Cover Page for Statistical Analysis Plan

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Statistical Analysis Plan

Protocol No.: COR-001-01

A PHASE 1/2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, COHORT DOSE-ESCALATION STUDY IN HEMODIALYSIS PATIENTS TO ASSESS THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF MULTIPLE IV DOSES OF COR-001

Sponsor:	Corvidia Therapeutics
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Redacted statistical analysis plan
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STATISTICAL ANALYSIS PLAN APPROVAL

Prepared by: [redacted]

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Sponsor Approval

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Name: [redacted]		
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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
CHr	Reticulocyte hemoglobin content
C_{max}/C_{min}	Maximum/minimum observed concentration
CRF	Case report forms
CRO	Contract research organization
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ERI	ESA resistance index (ESA weekly dose/[targeted dry weight in Kg*hemoglobin in g/dL])
ESA	Erythropoiesis-stimulating agent
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue [questionnaire]
ANCOVA	Analysis of Covariance
HR	Heart rate
hsCRP	High sensitivity C-Reactive Protein
ICF	Informed consent form
IL-6	Interleukin-6
IV	Intravenous
IVBP	IV Bag Protectant
IWRS	Interactive Web-Response System
kg	Kilogram
LVEDI	Left ventricular end diastolic index
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
LVESMI	Left ventricular end systolic volume index
MCV	Mean corpuscular hemoglobin
mg	Milligram
min	Minute
mL	Milliliter
MRI	Myocardial Resonance Imaging
MTD	Maximally Tolerated Dose
NT-proBNP	N-terminal pro-B-natriuretic peptide
PD	Pharmacodynamic
PK	Pharmacokinetic
SAA	Serum amyloid A
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation	Term
SEM	Standard Error of the Mean
SRC	Safety Review Committee
SOP	Standard operating procedure
$T_{½}$	Half-life
TSAT	Transferrin saturation

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Corvidia Therapeutics Protocol COR-001-01. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP has been developed using Protocol amendment 2 dated 20-Sep -2016 and the final eCRFs dated 05-JUL-2016.

Pharmacokinetic and pharmacokinetic-pharmacodynamic modeling analyses are described in the Data Analysis Plan for Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Modeling.

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

The primary objective of the study is to evaluate the safety of multiple doses of COR-001.

1.1.2 Secondary Objectives

The secondary objectives of the study include the following:

- To model the relationship of COR-001 pharmacokinetics and primary pharmacodynamics as assessed by free and total serum Interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP) and serum amyloid A (SAA)

- To evaluate the secondary pharmacodynamic effects of COR-001 as assessed by:
  - Hemoglobin
  - Erythropoiesis stimulating agent (ESA) resistance index (ERI)
  - Systemic iron availability (transferrin saturation (TSAT), reticulocyte hemoglobin concentration (CHr) and absolute reticulocyte count)
  - Systemic iron stores (serum ferritin and supplemental iron dose requirements)
  - Malnutrition-inflammation (pre-albumin, albumin)
  - Serum cardiac biomarkers (Troponin T and N-terminal pro-B-natriuretic peptide [NT-proBNP])
  - Left ventricular mass index (LVMI) by non-contrast Myocardial Resonance Imaging (MRI)
  - Physical function by handgrip strength and symptoms of fatigue

- To investigate the immunogenicity of COR-001

1.2 STUDY ENDPOINTS

1.2.1 Primary Safety Endpoint

Primary safety endpoint is characterization of the Maximally Tolerated Dose (MTD) or to establish that the highest dose examined did not exceed the MTD. MTD will be characterized based on the Dose-Limiting Toxicities (DLTs) defined in Section 1.2.2. Potential DLTs will be identified programmatically and through clinical review of adverse event information and lab information.

1.2.2 Secondary Safety Endpoints

- Description of the frequency of DLTs by treatment group.

- Dose-Limiting Toxicities are identified as follows:
  1. Confirmed (i.e., at least 2 consecutive measurements) Grade 3 neutropenia and representing a decline of > 25% from baseline
  2. Serious adverse events of infection in the presence of confirmed (i.e., at least 2 consecutive measurements) Grade 2 or higher new onset lymphopenia or new onset neutropenia.
  3. ≥ Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST)
  4. ≥ Grade 4 hematologic toxicity
  5. ≥ Grade 3 non-hematologic toxicity

  DLT was defined as any toxicity the relationship of which to the investigational agent cannot be ruled out as follows:

  - With the exception of Grade 3 non-hematologic events, Grade 3 (or higher) CTCAE toxicity of above events having an assessed relationship to the Study Drug of "definitely", "probably", "possibly", or "unlikely" will be considered DLTs.

  - Grade 3 non-hematologic toxicities having an assessed relationship to the Study Drug of "probably", or "possibly" will be considered DLTs.

  Note: "non-hematologic events" refer to DLT criteria 1, 2, 3, and 5 above.

- Description of the frequency of the events of interest by treatment group. The events of interest included:
  - Severe infusion-related reactions
  - Hypersensitivity reaction during the Study Drug infusion
  - Anaphylaxis occurring at any time, even if considered unrelated to the Study Drug

    Infusion-related reactions, hypersensitivity reactions, and anaphylaxis will be identifiable from a check box on the AE CRF and the CTCAE grade of the event and supported by data collected on the Infusion-related reaction/Hypersensitivity/Anaphylaxis CRF. The protocol defines hypersensitivity reactions and infusion-related reactions by their temporal relationship based on timing of onset during the study drug infusion.

- Description of additional safety assessments by treatment group: adverse events, vital signs, ECG, clinical laboratory, and anti-drug antibodies (binding and neutralizing).

1.2.3 Pharmacodynamic Endpoints

Data from COR-001-treated patients from Cohorts not exceeding the MTD will be pooled and data from all placebo patients will be pooled for the pharmacodynamic endpoint analyses. Dose-relationships will be explored by also presenting data by dose regimen (i.e., 2 mg Q2 weeks, 6 mg Q2 weeks, 20 mg Q2 weeks, and pooled placebo).

1.2.3.1 Primary Pharmacodynamic Endpoints

- Change from baseline (mean of Full Screening and Day 1 values) in hsCRP to Week 4 between treatment groups
- Change from baseline (mean of Full Screening and Day 1 values) in SAA to Week 4 between treatment groups

1.2.3.2 Secondary Pharmacodynamic Endpoints

- Change from baseline (mean of Screening and Day 1 values) in TSAT to Week 4
- Change from baseline (mean of Screening and Day 1 values) in the CHr to Week 4
- Change from baseline (mean of Full Screening and Day 1 values) in hsCRP to the mean of Weeks 10-12
- Change from baseline (mean of Full Screening and Day 1 values) in SAA to the mean of Weeks 10-12
- Change from baseline (mean of Full Screening and Day 1 values) in serum pre-albumin to the mean of Weeks 10-12 and albumin to Week 12
- Change from baseline (weekly mean of Screening) in ERI to Week 4
- Change from baseline (weekly mean of Screening) in ERI to the mean of Weeks 8 – 12
- Change from baseline (mean of Full Screening and Day 1 values) in Hemoglobin to Week 4
- Change from baseline (mean of Full Screening and Day 1 values) in Hemoglobin to Week 10-12
- Change from baseline (mean of Full Screening and Day 1 values) in Hemoglobin to Week 10-12, excluding hemoglobin values following a change in the total weekly ESA dose. A change is defined as the first time when the ESA weekly dose goes up by >25% or down by >25% relative to the previous week's dose.
- Change from baseline (weekly mean of Full Screening) in ERI to the mean of Weeks 10 – 12
- Change from baseline (mean of Full Screening and Day 1 values) in TSAT to Week 10-12
-
- Change from baseline (mean of Full Screening and Day 1 values) in the CHr to Week 10-12
-
- Change from baseline (mean of Full Screening and Day 1 values) in serum albumin to Week 12

Exploratory Pharmacodynamic Endpoints

- Description of the systemic iron availability (TSAT, absolute reticulocyte count,

hemoglobin, CHr) over time

• Description of markers of malnutrition-inflammation (pre-albumin and albumin) over time

• Description of systemic iron stores (serum ferritin, hepatic and splenic iron content by MRI, and supplemental iron dose requirements) over time

• Description of ERI change from baseline (weekly mean during the Screening Period) through Week 24

• Description of changes ESA and parenteral iron dose requirements from baseline (weekly mean during the Screening Period) to Evaluation Period (Weeks 8 – 12) and through Week 24

• Description of changes in LV mass index from Screening to Week 12
Description of changes in pre-dialysis, post-dialysis, and delta-serum Troponin and NT-proBNP (defined as the difference between the pre- and post-dialysis troponin) from baseline (mean of Screening) to Weeks 10 – 11

• Description of handgrip strength from baseline (during Screening) to Week 12

• Description of the FACIT fatigue score from baseline (during Screening) to Week 12

Specifically ERI is calculated as follows:

For patient receiving epoetin alfa:

$$\frac{\text{Total weekly dose of epoetin alfa (units)}}{\text{(hemoglobin [g/dL] * target dry body weight [kg])}}$$

For patients receiving darbepoetin alfa:

$$\frac{\text{Total weekly dose of darbepoetin alfa (mcg) * 300}}{\text{(hemoglobin [g/dL] * target dry body weight [kg])}}$$

For patients receiving methoxy polyethylene glycol-epoetin beta:

$$\frac{\text{Weekly dose of methoxy polyethylene glycol-epoetin beta (mcg) * 300}}{\text{(hemoglobin [g/dL] * target dry body weight [kg])}}$$

1.3 SUMMARY OF THE STUDY DESIGN

1.3.1 General Study Design and Plan

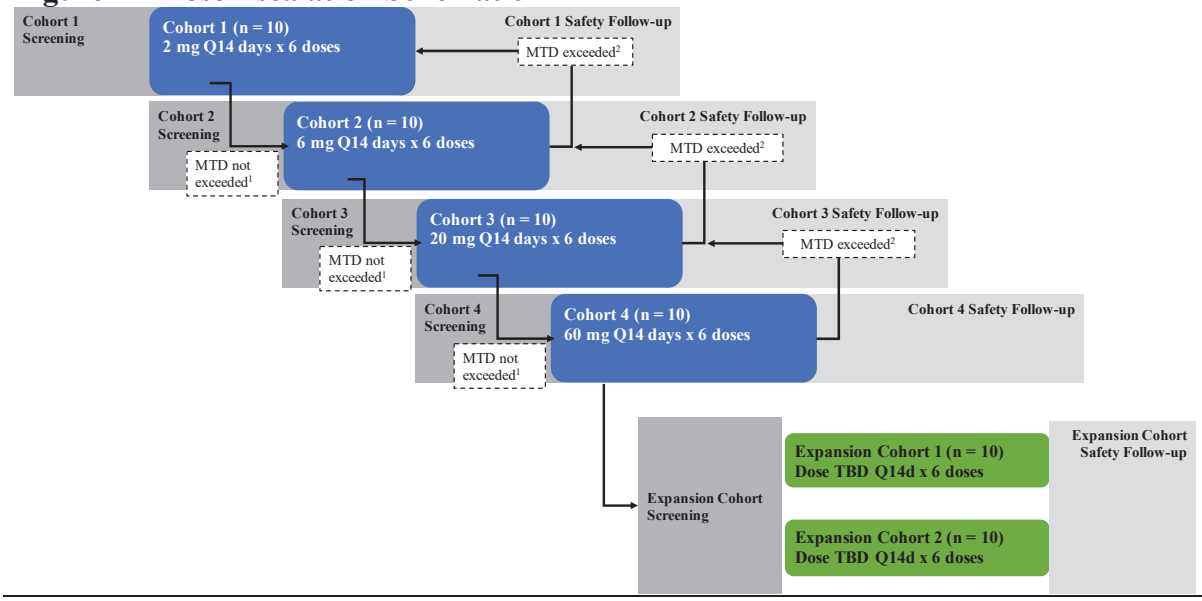
This is a randomized, double-blind, placebo-controlled trial designed to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of multiple doses of COR-001 or placebo administered to sequential cohorts of hemodialysis patients.

Within each dosing cohort ten hemodialysis patients will be randomized to COR-001 or placebo at ratio of 8 to 2. Prior to dose escalation there will be a formal safety review by the Safety Review Committee (SRC). The SRC will specifically determine whether MTD has been exceeded based on protocol-defined DLT occurring through Study Day 21 in the 8 actively-treated patients in the current cohort (see Figure 1). In addition, pharmacokinetic and pharmacodynamic results will be reviewed to assess the appropriateness of the next planned dose and to guide revision of the next dose to be evaluated, if necessary. The planned doses are shown in Table 1. These doses may be adjusted based on accruing data; however, the maximum dose to be studied will not exceed the planned total dose in Cohort 4 (60 mg every 14 days [6 doses]).

A single interim analysis was planned to enable future program planning.

Patients will undergo an up to 4-week Screening Period. Those who meet the entry criteria will be randomized on Day 1 (a dialysis day) (or Day -1 with approval) and will receive the first dose of study drug during dialysis. Additional visits will follow the schedule of events (Appendix A, Section 15.1 of protocol). All subsequent study drug infusions will also be administered during dialysis and study visits will coincide with regularly scheduled dialysis treatments. Patients dropping out for reasons unrelated to safety may be replaced. Following the 12-week Treatment Period, patients will be followed for an additional 12 weeks for safety. The patients will have completed their primary study participation at Week 24 (end of the Safety Follow-Up Period). Sparse blood samples will be additionally collected on Week 35 for anti-drug antibodies, pharmacokinetics, and IL-6 measurements as part of an Extended Follow-Up Period.

Figure 1 Dose Escalation Schematic



The MTD assessment will be based on safety data from Weeks 1 to 3. If more than 2 of 8 active patients in a cohort experience a DLT, the MTD will be considered to have been exceeded.
[1]If the MTD is not exceeded, dose escalation may continue.
[2]If the MTD is exceeded, a lower dose, including previously studied dose, may be selected.
The planned doses shown here may be adjusted based on accruing data. The highest dose that will be studied is a cumulative dose of 360 mg. Expansion cohorts to further evaluate doses below the dose that exceeded the MTD may be initiated at any time.

Table 1 Planned COR-001 Doses, Serial Dilutions and Administered Volumes

DOSE COHORT	DOSING REGIMEN	DRUG STOCK CONCENTRATION (MG/ML IN STERILE WATER)	# OF SERIAL DILUTIONS (1ML DRUG STOCK ADDED TO 2ML DILUTION VIAL FOR FINAL VOLUME OF 3ML)	DILUTED DRUG VOLUME TO BE USED (ML)	IVBP VOLUME TO BE ADDED TO SALINE INFUSION BAG (IN 100ML SALINE)	TOTAL VOLUME TO BE ADDED TO 100ML 0.9% SALINE
1	2 mg every 14 days	50	3	1.1	1.8	2.9
2	6 mg every 14 days	50	2	1.1	1.8	2.9
3	20 mg every 14 days	50	1	1.2	1.8	3.0
4	60 mg every 14 days	50	0	1.2 (0.6ml from 2 drug vials)	1.8	3.0

1.3.2 Sample Size and Statistical Power Considerations

The primary objective of this study is to determine the maximum tolerated dose. The MTD will be exceeded and stopping criteria for that dose will have been met if more than 2 of 8 COR-001-treated patients in a cohort experience a DLT (≥ 25%). With 8 patients dosed in each cohort and at the expected DLT rate of 25%, the probability of observing 2 or more patients with DLT is greater than 63% and the probability of observing at least 1 patient with DLT is 90%.
Sample size calculations were performed for hsCRP, TSAT, and CHr based on the literature (Coyne 2007 and Sieper 2013). For 80% power to observe an hsCRP difference from placebo of -10.6 mg/dL with a common standard deviation of 17.3 the sample size required is 43 patients in each group. With effect sizes ranging from 0.46 to 0.77, the sample size ranges from 76 to 28 patients. The sample size with 80% power required to observe a TSAT difference of 5.7 with a common standard deviation of 6.4 (effect size of 0.89) is 21 patients, with effect sizes ranging from 1.12 to 0.67 requiring 28 to 76 patients. The sample size with 80% power required to observe a CHr difference of 0.9 pg with a common standard deviation of 1.92 is 73, with effect sizes ranging from 0.59 to 0.35 requiring sample size from 47 to 128 patients. All sample size calculations were done with two sided t-tests and a significance level of $\alpha = 0.05$.

2. STATISTICAL METHODS

2.1 General Considerations

Unless otherwise specified, all study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values. Analysis of categorical variables will include frequency and percentage.

P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." 95% confidence intervals will be estimated for pharmacodynamic endpoints.

For the analyses to be used for SRC, the subjects will be summarized by treatment group within each cohort. The placebo group will not be pooled.

For the final CSR report, the subjects will be summarized according to their treatment group. The placebo subjects at each cohort will be pooled into one group, and the subjects treated with COR-001 will be summarized based on the dosing regimen.

2.2 Definitions of Analysis Sets

The number of subjects entered, the number and the percentage of subjects included in each analysis set, and the number and the percentage of subjects excluded from each analysis set will be presented by dose group, treatment and overall.

Intent-to-treat (ITT) analysis population: The ITT analysis population will be defined as all randomized patients. Treatment classification will be based on the randomized treatment. This will be the primary population for the analyses of disposition and baseline data.

Pharmacodynamic analysis population: The pharmacodynamic population will be defined as all ITT patients who were treated with their assigned study drug treatment, had any pharmacodynamic assessments, and did not have certain important protocol deviations described below. This will be the population for the pharmacodynamic analyses.

- $\geq$ 2 Missed doses or $\geq$ 2 incorrect doses
- Important protocol deviations that are determined to significantly affect interpretation of PD endpoints, identified prior to unblinding of the study.
    - Minor departures from the ESA dosing guidelines in the protocol will not be considered major deviations.

For subjects who do not receive the assigned dose at any time during treatment, the dose will be defined as the highest dose received.

Pharmacokinetics analysis population: The PK population will be defined as all patients who have any valid samples measured for Study Drug levels. This will be used for PK analysis.

Safety analysis population: The safety analysis population will consist of all patients randomized and treated with any amount of study medication (COR-001 or placebo). Treatment classification will be based on the actual treatment received. This population will be used for the safety analyses.

MTD analysis Population: The MTD analysis population will be a subset of safety analysis population by excluding subjects replaced due to a non-safety reason. This population will be used for MTD and DLT analyses.

2.3 TIME WINDOWS FOR ANALYSIS

If data are collected by visit, the data will be analyzed by visit based on the protocol-planned visits. If multiple records are collected for a visit, the latest record will be used for the summary for that visit. Unless otherwise specified, baseline is defined as the last non-missing value prior to initiation of study drug. Early termination visit will be mapped to the post-baseline scheduled visit. After mapping, if there is more than one visit in the same window, the scheduled visit will be used if available. If there is no scheduled visit in the same window, the mapped visit closer to the target assessment day will be used. If more than one visit has the equal distance to the target day, then the later one will be used. The unscheduled visit will not be included in the by-visit summary, but will be included in the outlier analysis.

The observational period for the study will start from informed consent and end with study completion (see Section 3.1 for the definition of study completion). Any event occurring after the defined observational period, even if collected on the CRF, may not be included in the summary statistical analysis. However, all data, including that reported after the defined observational period, will be included in the patient data listings.

2.4 HANDLING OF MISSING DATA

As a general rule, missing data values are not imputed unless otherwise specified and, in presentation of categorical variables, unknown and missing data may be presented as a separate category and the denominator will include unknown or missing values as appropriate.

2.5 PROTOCOL DEVIATIONS

2.5.1 ESA and Parenteral Iron Dose-Adjustments

Selected types of ESA dose adjustments will be summarized by treatment using descriptive statistics, including:

- Change in the total weekly dose of EPOGEN during Weeks 1-4 compared with the Week -2 or Week -1 dose

- Change in the total dose of ARANESP or MIRCERA during Weeks 1-4 compared with the mean weekly dose during screening (based on the last 2 doses prior to randomization) multiplied by 4.

- Start of parenteral or dialysate iron during Weeks 1- 4 in a patient not receiving parenteral or dialysate iron during the 3 weeks prior to randomization

- Discontinuation of parenteral iron during Weeks 1- 4 in a patient receiving parenteral or dialysate iron during the 3 weeks prior to randomization

- Change in the total dose of parenteral elemental iron during Weeks 1-4 compared with the mean weekly dose during Weeks -3, -2, and -1 multiplied by 4.

- More than one ESA dose increase in any 4-week period after Week 4.

The ESA and parenteral iron dosing guidelines in the protocol are as follows:

Weeks 1 - 4

- ESA doses are not to be adjusted or held during Weeks 1 through 4 unless one or more confirmed hemoglobin values (i.e., at least 2 consecutive measurements) or the patient's clinical status necessitates such due to a clear and present safety risk.
- Parenteral iron doses are not be adjusted or held during Weeks 1 through 4.
- Patients not receiving parenteral iron products during Screening must not be started on these during Weeks 1 through 4.
- The Medical Monitor must be contacted prior to any contemplated ESA or parenteral iron dose changes.

Weeks 5 – 24

- Changes to ESA dosing must be based on hemoglobin values that have been confirmed (i.e., at least 2 consecutive measurements).
- Do not increase the dose more frequently than once every 4 weeks. The recommended dose increase at any given time is 25%.
- Decreases in dose may occur more frequently than once every 4 weeks. The recommended minimum duration between dose reductions is 3 weeks.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose by 25%. A greater reduction may be made, if rise in hemoglobin is unacceptably rapid.
- The Medical Monitor must be contacted prior to any contemplated ESA dose changes that depart from the above protocol requirements and recommendations unless clinical urgency precludes this. If the Medical Monitor is not contacted in advance, please send a notification within 24 hours that an off-protocol ESA dose change was made.
- Patients not receiving parenteral iron products must not be started on these during Weeks 5 through 24.
- Parenteral iron doses are not to be adjusted or held during Weeks 5 through 24, unless approved

by the Medical Monitor.

2.5.2 Other Deviations

Protocol deviations other than those related to ESA and iron dosing will be identified by a combination of programmatic query of the database, manual data review, and the clinical operations protocol deviation tracker.

2.6 ANALYSIS SOFTWARE

The pharmacokinetic (PK) evaluation and PK/PD modeling will be performed by an independent pharmacometrician ([redacted]). All other summaries and statistical analyses will be generated using SAS® version 9.2 or later. See Data Analysis Plan for Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Modeling.

3. STUDY SUBJECTS

3.1 DISPOSITION OF SUBJECTS

The number of subjects screened and the number (percent) of subjects who failed screening and the reasons for screen failure will be summarized, as available, based on data reported on the Screening Failure CRF. The distribution of the number of randomized subjects enrolled will be summarized for each randomized treatment group in each dosing regimen (combining all placebo patients as one control group) and overall based on the ITT analysis population.

The number (percent) of randomized and treated subjects who completed treatment will be summarized by treatment group based on the ITT analysis population. The subjects discontinued from study treatment will be summarized according to the reasons for discontinuation, based on data reported on the End-of-Study CRF.

The number (percent) of randomized subjects who completed the study and who discontinued from the study will be summarized according to the reasons for discontinuation, based on data reported on the End-of-Study CRF.

4. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

4.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized by treatment group using descriptive statistics for the ITT, pharmacodynamic, and safety analysis populations. Continuous demographic and baseline variables include age, pre-dialysis weight at week -1, post-dialysis weight at week -1, height, body mass index (BMI) based on post-dialysis weight at week -1; categorical variables include sex, race, and ethnicity.

4.2 DIALYSIS SIGN AND SYMPTOMS

The number (percent) of subjects with each specific dialysis sign and symptom as recorded on the CRF will be summarized by treatment group and overall for safety analysis population.

4.3 MEDICAL HISTORY

- Kidney Disease History

Kidney disease history will be summarized separately from other medical histories. The duration of end stage renal disease (ESRD), Single pool Kt/V (spKt/V) within 8 weeks prior to the full Screening Period, number (percent) of subjects with kidney transplant, status of the transplanted kidney, primary cause of chronic kidney disease and dialysis access used during Week -2 will be summarized by treatment group and overall for safety analysis population.

- Selected Medical History

The number (percent) of subjects reporting selected medical history, including cardiovascular history, infection history and other history as recorded on the CRF, will be summarized by treatment group and overall for safety analysis population.

- Other Medical History

The other medical history verbatim descriptions (investigator terms from the CRF) will be classified into medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA Version 19.0. The prevalence of medical history events will be reported as the number (percent) of subjects by treatment group, SOC and PT for safety analysis population.

5. STUDY DRUG AND EXPOSURE

5.1 TREATMENT COMPLIANCE

Since the study drug will be administered as an intravenous infusion, the treatment compliance will not be provided. Information regarding study drug administration will be provided in data listings.

5.2 EXTENT OF EXPOSURE

Study drug will be administered by infusion once every other week for 11 weeks (6 doses) for the planned treatment regimens in the protocol. Exposure will be summarized using the cumulative frequency and percentage of subjects receiving ≥ 1 dose, ≥ 2 doses, … ≥ 5 doses, and 6 doses by treatment group. Descriptive statistics (number of subjects, mean, standard deviation, minimum, median, quartiles range, and maximum) for exposure will be summarized. In addition, the exposure (in days), defined as the date of the last dose of study drug – date of the first dose of study drug + 1 will be summarized. Exposure with respect to COR-001-01 blood levels will be described in the Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Modeling Data Analysis Plan.

5.3 PRIOR AND CONCOMITANT THERAPY

Erythropoiesis-stimulating agents and parenteral iron doses will be separately summarized (see Section 6).

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary. The number (percent) of subjects who took prior and concomitant medications will be summarized on the safety analysis population by treatment group, dose and Anatomical Therapeutic Chemical (ATC) Classification and WHO Drug preferred term.

6. ERYTHROPOIESIS-STIMULATING AGENTS AND PARENTERAL IRON DOSES

ESA dosing will be summarized separately for EPOGEN (epoetin alfa), ARANESP (darbepoetin alfa) and MIRCERA (methoxy polyethylene glycol-epoetin beta) respectively. Historic ESA doses prior to randomization will be summarized weekly by treatment group for the pharmacodynamic analysis population. The mean weekly dose from Week -10 through Week -1 will also be computed for all ESAs. Percent change from baseline in ESA dose, change in ESA dose with ESA normalized to EPOGEN units, and change in ESA to a threshold value will also be computed with all ESAs pooled.

The following analyses will be performed:

- Comparison of the mean weekly ESA dose expressed in EPOGEN units prior to randomization to the post-randomization mean weekly dose for each 4-week interval in the Treatment and Safety Follow-up periods (e.g. Weeks 1-4, 5-8, etc). Inferential statistics will be performed for the Week 8-12 and the Week 1-4 periods.

    - Conversion of MIRCERA and ARANESP doses to EPOGEN units will be as follows:

      MIRCERA or ARANESP dose in mcg * 300 = EPOGEN unit equivalent dose

- The percentage change from baseline with all 3 ESAs combined will be calculated for each 4-week interval in the Treatment and Safety Follow-up periods (e.g. Weeks 1-4, 5-8, etc). Inferential statistics will be performed for the Week 8-12 and the Week 1-4 periods.

- The number and percentage of subjects with dose change by +/- ≥25%, +/- ≥50%, and +/- ≥100% will be computed for each 4-week interval in the Treatment and Safety Follow-up periods (e.g. Weeks 1-4, 5-8, etc).

Calculation of the Baseline ESA Dose

The baseline dose will be the baseline mean weekly dose for each ESA as defined below multiplied by 4.

- For EPOGEN, the baseline will be the mean weekly dose based on the 2 weeks immediately prior to randomization multiplied by 4.

- For ARANESP and MIRCERA, the baseline will be the mean weekly dose based on the 2 doses immediately prior to randomization multiplied by 4.

- The baseline dose will be normalized as the average dose per week during the time period of the doses used to define the baseline multiplied by 4.

Calculation of the Post-Baseline ESA Dose

- The post-baseline dose will be calculated based on the sum of all doses during a given time interval and will be expressed as the average dose per week during that time period multiplied by 4 or the number of weeks in the interval.

- The intervals that will be described are Weeks 1-4, 5-8, 9-12, etc through Week 24. In addition, Weeks 8-12 (the endpoint) and Weeks 1-12 will be described.

Parenteral iron doses are generally expected to be administered weekly, every other week, or with each dialysis. Parenteral iron doses will be summarized based on elemental iron contained within the iron product administered. All parenteral iron products will be combined for the analyses. If dose units are reported in mL, these will be converted to mg of elemental iron as follows:

IRON PRODUCT	ELEMENTAL IRON
Ferric gluconate (e.g. Ferrlecit)	12.5 mg per mL
Ferumoxytol (e.g. Feraheme)	30 mg per mL
Ferric carboxymaltose (e.g. Ferinject)	50 mg per mL
Ferric pyrophosphate citrate (e.g. Triferic)	5.44 mg per mL
Iron sucrose (e.g. Venofer)	20 mg per mL

Post-randomization parenteral iron doses will be summarized in a similar way to ESA. No analyses will be performed using individual parenteral products, however.

7. PHARMACODYNAMIC ANALYSES

Data from COR-001-treated patients from cohorts not exceeding the MTD will be pooled and data from all placebo patients will be pooled for the pharmacodynamic endpoint analyses.

Descriptive analyses by dose in which all placebo patients are pooled will also be conducted.

7.1 PRIMARY PHARMACODYNAMIC ANALYSIS

Endpoints:
The primary pharmacodynamic efficacy of COR-001 compared to placebo will be assessed by evaluating the following:

- Change from baseline (mean of Full Screening and Day 1 values) in hsCRP to Week 4 between treatment groups
    - The Day 29 value will be used for this analysis, reflecting at least 4 weeks of completed treatment. To ensure comparability to the post-baseline value, only the pre-dialysis Screening values will be used for the baseline.

Analysis Set:
Pharmacodynamic analysis population

Method:
Number of patients (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values for the observed value and change from baseline will be reported. The difference in changes (COR-001 - Placebo) will be presented. An analysis of covariance (ANCOVA) model will be used for this purpose with dose (specific active dose or placebo pooled) as a factor and baseline value as a covariate. The least square means for each dose, the least square mean differences from placebo along with the associated 95% confidence intervals (CIs) and p-values will be presented.

7.2 SECONDARY PHARMACODYNAMIC ANALYSES

Endpoints:
1. Change from baseline (mean of Full Screening and Day 1 values) in hsCRP to the mean of Weeks 10-12
2. Change from baseline (mean of Full Screening and Day 1 values) in SAA to Week 4 between treatment groups
3. Change from baseline (mean of Full Screening and Day 1 values) in SAA to the mean of Weeks 10-12
4. Change from baseline (mean of Full Screening and Day1 values) in the free IL-6 to Week 4 between treatment groups
5. Change from baseline (mean of Full Screening and Day 1 values) in Hemoglobin to Week 4
6. Change from baseline (mean of Full Screening and Day 1 values) in Hemoglobin to Week 10-12
7. Change from baseline (mean of Full Screening and Day 1 values) in Hemoglobin to Week 10-12, excluding hemoglobin values following a change in the total weekly ESA dose. A change is defined as the first time when the ESA weekly dose goes up by >25% or down by >25% relative to the previous week's dose.
8. Change from baseline (weekly mean of Full Screening) in ERI to the mean of Weeks 9-12 and Weeks 10 –12

   a. The Screening ERI is defined as the ERI used to qualify the patient for the study per Inclusion Criterion #14
9. Change from baseline (mean of Screening and Day 1 values) in TSAT to Week 4
10. Change from baseline (mean of Full Screening and Day 1 values) in TSAT to Weeks 10-12
11. Change from baseline (mean of Screening and Day 1 values) in the CHr to Week 4
12. Change from baseline (mean of Full Screening and Day 1 values) in the CHr to Weeks 10-12
13. Change from baseline (mean of Full Screening and Day 1 values) in serum pre-albumin to the mean of Weeks 10-12
14. Change from baseline (mean of Full Screening and Day 1 values) in serum albumin to Week 12

Analysis Set:
Pharmacodynamic analysis population

Method:
Number of patients (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values for the observed value and change from baseline will be reported. The difference in changes (COR-001 - Placebo) will be presented. An ANCOVA model including dose as a factor and baseline value as a covariate will be used. The least square means for each dose, the least square mean differences from placebo along with the associated 95% CIs and p-values will be presented. In addition, for change from baseline in TSAT to week 4, a shift table analysis with the categories: <20%, 20%-30%, >30% - 50%, >50% will be presented. The weekly mean of ERI will be calculated and presented for all ESAs combined based on the formula in Section 1.2.3.2.

7.3 OTHER EFFICACY ANALYSES

Additional secondary objective is to explore the pharmacodynamic effects of COR-001 compared to placebo by evaluating changes in

- Change in hemoglobin from screening to peak hemoglobin (defined as per subject absolute maximal hemoglobin in g/dL)
- ERI and Hemoglobin from baseline (weekly mean during the Screening Period for ERI and mean of Full Screening and Day 1 for Hemoglobin) through Week 4, 12 and 24
- ERI and Hemoglobin from baseline (weekly mean during the Screening Period for ERI and mean of Full Screening and Day 1 for Hemoglobin) through Week 4, 12 and 24 stratified by baseline ERI tertiles
- ESA and parenteral iron dose requirements from baseline (weekly mean during the Full Screening Period) to Evaluation Period (Weeks 8 – 12) and through Week 24.

- Systemic iron stores (serum ferritin, hepatic and splenic iron content, and supplemental iron dose requirements) over time
- Markers of malnutrition-inflammation (pre-albumin and albumin) over time
- LV mass index from Screening to Week 12
- Pre-dialysis, post-dialysis, and delta-serum Troponin and NT-proBNP (defined as the difference between the pre- and post-dialysis troponin) from baseline (mean of Screening) to Weeks 10 – 11.
- Handgrip strength from baseline (during screening) to Week 12

FACIT fatigue score from baseline (during screening) to Week 12

For the above efficacy variables, the observed values and changes from baseline will be summarized by treatment group using descriptive statistics for Pharmacodynamic analysis population.

Specifically, the weekly mean of ERI will be calculated and presented individually for each ESA based on the formula in Section 1.2.3.2.

The mean of left and right handgrip strengths will be used for analysis no matter which hand is dominant.

The FACIT-F (Version 4) is a compilation of general questions divided into five primary domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being and Additional Concerns. The data in Additional Concern domain will be listed separately and considered the primary analysis for the FACIT-F. The total fatigue score will be calculated as a summation of the scores in the five primary domains. The observed value and change from baseline in total fatigue score will be summarized by treatment.

7.4 MAGNETIC RESONANCE IMAGING (MRI) SCAN

The actual value and percent change from baseline of MRI measurements such as LVMI, LVESVI, LVEDI, and LVEF will be summarized by visit and treatment group using descriptive statistics. MRI measurements other than the above (e.g. liver and spleen iron content [mean hepatic T2*] and [mean splenic T2*] and cardiac T1 map) are expected from only a subset of patients.

7.5 SENSITIVITY ANALYSES

Key anemia-related PD endpoints will be summarized separately for patients with and without off protocol ESA dosing. Protocol ESA dosing is defined in Section 2.5.1. The secondary and other PD endpoints based on measurements of TSAT, ferritin, CHr, hypochromic RBC, reticulocyte count, and hemoglobin will undergo the sensitivity analyses. These analyses will exclude patients who have off-protocol dosing of ESAs or iron during Weeks 1 – 4 as defined in Section 2.5.1.

Because hospitalizations are associated with multifactorial reduction in hemoglobin and missed ESA doses, a sensitivity analysis will be performed of the above two analyses in which analyses of ESA doses, ERI, and hemoglobin after the start date of the first SAE will be excluded.

8. SAFETY ANALYSIS

All safety analyses will be performed on the safety analysis population. Safety data presented by treatment group will be summarized on an 'as treated (treatment received)' basis.

8.1 PRIMARY SAFETY ANALYSIS

The primary safety analyses will provide data that will support the characterization of the MTD or to establish that the highest dose examined did not exceed the MTD.

Number (percent) of subjects who potentially experienced DLTs (defined in Section 1.1.2) will be reported by treatment group. The Adverse Events that are used to identify DLTs will be tabulated. The Adverse Events will be summarized by preferred term, CTCAE grade and relationship to study drug. Determination of the MTD will be made by the SRC. Specifically, the sponsor will use lab listings to identify possible lab-based DLTs. Any possible DLTs will be queried to be reported as AEs by the investigator and the investigator CTCAE grade, which will include the clinical information needed for some of the CTCAE lab definitions, e.g. "if symptomatic" or "if hospitalization needed", will be used for DLT determination.

8.2 SECONDARY SAFETY ANALYSIS

Number (percent) of subjects who experienced the events of interest: Severe ($\geq$ Grade 3) infusion-related reactions, hypersensitivity reactions during the Study Drug infusion, and/or anaphylaxis occurring at any time will be summarized by treatment group, preferred term, CTCAE grade, relatedness to the study drug and seriousness. All of these events will be identified from the Infusion-Related Reaction, Hypersensitivity, and Anaphylaxis CRF. Events on this list that appear to meet the protocol definition of hypersensitivity and anaphylaxis based on the Medical Monitor's review will be queried if they have not already been reported on the Infusion-Related Reaction, Hypersensitivity, and Anaphylaxis CRF.

Descriptive statistics will also be reported for additional safety assessments by treatment group, including adverse events, physical examination findings of possible infection, vital signs, ECG, clinical laboratory, and anti-drug antibodies (binding and neutralizing).

8.3 ADVERSE EVENTS

The adverse event verbatim descriptions (investigator terms from the CRF) will be classified into medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA, Version 19.0.

A treatment-emergent adverse event (TEAE) is defined as an AE that initiated or worsened on or after the date of first dose of study drug up to the end of safety follow-up. For AEs occurring on

the first dosing day, if the start time cannot be ascertained, the event will be counted as treatment-emergent.

Only those AEs and SAEs that are treatment-emergent will be included in summary tables. All AEs and SAEs, treatment emergent or otherwise, will be presented in subject data listings.

TEAEs and SAEs will be summarized by treatment group. The incidence of AEs will be reported as the number (percent) of subjects with AEs within SOC and PT. The incidence of AEs with onset within Weeks 1-12 and Weeks 13-24 will also be summarized. Subjects will be counted only once within a SOC and PT, even if the subject experienced more than one event within a specific SOC and PT. The number (percent) of subjects with events will also be summarized by highest CTC grade as well as by closest relationship. If more than one event occurred with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to Study Drug, respectively.

Patient counts and percentages will be presented for the following summaries by treatment group and overall:

- Overall summary of TEAE's
- All TEAEs by SOC and PT;
- TEAEs related to study drug by SOC and PT;
- TEAEs by relationship to study drug by SOC and PT;
- TEAEs by highest severity grade by SOC and PT;
- Summary of TEAE meeting Dose-Limiting Toxicity Criteria (Study Days 1 – 21) by SOC and PT;
- All TESAEs by SOC and PT;
- All AEs leading to discontinuation of study drug by SOC and PT;

A subject data listing of all AEs leading to death, if any, will be provided.

Following Database Lock 1 and 2 (as described in Section 11), two versions of the Overall summary of TEAE's and all TEAE's by SOC and PT, AEs leading to discontinuation of study drug by SOC and PT, and all TESAEs by SOC and PT will be created. Version 1 will include only frozen AE data. Version 2 will include all AEs.

8.4 Clinical Laboratory Parameters

For all quantitative parameters listed in Appendix D of the protocol except for the laboratory measurements performed for the pharmacodynamic endpoint analyses (see Section 7), the actual value and change from baseline will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Appendix D of the protocol will be summarized using frequencies (number and percent of subjects). Percentages will be based on the number of subjects with non-missing results.

For the laboratory parameters that are collected with CTCAE grade, the number and percent of subjects with results that are ≥ grade 4 for hematology parameters, as well as the number and percent of subjects with results that are ≥ grade 3 in non-hematology parameters will be summarized. The shift summary of hematology and non-hematology laboratory parameters in CTC grade to the worst abnormal will also be presented. Note that the CTC grades are based on the laboratory values only and do not consider clinical consequences or interventions that define the grade. Therefore, the CTC grades 1 through 4 will be considered the highest potential CTC grade for the laboratory values for which the grading definition requires knowledge of information other than the laboratory value.

The laboratory measurements from Protocol Appendix D panel 5 Hematology will be used for lab-based hematologic toxicity assessment.

The percentage of patients exceeding pre-defined absolute and relative threshold values across the entire treatment period, across the entire safety follow up period, and across both of these period will be summarized (See Table 2).

Table 2: Pre-defined Threshold Value for Laboratory Parameters

Parameter	**Criteria**
ALT	> 3X ULN
AST	> 3X ULN
ALT and AST	Both > 3X ULN
ALT, AST and Total Bilirubin	ALT > 3X ULN and AST < 3X ULN and Total Bilirubin > 2 ULN
Hemoglobin	Increase > 1 g/dL in 2 weeks
Hemoglobin	> 2 g/dL in 4 weeks
Hemoglobin	> 12 g/dL on 2 consecutive assessments
Hemoglobin	> 13 g/dL on 2 consecutive assessments
Hemoglobin	< 8 g/dL on 2 consecutive assessments

Baseline for the laboratory parameters will be defined as mean of Week -1 and Day 1 values.

8.5 INFUSION-RELATED REACTIONS, HYPERSENSITIVITY REACTIONS, AND ANAPHYLAXIS

The infusion related reactions, hypersensitivity reactions, and anaphylaxis events will be summarized by treatment group using frequencies (number and percent of subjects).

8.6 INFECTION DETAILS

A subject listing for the infection details captured in CRF will be provided. Additionally, a summary table will be generated summarizing types of infection and type of infectious agent if known (e.g., bacteria, virus, fungus, etc.).

8.7 DIALYSIS DETAILS

For each dialysis, the duration in minutes, target dry weight and frequencies (number and percentage) of dialysis access used, and net ultrafiltration volume will be summarized descriptively.

8.8 VITAL SIGNS, PHYSICAL EXAMINATION FINDINGS, AND ECG

8.8.1 Vital Signs

According to the collection schedule, the observed value of vital signs parameters (diastolic and systolic blood pressure, pulse rate, respiration rate and temperature) and change from baseline in these parameters will be summarized in three separate tables. One for pre-dialysis by visit, with baseline being the pre-dialysis values at week -1. One for post-dialysis by visit, with baseline being the post-dialysis values at week -1. And the third table for pre- and post-infusion by visit, with baseline being the pre-infusion values at that visit; in this table change from pre- to post-infusion within each infusion session will also be provided. As pre-dialysis weight is collected in a different schedule than other vital signs, two separate tables for pre-dialysis weight and BMI, post-dialysis weight and BMI will be provided separately.

In addition, the percentage of patients exceeding pre-defined absolute and relative threshold values across the entire treatment period, across the entire safety follow up period, and across both of these period will be summarized (see

Table 3). When calculating the percentages, numerator will be the number of subjects with normal baseline with respect to the specific criterion and at least 1 post-baseline outlier value within the analysis period; and denominator will be the number of subjects with a baseline and at least 1 post-baseline assessment within the analysis period. A subject may be counted more than in multiple categories for a given parameter. Three tables will be provided separately for pre-dialysis values, post-dialysis values and pre-/post-infusion values. All results (regardless of scheduled or unscheduled) will be considered in this summary.

Table 3: Pre-defined Threshold Value for Vital Signs

Parameter	Criteria
Systolic Blood Pressure (SBP)	>20 mmHg increased or decreased from baseline
SBP	> 30 mmHg increased or decreased from baseline
SBP	>180 mmHg
SBP	<95 mmHg
Heart Rate (HR)	>100 beats per minute
HR	<50 beats per minute
Respiration Rate	>24 breaths per minute
Weight (pre-dialysis)	>5 kg increased from baseline pre-dialysis weight
Weight (pre-dialysis)	>5 kg decreased from baseline pre-dialysis weight
BMI	>10% increased from baseline
BMI	>10% decreased from baseline

8.8.2 Physical Examination

A subject listing of physical exam findings of signs of infection will be provided.

In addition, Physical examination clinically significant new or worsening findings will be reported as adverse events and will therefore be summarized as described for adverse events.

8.8.3 12-Lead ECG

ECG interpretation (normal vs. abnormal) will be summarized using frequency and percentage at each visit by treatment group. Observed values and change from baseline in ECG intervals (PR, QT, HR, and QTcF), rhythm and heart rate will be summarized descriptively at each visit by treatment group.

The percentage of patients exceeding pre-defined absolute and relative threshold values across the entire treatment period, across the entire safety follow up period, and across both of these periods will be summarized (see Table_4). When calculating the percentages for the criterion related to a threshold, the numerator will be the number of subjects with normal baseline with respect to the specific criterion and at least 1 post-baseline outlier value within the analysis period; and denominator will be the number of subjects with normal baseline with respect to the specific criterion and at least 1 post-baseline assessment within the analysis period. When calculating the percentages for the criteria related to change from baseline, the numerator will be the number of subjects meeting the criterion; and denominator will be the number of subjects with a baseline and at least 1 post-baseline assessment within the analysis period. A subject may be counted in multiple categories for a given parameter. All results (regardless of scheduled or unscheduled) will be considered in this summary.

Table 4: Pre-defined Threshold Value for ECG

Parameter	Criteria
PR Interval	>200 msec
QTcF	> 450 msec
QTcF	> 480 msec
QTcF	> 500 msec
QTcF	Increase from baseline >30 msec
QTcF	Increase from baseline >60 msec

8.9 ANTIBODIES TO COR-001

The immunogenic potential of COR-001 will be assessed by summarizing the number and percentage of patients who develop detectable anti-drug antibodies (ADA) by dose. Anti-drug antibody titers will be summarized descriptively for ADA positive samples and the impact of ADA on PK will be assessed if data allows. Neutralizing capacity of any detected ADA will be summarized.

9. PHARMACOKINETIC ANALYSIS AND PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

A patient listing of all serum concentration-time data for each dose group will be presented. High-sensitivity CRP (hsCRP) and serum IL-6 will also be presented in listings. Analyses of PK and PK-PD modeling are described in the Data Analysis Plan for Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Modeling.

10. INTERIM ANALYSES AND SAFETY REVIEW COMMITTEE (SRC)

10.1 SAFETY REVIEW COMMITTEE

A Safety Review Committee (SRC) is established and will apply its judgment to the conduct of this study in order to ensure the safety of study participants. The SRC will review unblinded safety data prior to dose escalation (i.e., higher total dose than studied in the preceding cohorts). The reviews will occur after all patients in a cohort have completed 21 days of treatment (or last visit, if prematurely discontinued). The Sponsor will consider SRC recommendations when determining the dose for the next cohort. Following completion of the dose-escalation phase of the study, the SRC will meet approximately every 1 - 2 months until all subjects have completed safety follow-up period or terminated early to review accruing safety data.

The full activities and responsibilities of the SRC are described in the SRC charter.

10.2 INTERIM ANALYSIS

A single interim analysis will be conducted for the purpose of guiding future COR-001 clinical program activities. There are no stopping rules associated with the interim analysis and therefore no statistical adjustment for multiplicity will be made. The interim analysis will be conducted, at earliest, once all cohorts below that which exceed the MTD, excluding any expansion cohorts, have completed the study through Week 4 (or final visit, if prematurely discontinued).

The following endpoints will be assessed in the interim analysis:

- PD parameters: hsCRP, SAA, free and/or total serum IL-6, as well as, hemoglobin, TSAT, CHr, pre-albumin, and albumin
- Change in hemoglobin from screening to peak hemoglobin (defined as per subject absolute maximal hemoglobin in g/dL)
- Change from baseline (mean of Full Screening and Day 1 values) in Hemoglobin to Weeks 10-12, excluding hemoglobin values following a change in the total weekly ESA dose. A change is defined as the first time when the ESA weekly dose goes up by >25% or down by >25% relative to the previous week's dose.
- ERI
- Hemoglobin and ERI stratified by baseline ERI (<median or >=median)
- Cardiac biomarkers: Pro-NT-BNP and troponin
- MRI outcome: LVMI, LVESVI, LVEDVI, and LVEF
- Handgrip strength
- FACIT fatigue score

The summary approach for these listed endpoints will be the same as described in the SAP and will follow the specifications below for presentation in order to mask the treatment-level data:

- By masked treatment group (e.g. Treatment A, Treatment B, and etc.). Subjects receiving placebo from all cohorts will be combined as one of the treatment groups
  - Both PD analysis population and Per-Protocol analysis population will be performed on masked data
- Pooled treatment vs pooled placebo
- Pooled responder analysis defined as change from baseline in PD parameter for all patients (regardless of active vs placebo assignment) who achieve a ≥50% reduction in hsCRP

To avoid identification of individual patients, the number of subjects, minimum, maximum values, and raw numbers for the percentages (i.e. numerator and denominator) will not be presented. Only the means, standard deviations, and percentages will be presented. The sponsor personnel will only receive the masked treatment group-level information and have no access to actual treatment-level information nor subject-level treatment information.

11. DATABASE LOCK

The database will be locked sequentially to enable program planning.

- Database Lock 1 will occur after the last patient in Cohort 6 completes the Week 12 visit or early terminates prior to Week 12. All visit-specific case-report forms for all completed visits, including unscheduled visits, occurring prior to the database cutoff date will be frozen for patients in all cohorts. Because patients in Cohort 1-4 will already have completed the study, the vast majority of data will be locked at this time. Handling on non-visit specific CRFs is described below. Because the primary and secondary pharmacodynamic endpoints are based on time points through Week 12; therefore, these data will be locked with Database Lock 1 and be unaffected by subsequent database locks.

- Database Lock 2 will occur after the last patient in Cohort 6 completes the Week 24 visit or early terminates prior to Week 24. All visit-specific case-report forms for all completed visits not already locked during Database Lock 1, including unscheduled visits, occurring prior to the database cutoff date will be locked for patients in all cohorts. Handling on non-visit specific CRFs is described below.

- Database Lock 3 will occur after the last patient in Cohort 6 completes the Week 35 visit or early terminates prior to Week 35. All visit-specific case-report forms for all completed visits not already locked during Database Locks 1 and 2, including unscheduled visits, will be locked for patients in all cohorts. Adverse events, concomitant medications, and other log CRF page and end of study CRF will be handled as described below.

Database Locking Rules for Visit Non-Specific CRFs

- Adverse events, Infection Details, and Infusion-Related Reaction CRFs will be locked at Database Locks 1 and 2 if either of the below apply.

    - The AE or corresponding SAE of infection or infusion-related reaction has an end date. If the event is an SAE, the SAE case must also have been closed.

    - The patient completed the study, died, or was withdrawn from the study.

    All remaining events will be locked at the time of Database Lock 3.

- Concomitant Medications will be locked at Database Locks 1 and 2 if any of the below apply:

    - The concomitant medication indication is an AE and there is an end date for the corresponding AE or the patient died or the patient was withdrawn from the study. In case of SAE, SAE case must also be closed.

    - The concomitant medication indication is not AE and there is an end date for the

concomitant medication or the patient died or the patient was withdrawn from the study.

All remaining concomitant medications will be locked at the time of Database Lock 3.

- End of Study CRF
    - The End of Study CRF will be frozen at the time of Database Lock 1 or Database Lock 2 if the Week 35 visit has been completed or the patient died or with patient was withdrawn from the study at the time of the lock. Any remaining CRFs will be locked at the time of Database Lock 3.

12. SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

The study protocol was amended on 20 September 2016 (Amendment 2). The Statistical Analysis Plan is developed based on this version of the protocol. Any further analysis changes made after this SAP is finalized will be documented with a SAP amendment or described in the clinical study report (CSR).

13. REFERENCES

1. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV, Rizkala AR; DRIVE Study Group. Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with Elevated Ferritin (DRIVE) Study. J Am Soc Nephrol 2007; 18(3):975-84.ICH guidance for industry E3 Structure and Content of Clinical Study Reports, 1996
2. Sieper J, Braun J, Kay J, Badalamenti S, Radin A, Jiao L, Fiore S, et al. Sarilumab for the treatment of ankylosing spondylitis: results of a Phase II, randomised, double-blind, placebo-controlled study (ALIGN). Ann Rheum Dis 2015; 74:1051–1057.

14. MOCK TABLES, LISTINGS AND FIGURES (TLFS)

The study TLF shells will be provided in a separate document, which will show the content and format of all tables, listings, and figures in detail.