STATISTICAL ANALYSIS PLAN

A Phase 1b dose-escalating study with Iron Sucrose (FeS), in healthy volunteers and subjects with chronic kidney disease stage 3-4

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List of ACRONYMS/Abbreviations

Abbreviation	Definition
AE	Adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ARB	angiotensin-receptor blockers
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
Cr	creatinine
CRO	contract research organization
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FeS	Iron sucrose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
HO-1	Heme oxygenase
ICF	informed consent form
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IND	investigational new drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
NOAEL	no-observed-adverse-effect level
POC	Proof of Concept
PP	Per Protocol
SAS	Statistical Analysis System
TEAE	treatment emergent adverse event

1. INTRODUCTION

This is a Phase 1b single-center, dose-escalating study to evaluate the pharmacodynamic effect of FeS in healthy volunteers and in subjects with stage 3-4 chronic kidney disease (CKD). The following biomarkers will be used as surrogate measures of protective activity: Haptoglobin, Ferritin, Hemopexin, IL-10, and Heme Oxygenase-1.

The purpose of this statistical analysis plan (SAP) is to specifying the statistical approaches for the data analysis prior to database lock. This SAP covers the planned analyses of all data collected on the electronic case report forms (eCRFs). This SAP supersedes the statistical methods described in the clinical protocol. Deviations/changes from the planned analyses described in this SAP will be identified, with justification, in the appropriate section of the clinical study report. This SAP is developed based on the clinical study protocol REN-002, version 1.0, dated 10 October 2018.

The reader of this SAP is encouraged to also read the clinical protocol and other related documents for details on the planned conduct of this study. Operational aspects related to the collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

2. STUDY OBJECTIVES

The primary objectives of the study are to evaluate:

1. The effect of Iron Sucrose (FeS) on biomarkers which are potential surrogates for cytoprotective activity in healthy volunteers and in subjects with stage 3-4 CKD.
2. To establish the biomarkers response to different doses of FeS.
3. Evaluate safety of FeS in comparison to levels of cytoprotective biomarkers.

3. STUDY OVERVIEW

This is a Phase 1b, single-center, dose-escalating study to evaluate the pharmacodynamic effect of FeS in healthy volunteers and in subjects with stage 3-4 CKD. The following biomarkers will be used as surrogate measures of protective activity: Haptoglobin, Ferritin, Hemopexin, IL-10, and Heme Oxygenase-1. Additionally, the P21 biomarker will be monitored at various points of the study.

Subjects who meet all inclusion criteria and none of the exclusion criteria are eligible to be enrolled into the study.

The study is designed as follows:

- A screening period with baseline evaluations for study eligibility.
- If subjects meet eligibility criteria, they will receive FeS IV on study day1.
- Subjects will stay in the clinic for the initial 24 hours after administration of FeS and will be discharged at the end of Day 2 if no safety issues appear.
- The study will be dose-escalating in 3 groups of 6 subjects consisting of 3 healthy volunteers and 3 subjects with CKD, evaluating doses of 120 mg FeS, 240 mg FeS and 360 mg FeS.

- Subjects will be followed for 8 days after the dose of FeS. Response biomarkers will be assessed at baseline and 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours after study drug administration.
- Total study duration will be 8 days for each subject, in addition to a screening period of up to 14 days.

Up to a total of 18 subjects consisting of 9 healthy volunteers and 9 chronic kidney disease subjects will receive single escalating doses of FeS. Six subjects consisting of 3 healthy volunteers and 3 subjects with CKD will be enrolled in one of three dose levels, starting at the lowest dose of 120 mg FeS.

For a complete list of assessments performed throughout the study, see the Time and Events Schedule (Section 13).

4. EFFICACY AND SAFETY VARIABLES

Efficacy Variables

- Percent change from baseline in biomarkers at each postbaseline time point
- Change from baseline in biomarkers at each postbaseline time point

The biomarkers include the following pharmacodynamic variables

- Haptoglobin (Hp)
- Ferritin
- Hemopexin
- IL-10
- Heme Oxygenase 1 (HO-1)
- P21

Safety Variables

- Treatment-emergent adverse events
- Infusion-related reactions
- Clinical laboratory tests
- ECG
- Vital signs
- Physical exams
- Concomitant medications

5. DEFINITIONS

Terminology	Definitions
Enrolled	Subjects who signed the informed consent, and are randomized to the study
Completer	Subjects who complete the End of Study (EOS) visit
Study Day	Day 1 is defined as the date subject took the study medication. Study Day for event post Day 1 is calculated as Event Date – Day 1 Date +1. Study Day for event prior to Day 1 is calculated as Event Date – Day 1 Date.
Baseline	Baseline is defined as the non-missing value collected most recent to and before the study of the study medication infusion
Prior Medication	Medication started and ended prior to the study drug infusion
Concomitant Medication	Medication taken on/after the study drug infusion. Concomitant medication may start prior to study drug infusion
Treatment-emergent	Adverse event with onset date/time on or after the start of study drug infusion

6. ANALYSIS POPULATIONS

The **Safety Analysis Population** will include all subjects who received study medication. This population will be used for all demographics, baseline characteristics, and safety summaries.

7. STATISTICAL METHODS OF ANALYSIS

7.1. General Principles

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). All analyses and tabulations will be performed using SAS® Version 9.4 or later. Continuous variables will be summarized using descriptive statistics (sample size [n], mean, standard deviation [SD], minimum, median, and maximum). Categorical variables will be tabulated with number and percentage of subjects. Unless otherwise noted, percentages will be based on the number of subjects from the population, as appropriate.

All individual subject data will be provided in listings. All listings will be sorted by dose group, CKD status (CKD patients versus healthy volunteer subjects), and collection date and time, where applicable.

Unless otherwise noted, tabulations of categorical data will present only those categories appearing in the data.

7.1.1. Handling Missing Values

7.1.1.1. Study Drug Administration Date or Time

It is expected that all necessary information on study drug administration (start and stop date and time) will be complete. Any such information that is missing and cannot be obtained through query resolution may be imputed, on a case-by-case basis, in a conservative manner that minimizes bias.

7.1.1.2. Adverse Event or Concomitant Medications Dates or Times

For AEs or concomitant medications with missing or partially missing start/stop date/time, the following imputation rules will be used when determining treatment-emergent or prior/concomitant status:

For partial start date/time:

- If the year is unknown, then the date will be assigned as the date and time of first dose of study treatment.
- If the month is unknown, then:
  - i) If the year matches the year of study drug administration, then the month and day will be imputed to be the first month and day.
  - ii) Otherwise, 'January' will be assigned.
- If the day is unknown, then:
  - i) If the month and year match the month and year of the dose of the study drug administration date, then the day of the dose of earliest study drug administration date with matching month and year will be imputed.
  - ii) Otherwise, '01' will be assigned.
- If the time is unknown, then:
  - i) If the date (day, month, and year) matches the date of an administration of study drug, then the time of dose of study drug time from that date will be imputed.
  - ii) Otherwise, '00:00' will be assigned.

For partial stop date/time:

- If the year is unknown, then the date will be assigned as the date subject discontinued from study, and the time will be set to the last time of the day ('23:59').
- If the month is unknown, then the month subject discontinued from study will be assigned.
- If the day is unknown, then the last day of the month will be assigned.
- If the time is unknown, then the last time of the day will be assigned ('23:59').

7.1.2. Multiplicity Adjustments

Not applicable. This is an early phase exploratory study.

7.1.3. By-Center Analyses

Not applicable. This is a single-center study.

7.2. Subject Disposition

Subject disposition will be tabulated by dose group and overall and will present the number and, when appropriate, percentage of subjects who were:

- Enroled
  - Not treated
  - Treated
- Completed the study as planned
- Discontinued from the study, and
- Reasons for discontinuation from the study

Percentages for all rows will use the number of subjects treated as the denominator.

Data will be summarized for the pool of CKD patients and healthy volunteers.

7.3. Description of Demographics and Baseline Characteristics

7.3.1. Demographics

The summary of demographic data will present:

- Age (years) – descriptive statistics
- Sex – n (%)
- Ethnicity – n (%)
- Race – n (%)

Age is calculated from the date the subject signed the informed consent form (ICF) and birth. It is presented as the number of years, rounding down to the nearest integer year. For partial birthdates, impute the first of the month for missing day and January for missing month to calculate age. It is presumed that birth year is known.

The demographic summary will present the data for each dose group and overall as well as by CKD status.

7.3.2. Baseline Characteristics

The summary of baseline characteristic data will present:

- Physical examination and weight
- Electrocardiogram

Descriptive statistics (n, mean, SD, median, minimum and maximum) will be provided by dose group for the Safety Analysis Set.

7.4. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date and time prior to the start of study drug administration.

Concomitant medications are defined as medications taken after the start of study drug administration (i.e., started prior to the start of study drug administration and continued after or started after the start of study drug administration).

Prior and concomitant medications will be listed for each subject with pertinent variables.

7.5. Measurements of Treatment Compliance

Study treatment is administered by the site personnel other than the subject him/herself, therefore compliance is assured.

7.6. Efficacy Analysis

7.6.1. Percent Chamge in Response Biomarkers

The efficacy endpoint is the percent change (PCH_T) in each response biomarker relative to the Baseline period.

PCH_T will be calculated as 100 x (T – B)/B, where T and B are Response biomarker at 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours post dose (T) and baseline period (B).

PCH_T will be analyzed using a Mixed-Effect Model for Repeated Measure (MMRM) as follows:

- A 2-way MMRM pooling CKD patients and healthy subjects together
- A 2-way MMRM for CKD patients
- A 2-way MMRM for Healthy subjects

The model will include dose level, visit (Day 1 2, 4, 8, 12, 18, and 24 hours, Day 2, Day 3, Day 4, Day 5, and Day 8), and dose-by-visit interaction as factors and baseline response biomarker as covariate. The model parameters will be estimated using the restricted maximum likelihood method with the toeplitz variance-covariance matrix and Kenward-Roger estimate for the denominator degrees of freedom. Least squares mean (LSM) and the associated 95% confidence interval (CI) for each dose level will be presented at each time point. Percent change from baseline will be analyzed by the t-test from the model for statisticial significance. The between dose comparison will be performed using constrast in the main effect and the simple contrast at each time point. The difference in LSM between doses, the 95% CI and the t-test for the difference will also be presented. Results will be presented for the pooled population, as well as for the CKD and healthy populations separately.

As a sensitivity analysis, percent change from baseline at each time point and between dose difference in percent change from baseline will be analyzed respectively by the Wilcoxon signed-rank test and the Wilcoxon rank-sum test.

Additionally, LSM for each dose group will be plotted over time for the CKD patients and healthy volunteers pooled population as well as for each population separately. Dose response relationship will be examined graphically and may be analyzed where appropriate.

A sample SAS code is provided as follows. The code assumes that "visit" has 10 values (2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours), "dose" is coded as 1 = 120 mg FeS, 2 = 240 mg FeS, and 3 = 360 mg FeS, "ckd" is coded as 2=CKD patients and healthy volunteers pooled, 1 = patients with CKD, 0 = healthy colunteers, and "resp" = PCH_T, the % change from baselin being analyzed.

```
ODS OUTPUT LSMEANS=lsm DIFFS=diff ESTIMATE=estm;
PROC MIXED DATA=XXXX METHOD=REML;
     BY ckd;
     CLASS dose usubjid visit;
     MODEL resp = base visit dose dose*visit / DDF=KR2;
     REPEATED visit / SUBJECT=usubjid(dose) TYPE=CS;
     LSMEANS dose / DIFF CL;
     LSMEANS dose*visit / PDIFF CL;
RUN;
ODS OUTPUT CLOSE;
```

Note: Depending on the convergence status in the computation, Toeplitz (toep), 1st order autoregressive AR(1), and compound symmetry (CV) variance-covariance matrix will be applied sequentially. The final analysis will be based on the first matrix leading to the convergence in the computation.

7.6.2. Absolute Chamge

In addition to the percent changes from baseline, absolute change from baseline will also be analyzed using MMRM. The method of analysis will be identical after replacing variable "resp" with "T-B"in Section 10.6.1.

7.7. Safety Analyses

No inferential statistics are planned for any safety assessment.

7.7.1. Adverse Events

Safety assessments will be based mainly on the nature, frequency, relationship, and severity of adverse events (AEs). All AEs will be listed with onset/stop day, relationship to study drug, severity, action taken, and outcome. Pertinent subject information including dose group and demographics will also be included. Separate listings will be provided for TEAEs leading to study discontinuation, treatment-emergent serious AEs (TESAEs), and infusion-related TEAEs.

7.7.2. Laboratory Test

Hematology, biochemistry, and urinalysis (pH and specific gravity) test results and their change from baseline will be summarized by dose group and visit using descriptive statistics.

A complete lab data listing, including hematology, biochemistry, and urinalysis will be provided for all subjects. Abnormal results will be flagged.

7.7.3. Vital Signs

Vitals signs are resting heart rate (bpm), pulse (beats per minute), oral body temperature (^oC), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg). Vital signs will be

summarized by dose group at each scheduled timepoint. Summaries will present both actual and change-from-baseline results.

7.7.4. ECG

The investigator evaluation for the overall ECG findings by normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS) will be tabulated with number and % of subjects at each time point.

7.8. Interim Analysis

No interim analyses are planned for this study.

8. SAMPLE SIZE CALCULATIONS

No formal sample size calculation has been performed for the study. However, it is believed that 6 subjects per dose group will be adequate to establish differences in biomarker response between groups.

9. REFERENCES

10. TIME AND EVENTS SCHEDULE OF STUDY PROCEDURES

Study Day	**Screening**	**1**	**2,3,4,5,8(EOS)[1]**
Parameter	**Within 14 days prior to first dose**		
Written informed consent	X		
Eligibility criteria	X		
Demographics	X		
Medical history	X		
Physical examination and weight	X	X[2]	
Electrocardiogram	X	X[1,2]	
Vital signs	X	X[2]	X
Serum chemistry[7,8]	X	X[2]	X
Hematology[7,8]	X	X[2]	X
Response biomarkers[7, 10]		X[2,3]	X
Urinalysis including sediment[8]	X	X[2]	X
Urine pregnancy test[9]	X	X	X at Day 8 (EOS)
Urine drug/alcohol/cotinine screen	X		
Confinement in clinical testing unit[4]		X[4]	
FeS IV		X[5]	
Discharge from clinical testing unit			X[6]
Prior/Concomitant medications	X	X	X
Adverse events		X	X
Investigational product reconciliation			X

1 Day 8 (EOS) visit will occur (± 1) days after administration of FeS.
2 Baseline parameters performed prior to dosing on Study Day 1.
3 Additional biomarker samples collected at 2, 4, 8, 12, 18 hours (±15 minutes) after completion of IV dose
4 Subjects will be confined in the clinical testing unit a minimum of 24 hours from the morning of Study Day 1 until after collection of the 24-hour post-dose sample on Study Day 2.
5 FeS will be administered as an IV dose after Baseline ECG, vital signs and blood and urine samples are collected.
6 Discharge from unit following evaluations and sample collection required on Study Day 2
7 Measured fasting (nothing by mouth except water, coffee or tea, with or without milk and/or sugar, and essential medications only for a minimum of 8 hours prior to sample collection at the clinic).
8 Parameters to be measured are detailed in Protocol Appendix 1.
9 For women of childbearing potential using kits supplied by the laboratory
10 Haptoglobin, Ferritin, Hemopexin, IL-10, P21 and HO-1.

11. CONVENTIONS FOR THE PRESENTATIONS OF TABLES, LISTINGS, AND FIGURES

- Report output will be provided as MS Word Rich Text Format (RTF) and Portable Document Format (PDF) generated using SAS.
- Font – Times New Roman font with minimum of 9 point font size for tables and 7 point for listings.
- Margins – Minimum of 1.2" bound edge margin (top margin for landscape) and 0.5" other margins on 8.5"x11" paper as per the FDA guidance for e-submission.
- Continuous data will be summarized using n (number of subjects with non-missing observations), mean, median, standard deviation (SD), minimum value, and maximum value.
- Categorical data will be summarized using the frequency count and percentage (n, %) of subjects in each category.
- Number of subjects with non-missing values or number of subjects with missing values (eg, Not Done) will be presented, where appropriate. Subjects with missing values will not contribute to the denominator of percentage calculations.
- Counts of zero in any category will be presented without percentage.
- Precision of summary statistics:
    - Sample size (n, N) and number of missing responses (if displayed) – Integer.
    - Mean, confidence interval – One additional decimal place than reported/collected.
    - Standard deviation – Two additional decimal places than reported/collected.
    - Median other percentile – One additional decimal place than reported/collected.
    - Minimum, maximum – Same number of decimal places as reported/collected.
    - Ratios – two decimal places.
    - Percentages – one decimal place generally, or two decimal places for <0.1%.
- P-values will be reported to 4 decimal places. Values that are less than <0.0001 will be presented as "<0.0001". Similarly, large p-values will be presented as ">0.9999".
- Data listings will be sorted in the order of dose group, subject ID, assessment date/time and assessment name.
- Dates will be presented in the ISO-8601 format YYYY-MM-DD. Times will be displayed in 24-hour clock format.
- Numbering for tables, figures and listings will follow ICH E3 Guidelines.
- The shell provides a general guidance for how the data will be presented. The actual presentation may be modified to accommodate the page size restriction.
- For TFLs with multiple pages, page numbers will be included.
- All TFLs will have SAS program names and folder names in the footnote for tracking purpose.

12. LIST OF TABLES

Note, all tables will be repeated for CKD Patients Population and Healthy Subjects Population with Table numbers changed to Table 14.x-x.x.2 and 14.x-x.x.3 from 14.x-x.x1, respectively.

Table 14.1-1.1: Tabulation of Subject Disposition – CKD and Healthy Subjects Pooled

	360 mg FeS [N=XX] n (%)	240 mg FeS [N=XX] n (%)	120 mg FeS [N=XX] n (%)	Total [N=XX] n (%)
Screened				xx
Enrolled	xx	xx	xx	xx
Not Treated	xx	xx	xx	xx
Treated	xx (100)	xx (100)	xx (100)	xx (100)
Safety Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Modified Intent to Treat Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pharmacokinetic Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued from Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for discontinuation				
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note to programmer: *For reasons for discontinuation only those reasons that appear in the data will appear on the table. All percentages are based on the number of enrolled and treated subjects.*

Table 14.1-2.1: Summary of Subject Demographics - CKD Patients and Healthy Subjects Pooled

	Statistic	360 mg FeS [N=XX]	240 mg FeS [N=XX]	120 mg FeS [N=XX]	Total [N=XX]
Age (yrs)	n	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x
	SD	x.xx	x.xx	x.xx	x.xx
	Median	xx	xx	xx	xx
	Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Sex					
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity					
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race					
American Indian/Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black/African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian/Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 14.1-3.1: Summary of Subject Characteristics at Baseline – CKD Patients and Healthy Subjects Pooled

		360 mg FeS [N=xx]	240 mg FeS [N=XX]	120 mg FeS [N=xx]
Weight (kg)	n	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
Height (cm)	n	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
BMI (kg/m2)	n	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x

Table 14.2-1.1.1: MMRM Analysis of Percent Change from Baseline in Ferritin (Fe) – CKD Patients and Healthy Volunteers Pooled, MITT Population

Time Point	Statistic	360 mg FeS [N=XX]	240 mg FeS [N=XX]	120 mg FeS [N=XX]
Baseline	n	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
2 hours				
Actual	n	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
% change from				
Baseline	n	xx	xx	xx
	Mean	xxx.x	xxx.x	xxx.x
	SD	xxx.xx	xxx.xx	xxx.xx
	Median	xxx.x	xxx.x	xxx.x
	Min, Max	xxx.x, xxx.x	xxx.x, xxx.x	xxx.x, xxx.x
	LS Mean	xxx.x	xxx.x	xxx.x
	95% CI of LS Mean	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
	LSM Difference from 120mg FeS	xxx.x	xxx.x	
	95% CI of Difference from 120mg FeS	(xx.x, xx.x)	(xx.x, xx.x)	
	MMRM P-value for Difference from 120mg FeS	0.xxxx	0.xxxx	
	CMH P-value for Difference from 120mg FeS	0.xxxx	0.xxxx	
	LSM Difference from 240mg FeS	xxx.x		
	95% CI of Difference from 240mg FeS	(xx.x, xx.x)		
	MMRM P-value for Difference from 240mg FeS	0.xxxx		
	CMH P-value for Difference from 120mg FeS	0.xxxx	0.xxxx	
. . .				
168 hours	. . .			
	. . .			
Overall	. . .			
	. . .			

Note: MMRM model includes Dose, Time Point, and Dose-by-Time Point interaction as factor variables, Baseline as covariate, and Subject as repeated measure unit over Time Points. The between dose comparison at each time point is based on the simple contrast and the Overall betwee dose comparison is based on the contrast for the main effect. CMH test at each time point is stratified by baseline quintiles. The Overall CMH test is stratified by Time Point and baseline quintiles. Modified ridit scores are used in the computation.

Note to programmer: *Time points are:* baseline, Day 1 2, 4, 8, 12, 18, and 24 hours, Day 2, Day 3, Day 4, Day 5, and Day 8.

Use 14.2-1.1.1 shell for

Table 14.2-1.2.1: MMRM Analysis of Change from Baseline in Ferritin – CKD Patients and Healthy Subjects Pooled

Table 14.2-2.1.1: MMRM Analysis of Percent Change from Baseline in Haptoglobin (Hp) – CKD Patients and Healthy Subjects Pooled

Table 14.2-2.2.1: MMRM Analysis of Change from Baseline in Haptoglobin (Hp) – CKD Patients and Healthy Subjects Pooled

Table 14.2-3.1.1: MMRM Analysis of Percent Change from Baseline in Hemopexin – CKD Patients and Healthy Subjects Pooled

Table 14.2-3.2.1: MMRM Analysis of Change from Baseline in Hemopexin – CKD Patients and Healthy Subjects Pooled

Table 14.2-4.1.1: MMRM Analysis of Percent Change from Baseline in *IL-10* – CKD Patients and Healthy Subjects Pooled

Table 14.2-4.2.1: MMRM Analysis of Change from Baseline in *IL-10* – CKD Patients and Healthy Subjects Pooled

Table 14.2-5.1.1: MMRM Analysis of Percent Change from Baseline in Heme Oxygenase 1 (HO-1) – CKD Patients and Healthy Subjects Pooled

Table 14.2-5.2.1: MMRM Analysis of Change from Baseline in Heme Oxygenase 1 (HO-1)

Table 14.2-6.1.1: MMRM Analysis of Percent Change from Baseline in P21 – CKD Patients and Healthy Subjects Pooled

Table 14.2-6.2.1: MMRM Analysis of Change from Baseline in P21 – CKD Patients and Healthy Subjects Pooled

Table 14.2-7.1.1: MMRM Analysis of Percent Change from Baseline in Serum Creatinine – CKD Patients and Healthy Subjects Pooled

Table 14.2-7.2.1: MMRM Analysis of Change from Baseline in Serum Creatinine – CKD Patients and Healthy Subjects Pooled

Table 14.3-1.1.1: Summary of Hematology over Time – CKD Patients and Healthy Subjects Pooled

Hemoglobin (Unit)

		360 mg FeS [N=XX]		240 mg FeS [N=XX]		120 mg FeS [N=XX]	
Timepoint	Statistic	Observed Value	Change From Baseline	Observed Value	Change From Baseline	Observed Value	Change From Baseline
Baseline	n	xx		xx		xx	
	Mean	xx.x		xx.x		xx.x	
	SD	xx.xx		xx.xx		xx.xx	
	Median	xx.x		xx.x		xx.x	
	Min, Max	xx.x, xx.x		xx.x, xx.x		xx.x, xx.x	
2 hours	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
4 hours	n	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

Note to programmer: *Hematology parameters are Hemoglobin, Hematocrit, Erythrocyte count (red blood cells), Differential leukocytes, Total leukocytes (white blood cells), Platelets*

Time points, in order of appearance, for this table are: baseline, 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours. *Only included change from baseline for post-baseline assessments.*

Use 14.3-1.1 for

Table 14.3-1.2.1: Blood Chemistry: Change from Baseline Classification by Time Point - CKD Patients and Healthy Subjects Pooled

Total protein, Albumin, Bicarbonate, Blood urea nitrogen (BUN), Creatinine, Total bilirubin, Alkaline phosphatase, Glucose, Sodium, Potassium, Inorganic phosphate, Calcium (total and ionized), Magnesium, Gamma-glutamyl transferase

Table 14.3-1.3.1: Urinalysis: Change from Baseline Classification by Time Point - CKD Patients and Healthy Subjects Pooled

pH, Specific Gravity

Use 14.3-1.1.1 shell for

Table 14.3-2.1: Summary of Vital Signs over Time – CKD Patients and Healthy Subjects Pooled

Note to programmer: *Vital signs, in order of appearance, for this table are Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Pulse (bpm), Oral Body Temperature (°C), Respiratory Rate (bpm).*

Time points, in order of appearance, for this table are: baseline at 2, 4, 8, 12, 18, 24, 48, 72, 96 and 168 hours.

Table 14.3-3.1: Tabulation of Investigator's Overall Evaluation of ECG Findings - CKD Patients and Healthy Subjects Pooled, Safety Population

Time Point	Evaluation	360 mg FeS [N=XX] n (%)	240 mg FeS [N=XX] n (%)	120 mg FeS [N=XX] n (%)	Total [N=XX] n (%)
Predose	n	xx	xx	xx	xx
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, Not Clinically Significant	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, Not Clinically Significant	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
0.5 hour postdose	n	xx	xx	xx	xx
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, Not Clinically Significant	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, Not Clinically Significant	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 hour postdose	n	xx	xx	xx	xx
	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, Not Clinically Significant	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal, Not Clinically Significant	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
. . .					

13. LIST OF FIGURES

Figure 1.1: Plot of Least Square Means (95% CI) of Ferritin (unit) Over Time by Dose Group – CKD Patients and Healthy Subjects Pooled

Figure 1.2: Plot of Least Square Means (95% CI) of Ferritin (unit) Over Time by Dose Group - CKD Patients, MITT Population

Figure 1.3: Plot of Least Square Means (95% CI) of Ferritin (unit) Over Time by Dose Group – Healthy Subjects, MITT Population

Figure 2.1: Plot of Mean (± SE) Haptoglobin (unit) Over Time by Dose Group – CKD Patients and Healthy Subjects Pooled, PK Population

Figure 2.2: Plot of Mean (± SE) Haptoglobin (unit) Over Time by Dose Group – CKD Patients, PK Population

Figure 2.3: Plot of Mean (± SE) Haptoglobin (unit) Over Time by Dose Group – Healthy Subjects, PK Population

Repeat for Hemopexin, IL-10, Heme Oxygenase 1, P21, and Serum Creatinine

Programmer's note: annotate the curve with 'P=0.0xx" for the time points where the t-test for the change from baseline is significant

14. LIST OF LISTINGS

1. Disposition
2. Demographics and Body Characteristics
3. Medical History
4. Study Drug Administration
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7. Efficacy Biomarkers over Time
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12. ECG Evaluation
13. Vital Signs