23)	12628.8 (13967.36)
Percent Change from Baseline		
N	52	51
Mean (SD)	7.3 (67.66)	37.3 (106.09)
ANCOVA with Covariate of Baseline Hgb		
LS Mean Percentage Change from Baseline (SE)	4.9 (12.07)	39.8 (12.18)
LS Mean Difference from Placebo (SE) (95% CI)	-35.0 (17.20) (-69.1, -0.8)	
P-Value	0.045	

The percent change in actual ESA dose usage from baseline to EoT in the MITT population is also presented. Subjects who had actual SFP had a LS mean in percent increase in actual ESA dose from baseline at EoT of 11.3% compared to the placebo group increase of 43.4%. The SFP group had treatment difference in actual ESA dose from placebo with an LS mean value of -32.1% that lead to a nominal p-value of 0. 098.

Table 32 Percent Change from Baseline in Actual ESA Dose, MITT

	SFP (N=52)	Placebo (N=51)
Baseline Actual ESA Dose (U/week)		
N	52	51
Mean (SD)	9177.5 (5505.07)	8835.6 (5449.02)
End-of-Treatment		
N	52	51
Mean (SD)	9409.9 (7070.24)	12385.8 (13926.29)
Percent Change from Baseline		
N	52	51
Mean (SD)	12.5 (85.27)	42.2 (107.25)
ANCOVA with Covariate of Baseline Hgb		
LS Mean Percentage Change from Baseline (SE)	11.3 (13.51)	43.4 (13.64)
LS Mean Difference from Placebo (SE) (95% CI)	-32.1 (19.26) (-70.3, 6.1)	
P-Value	0.098	

MMRM Model:
To incorporate the ESA dose usage over time, a MMRM model was used to test the Null Hypothesis the ITT population. For both percent change from baseline in prescribed ESA dose and in actual ESA dose, the nominal p-values were greater than 0.05.

Table 33 Percentage Change from Baseline Prescribed ESA Dose, ITT

	SFP (N=54)			Placebo (N=54)		
	ESA Dose/wk	Change from Baseline	% Change from Baseline	ESA Dose/wk	Change from Baseline	% Change from Baseline
N	52			51		
Baseline ESA Epoetin U/wk Mean (SD)	9483.2 (5413.9)			9205.9 (5500.1)		
N	52	52	52	51	51	51
EoT Prescribed ESA dose Epoetin U/wk Mean (SD)	9871.2 (7523.2)	387.9 (5556.2)	7.3 (67.66)	12628.8 (13967.4)	3422.9 (11641.9)	37.3 (106.9)
MMRM LS Mean (SE) (95% CI)			2.8 (6.60) (-10.3, 15.9)			9.5 (6.62) (-3.7, 22.6)
MMRM LS Mean % Difference from Placebo (SE) (95% CI) P-value	-6.7 (8.51) (-23.6, 10.2) 0.435					

Table 34 Percentage Change from Baseline Actual ESA Dose, ITT

	SFP (N=54)			Placebo (N=54)		
	ESA Dose/wk	Change from Baseline	% Change from Baseline	ESA Dose/wk	Change from Baseline	% Change from Baseline
n	52			51		

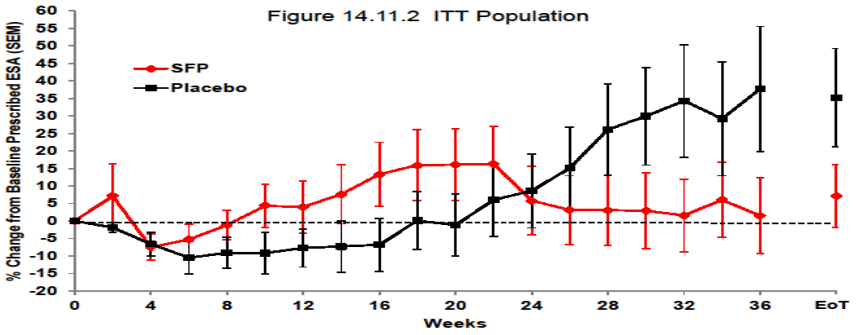
Baseline ESA Epoetin U/wk Mean (SD)	9177.5 (5505.1)			8835.6 (5449.0)		
n	52	52	52	51	51	51
EoT Prescribed ESA dose Epoetin U/wk Mean (SD)	9409.9 (7070.2)	232.4 (5581.0)	12.5 (85.27)	12385.8 (13926.3)	3550.2 (11467.6)	42.2 (107.25)
MMRM LS Mean (SE) (95% CI)			7.9 (8.05) (-8.1, 23.8)			15.7 (8.08) (-0.4, 31.7)
MMRM LS Mean % Difference from Placebo (SE) (95% CI) P-value	-7.8 (10.38) (-28.4, 12.8) 0.454					

Reviewer's comments:

The non-significant nominal p values in both the prescribed and actual ESA dose in the ITT population did not seem to demonstrate sufficient evidence of effectiveness of the study drug in reducing the prescribed ESA dose. Sensitivity analysis results appear to agree with this finding.

In addition, the percentage change from baseline in prescribed ESA dose by study week is plotted and presented below to provide a better understanding of the effect of the study drug on the prescribed ESA dose throughout the trial,.

Figure 4 Percent Change from Baseline in Prescribed ESA Dose by Study Week



Reviewer Comments: *The plot above raises concern on the interpretation of the efficacy of the study drug over the placebo at the end of treatment, because the mean percent change from baseline in prescribed ESA dose was higher in SFP group than in the placebo group for the first 24 weeks of the 36 weeks study period. In other words, for the first two-third of the study period, subjects in SFP group needed more prescribed ESA dose than the subjects in the placebo group. After week 24, the percent change of prescribed ESA dose in SFP group started to decline and became lower than the placebo group.*

2.3 Evaluation of Safety

Please refer to clinical review on the Safety issues of study SFP-4-RC, SFP-5-RC, and NIH-FP-01.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Gender, Race, Age, and Geographic Region

Subgroup analysis results are presented in this section by gender, race and age. The subgroup analysis by geographic region was not performed because almost all subjects are from US.

3.1.1 SFP-4-RC

Table 35 shows the primary efficacy analysis result in subgroups of gender, age and race in study SFP-4-RC. In this study, subjects tend to be male, white, and less than 65 years old. The magnitudes of the LS mean differences between the two treatment groups from the ANCOVA model appear to be supportive of the primary efficacy finding except two subgroups (patients younger than 65 years old and black). However, due to the non-randomized nature of the subgroup analyses and small sample sizes in some subgroups, the interpretation of results should be taken with caution.

Table 35 Reviewer's Analysis: Primary Efficacy Result in Subgroups of Gender, Age, and Race

		N (%)	LS Mean difference from Placebo (STD)	95% CI
Gender	Male	207 (67.9%)	0.37 (0.174)	(0.03, 0.72)
	Female	98 (32.1%)	0.31 (0.235)	(-0.16, 0.78)
Age	<65 years	208 (68.2%)	0.28 (0.170)	(-0.05, 0.62)
	>= 65 years	97 (31.8%)	0.44 (0.251)	(-0.06, 0.94)
Race	White	168 (55.1%)	0.43 (0.184)	(0.07, 0.80)
	Black	98 (32.1%)	0.18 (0.255)	(-0.33, 0.68)
	Other	39 (12.8%)	0.46 (0.428)	(-0.41, 1.33)

3.1.2 SFP-5-RC

Table 36 shows the primary efficacy analysis result in subgroups of gender, age and race in study SFP-5-RC. Similar to study SFP-4-RC, subjects tend to be male, white, and less than 65 years old. The magnitude of the LS mean difference between the two treatment groups from the ANCOVA model is comparable among white, black and other, and in general, supportive of the primary efficacy finding. Female subjects and subjects who are 65 years or older had higher LS mean difference than their counterparts. Due to the non-randomized nature of the subgroup analyses and small sample sizes in some subgroups, the interpretation of results should be taken with caution.

Table 36 Reviewer's Analysis: Primary Efficacy Result in Subgroups of Gender, Age, and Race

		N (%)	LS Mean difference from Placebo (STD)	95% CI
Gender	Male	175 (59.5%)	0.14 (0.194)	(-0.24, 0.53)
	Female	119 (40.5%)	0.59 (0.206)	(0.18, 0.1)

Age	<65 years	197 (67.0%)	0.22 (0.180)	(-0.14, 0.57)
	>= 65 years	97 (33.0%)	0.54 (0.226)	(0.09, 0.99)
Race	White	156 (53.1%)	0.34 (0.204)	(-0.06, 0.74)
	Black	118 (40.1%)	0.32 (0.218)	(-0.11, 0.76)
	Other	20 (6.8%)	-0.27 (0.595)	(-1.54, 1)

3.1.3 NIH-FP-01

Table below shows the primary efficacy analysis result in subgroups of gender, age and race in the NIH-FP-01 study. Again, subjects in this study tend to be male, white, and less than 65 years old. The magnitude of the percent change LS mean difference between the two treatment groups from the ANCOVA model is comparable among the age group. The magnitude of the percent change LS mean difference is larger for female and white subjects. Due to the non-randomized nature of the subgroup analyses and small sample sizes in some subgroups, the interpretation of results should be taken with caution.

Table 37 Reviewer's Analysis: Primary Efficacy Result in Subgroups of Gender, Age, and Race

		N (%)	% change LS Mean difference from placebo (SE)	95% CI
Gender	Male	67 (62.0%)	4.4 (20.75)	(-37.1, 46.0)
	Female	41 (38.0%)	-79.4 (27.23)	(-134.6, -24.2)
Age	<65 years	74 (68.5%)	-36.9 (21.66)	(-80.1, 6.3)
	>= 65 years	34 (31.5%)	-41.5 (29.91)	(-102.9, 19.8)
Race	White	66 (61.1%)	-51.7 (25.51)	(-102.7, -0.6)

	Black	42 (38.9%)	-11.8 (21.16)	(-54.7, 31.2)

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

4.1.1 SFP-4-RC

Summary of Efficacy Results:

In this study, SFP group had smaller change from baseline in Hgb level than the placebo group based on the protocol specified analysis. The reduction in the least square mean change from baseline between treatment groups was 0.35 g/dL smaller in the SFP group compared to the placebo group with p-value equals to 0.01 (LS means= 0.06 g/dL vs -0.3 g/dL for SFP and placebo, respectively). Sensitivity analyses and subgroup analyses appear to be supportive of the results from the primary efficacy analyses. The change from baseline in the key secondary endpoints such as ferritin, CHr, and $TSAT_{UIBC}$ were also numerically smaller in SFP group than in placebo group. However, these secondary endpoint analyses were considered as exploratory, thus no valid statistical inference should be drawn from them.

Summary of Statistical Issues:

1. A large extent of subjects who discontinued the study treatment before the planned 48 weeks.

2. The EoT Hgb values represents various time points and it is difficult to draw inference over the entire 48 weeks.

3. Differential reasons for treatment discontinuation due to protocol mandated anemia management changes could impact the estimation of the magnitude of the treatment effect on Hgb level.

4.1.2 SFP-5-RC

Summary of Efficacy Results

Similar to SFP-4-RC, in this study, SFP group had smaller change from baseline in Hgb level than the placebo group based on the protocol specified analyses. The reduction in the least square mean change from baseline between treatment groups was 0.35 g/dL smaller in the SFP group compared to the placebo group (LS means=-0.04 g/dL vs -0.39 g/dL for SFP and placebo, respectively; p-value=0.01). Sensitivity analyses and subgroup analyses appear to be supportive of the results from the primary efficacy analyses. The change from baseline in ferritin, CHr, and $TSAT_{UIBC}$ was numerically smaller in SFP group than in placebo group. However, these secondary endpoint analyses were considered as exploratory, thus no valid statistical inferences should be drawn from them.

Summary of Statistical Issues:

1. A large extent of subjects who discontinued the study treatment before the planned 48 weeks.

2. The EoT Hgb values represent various time points and it is difficult to draw inference over the entire 48 weeks.

3. Differential reasons for treatment discontinuation due to protocol mandated anemia management changes could impact the estimation of the magnitude of the treatment effect on Hgb level.

4.1.3 NIH-FP-01

Summary of Efficacy Results:

In summary, at the EoT, subjects in SFP group had a numerically smaller increase in the mean percent change from baseline in both prescribed and actual ESA doses (LS means difference=-32.3 % [5.0% vs 37.3% for SFP and placebo, respectively] and -29.6 % [11.1% vs 40.7% for SFP and placebo, respectively] for prescribed and actual ESA doses, respectively). However, both analyses had nominal p-values greater than 0.05 in the ITT population (nominal p-value=0.052 and 0.111 for mean percent change from baseline in both prescribed and actual ESA doses, respectively). Sensitivity analyses using MITT population showed the results are not robust.

Summary of Statistical Issues:

1. There is no replication of the results.

2. There is no formal sample size or power calculation presented. The statistical tests were described as exploratory, not conclusive in the protocol.

3. It is difficult to draw inference to the efficacy of Triferic on reducing the prescribed ESA dose to maintain desired Hgb level because subjects in the SFP group had higher mean percent change from baseline in prescribed ESA dose for the first two-third of the 36 weeks study period, in addition, the difference between the two treatment groups had a nominal P-value of 0.052 using the ITT analysis population.

4.2 Conclusions and Recommendations

Triferic is intended to treat iron loss or iron deficiency to maintain Hgb in adult patients with HDD-CKD. In SFP-4-RC and SFP-5-RC conducted for this use, patients were randomized (1:1) to treatment with SFP or placebo at each dialysis session for up to 48 weeks. Efficacy was assessed as the mean change in Hgb from baseline up to EoT compared between the SFP and the placebo groups. In summary, this review confirms the improvement of mean change in Hgb from baseline to EoT for both SFP-4-RC and SFP-5-RC in favor of the Triferic group. Due to the concern of early treatment discontinuation, differential reasons of early discontinuation and the results represent various time values, whether or not Triferic can sufficiently provide maintenance of Hgb level cannot be confirmed. Also, this statistical review cannot confirm that Triferic reduces the prescribed dose of ESA required to maintain desired Hgb levels based on a single study (NIH-FP-

01), because the study was exploratory in nature, no formal sample size or power calculations planned, and it was difficult to interpret of the efficacy of Triferic over the placebo at the end of treatment due to the cross-over of the prescribed ESA dose levels between treatment groups.

Reviewer's comments:
The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met in the afternoon session, on November 6, 2014 at the FDA White Oak Campus, Silver Spring, Maryland to discuss this NDA. The committee voted in favor of Triferic by a vote of 8 to 3.

4.3 Labeling Recommendations

Based on this statistical review, summaries of the primary efficacy results in the ITT population from study SFP-4 and SFP-5 are appropriate to be included in the labeling. However, whether or not Triferic can maintain the Hgb level over time cannot be confirmed from the data. Whether or not summary results of the secondary endpoints (e.g. in ferritin, CHr, and $TSAT_{UIBC}$) may provide important information for the prescribers will be deferred as clinical decision.

References

1. Kieser, M. and Friede, T. 2003. Simple procedures for blinded sample size adjustment that do not affect the type I error rate. *Stat. Med.* **22**:3571-3581.

2. Shih, W. and Gould, A. 1992. Sample size reestimation without unblinding for normally distributed outcomes with unknown variance. *Communications in Statistics (A)-Theory and Methods* **21**:2833-2853.

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/s/

LOLA LUO
12/24/2014

YUAN L SHEN
12/24/2014

RAJESHWARI SRIDHARA
12/24/2014

NDA/BLA Number: **Applicant: Rockwell Medical, Inc.** **Stamp Date: 3/24/2014**

NDA 206317

Drug Name: Triferic (Soluble Ferric Pyrophosphate) **NDA/BLA Type: Regular**

On **initial** overview of the NDA/BLA application for RTF: No

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			May need to request more information for clarification purpose

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____√____

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.			√	The statistical methods used in the study are not novel.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			√	**Please defer to clinical team**
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			Need more information.

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