Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT02868229
Sponsor trial ID:	NN6018-4791
Official title of study:	A Phase 1/2 Randomised, 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
Document date:	20 November 2017

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

DRUG NAME: COR-001 (human monoclonal antibody to IL-6)

PROTOCOL NUMBER: COR-001-01
Amendment 3

PHASE: 1/2

TRIAL SPONSOR: Corvidia Therapeutics
35 Gatehouse Drive
Waltham MA 02451

MEDICAL MONITOR: [redacted]

PROTOCOL DATE: Original: 19 April 2016
AMENDMENT DATE: Amendment 1: 23 May 2016
Amendment 2: 20 September 2016
Amendment 3: 20 November 2017

Redacted protocol
Includes redaction of personal identifiable information only.

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "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", and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and all locally applicable laws.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Corvidia Therapeutics.

_____

Signature of Principal Investigator

_____ _____

Name of Principal Investigator (Print) Date (DD Month YYYY)

CLINICAL STUDY PROTOCOL APPROVAL SIGNATURE PAGE

Product name: COR-001
Protocol Title: 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

Protocol number: COR-001-01 Amendment 3
Release date: November 20, 2017

We, the undersigned, confirm that this Clinical Study Protocol is accurate.

Signed: [redacted] Date: [redacted]

Signed: [redacted] Date: [redacted]

Amendment 1 Summary of Changes

Protocol Section	Description of Change	Old	New	Rationale for Change
Synopsis *Section 3.1* *Section 3.2* *Section 3.5.4* *Section 3.6*	Addition of text	NA	"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."	Underscore that prior to dose escalation, planned doses will be re-evaluated based on emerging pharmacokinetic and pharmacodynamic data
Synopsis *Section 4.1*	Inclusion Criterion #15 Hemoglobin range revised	During the 4 weeks prior to randomization, the mean of 3 consecutive hemoglobins between ≥ 8.5 and ≤ 12 g/dL, with the difference between the first and last measurements being <1.2 g/dL.	During the 4 weeks prior to randomization, the mean of 3 consecutive hemoglobins between ≥ 8.5 and ≤ 11 g/dL, with the difference between the first and last measurements being <1.2 g/dL.	Better alignment with ESA prescribing information
Synopsis *Section 3.5.4* *Section 3.6* *Section 5.1.4* *Appendix 15.1*	Dosing schedule revised from every 7 days to every 14 days. Corresponding changes to all tables and figures.	Planned dosing regimens: 1 mg Q7 days; 3 mg Q7 days, 10 mg Q7 days; and 30 mg Q7 days	Planned dosing regimens: 2 mg Q14 days; 6 mg Q14 days, 20 mg Q14 days; and 60 mg Q14 days	Align COR-001-01 dosing frequency with primate toxicology study dosing frequency
Section 3.6	DLT threshold rationalization	NA	Dose-Limiting Toxicity criteria and rules for MTD will be pre-defined. Because of the high background frequency of Grade 2 and 3 adverse events in hemodialysis patients (not dissimilar from cancer populations),	Clarification and rationalization of DLT thresholds

			the DLT threshold will be defined using a threshold of ≥ Grade 3 events.	
Section 4.4	Addition of dose-escalation rule	NA	In addition, if 1 of 8 COR-001-treated patient in a cohort experiences a Grade 4 or 5 DLT, the dose will not be escalated.	Avoids dose-escalation if a single Grade 4 or 5 DLT was observed
Section 5.1.3	Stool occult blood test revision	Stool cards	Stool tests Stool samples	Central lab stool testing does not use cards
Section 5.1.4	Revision of weekly study activity descriptors	Study activities described based on weekly dosing	Study activities described based on every two week dosing	Updated study activity timing to align with every two week dosing and added additional PK/PD time points
Section 6.1.1	Update of drug reconstitution and administration instructions, tables and schematics	NA	Revised text, tables and schematics	Provide updated instructions for COR-001 and associated administration materials handling based on revised dosing schedule
Schedule of Events	Revised PK and PD sampling	PK/PD schedule appropriate to weekly dosing	PK/PD schedule appropriate to every other week dosing	Align PK/PD assessments with revised dosing schedule and add additional PK/PD time points. Assess potential for dialysis clearance of COR-001.
Schedule of Events	ADA sampling during Treatment Period	Weekly	Every 2 weeks prior to dosing	ADA sampling adjusted to match revised dosing schedule

Schedule of Events	Addition of footnote 14	NA	Visit window may be extended to +4 days only in instances when the study drug was missed on the targeted visit day and also could not be given during the dialysis visit after the missed dose.	Proportional increase in visit window for drug dosing (i.e. from 2-day window for q7day dosing to 4-day window for q14d dosing)
Synopsis *Section 4.1*	Correction of ERI formula	Multiplier of 300 in the denominator; result expressed in mcg/kg per dL	Multiplier of 300 in the numerator; result expressed in units/kg per dL	Corrected error in conversion for darbepoetin and methoxy polyethylene glycol-epoetin beta to epoetin equivalents for calculation of ERI
Schedule of Events	Revised timing of cardiac markers pro-NT-BNP and troponin at terminus of treatment period	Weeks 10, 11, 12	Week 11 Day 71, Week 11 Day 75, Week 12	Maintain timing of these markers with the last 3 visits of the Treatment Period (Day 71, Day 75, and Week 12)
Table of Contents	Updated	NA	NA	Updated to reflect changes listed above
Title page, footers, typographical and formatting errors	Update of protocol data and version number Appendix E	Original April 19, 2016	Amendment 1 May 23, 2016	Document version management. Correction of typographical and formatting errors. Addition of missing FACIT-F page.

Amendment 2 Summary of Changes

Protocol Section	Description of Change	Old	New	Rationale for Change
Synopsis	Number of study sites increased	Approximately 10	Approximately 15	Initial screening activities suggested need for additional sites to meet enrollment goals
Synopsis *Section 3.1.3*	Removal of total IL-6 from the primary PD endpoint	"Change from baseline (mean of Screening and Day1) in the free and total IL-6 to Week 4 between treatment groups"	"Change from baseline (mean of Screening and Day1) in the free IL-6 to Week 4 between treatment groups"	Technical limitations of assay
Synopsis *Section 3.4*	Revised definition of the start of the Initial and Full Screening Periods	Defined by the signing of the Short and Long ICFs, respectively	Defined by the first study procedure in the Initial Screening Period and the Week -2 date, respectively	To allow additional time for the consenting process
Synopsis *Section 4.1*	Inclusion Criterion #1 Age range revised	Age 18 through 80 years, inclusive, at the time of signing of the ICF	Age $\geq$ 18 years at the time of signing of the ICF.	Facilitate enrollment of a more representative population of dialysis patients by allowing older patients who otherwise meet entry criteria including investigators evaluation of individual risk (Exclusion #18)

Protocol Section	**Description of Change**	**Old**	**New**	**Rationale for Change**
Synopsis *Section 4.1*	Inclusion Criterion #7: Reduction of IL-6 threshold for entry into the study	"Two serum IL-6 levels ≥ 5 pg/mL measured at least 1 week apart during the Screening Period."	"Two serum IL-6 levels ≥ 4 pg/mL measured at least 1 week apart during the Screening Period."	IL-6 ≥4 pg/mL on current platform is equal to IL-6 ≥ 5 pg/mL in historical cohorts used to plan the study
Synopsis *Section 4.1*	Inclusion Criterion #4: Removed requirement that patient must be able to read	"The patient is able to read and give written informed consent and has signed a consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IEC)."	"The patient is able to give written informed consent and has signed a consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IEC)."	To allow patients unable to read to participate in the study
Synopsis *Section 4.1*	Inclusion Criterion #8: Allowance of up to one missed Epogen dose in Week -3 and removal of this requirement from Weeks -2 and -1	"Epoetin alfa must not have had any doses missed or held during Week -3 prior to Randomization."	"Epoetin alfa must not have had more than one dose missed or held during Week -3 weeks prior to Randomization."	Because it is total weekly dose that is intended to be stable, missed or held doses that do not result in a change in total weekly dose (per IC #9) are allowable. Facilitate enrollment without compromising original intention.

Protocol Section	**Description of Change**	**Old**	**New**	**Rationale for Change**
Synopsis *Section 4.1*	Inclusion Criterion #9: Clarified that "dose" referred to total weekly dose Clarified criterion for patients receiving a dose on both Week -2 and Week -1	***"For ESAs dosed less often than weekly:*** Any dose given during Full Screening Week -2 and Week -1 is unchanged from the immediately preceding dose."	***"For ESAs dosed less often than weekly:*** Any dose given during Full Screening Week -2 and Week -1 is unchanged from the immediately preceding dose." Note: If a dose was given on both Week -2 and Week -1, then both doses are the same. (These 2 doses may be different than earlier doses)."	Clarification
Synopsis *Section 4.1*	Inclusion Criterion #10: Change of "i.e." to "e.g." and addition of instruction for less frequent than weekly dosing.	"Has been receiving intravenous (IV) or dialysate iron regularly and continuously (i.e., with each dialysis or each week) during the 3 weeks prior to randomization" ". . . regimen has been stable (same elemental iron dose, same frequency, and same iron product) with no more than 2 missed or held doses if dosed with each dialysis and no missed or held doses (if dosed weekly) during this time frame."	"Has been receiving intravenous (IV) or dialysate iron regularly and continuously (e.g., with each dialysis or each week) during the 3 weeks prior to randomization" " . . . regimen has been stable (same elemental iron dose, same frequency, and same iron product) with no more than 2 missed or held doses if dosed with each dialysis and no missed or held doses (if dosed weekly or less frequently) during this time frame."	Correction of typo and omission of instruction for patients receiving IV iron less often than weekly

Protocol Section	**Description of Change**	**Old**	**New**	**Rationale for Change**
Synopsis *Section 4.1*	Inclusion Criterion #17: Clarification that B-12 and folate above the reference range are allowable	"Serum Vitamin B-12 and folate levels within the laboratory normal range during Full Screening."	"Serum Vitamin B-12 and folate levels above the laboratory lower normal range during Full Screening."	Clarification
Synopsis *Section 4.2*	Exclusion Criterion #6: Removal of exclusion related to PPD in favor of Quantiferon TB testing only	"Positive tuberculosis blood test at Screening or history of a positive PPD or positive tuberculosis test."	"Positive tuberculosis blood test at Screening"	Clarification that the blood TB test at Screening is to be used to determine TB status as this is more the more sensitive test.
Synopsis *Section 4.2*	Exclusion Criterion #20: Revised to 2 months	"Myocardial infarction during the 3 months prior to Full Screening or during Screening."	"Myocardial infarction during the 2 months prior to Full Screening or during Screening."	Adequate cardiac recovery expected within 2 months
Section 3.1.1	Revise matrix for PK sample	Plasma COR-001	Serum COR-001	Correction of an error
Section 5.4	Align the AE and DLT sections by removing the "definitely" category from the DLT definition	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 "definitely", "probably", or	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 "probably", "possibly", or "unlikely" will be considered DLTs. Grade 3 non-hematologic toxicities having an assessed relationship to the Study Drug of	Improve consistency

Protocol Section	Description of Change	Old	New	Rationale for Change
		"possibly" will be considered DLTs.	"probably" or "possibly" will be considered DLTs.	
Section 5.4	Clarified which DLT events are considered "non-hematologic"	None	Note: "non-hematologic events" refer to DLT criteria 1, 2, 3, and 5 above.	Clarification
Section 5.2	Screening MRI allowed during Week -2 without monitor approval	Schedule MRI during Week -1 or Week -2 with monitor approval	Schedule MRI during Full Screening	Accommodate site logistics
Section 5.3.1	Screening procedures' modification added for patients being re-screened	None	Genotype testing does not need to be repeated Cardiac MRI, TB testing, and stool occult blood testing does not need to be repeated if performed within 12 weeks of re-screening Week -2. Initial Screening medical history: not required to be repeated. Confirmation of eligibility remains a procedure during Full Screening.	Streamline procedures for re-screened patients
Section 12.3.2	Addition of a new analysis population	None	**MTD analysis Population**: The MTD analysis population will be defined as a subset of safety analysis population by excluding subjects replaced due to a non-safety reason.	Addresses possible situation that affects that denominator for MTD determination

Protocol Section	Description of Change	Old	New	Rationale for Change
			Treatment classification will be based on the actual treatment received This population will be used for MTD and DLT analyses.	
Section 12.5	Add constraints on information revealed at the interim analysis	The Sponsor will become unblinded during the interim analysis but all other blinded parties will remain blinded	The Sponsor personnel will only receive the treatment group-level information and have no access to subject-level treatment information	Greater specificity
Schedule of Events	Addition of hsCRP to the Initial Screening Procedures	None	hsCRP added	Gather additional data, including in those failing Initial Screening, to assess correlation between hsCRP and IL-6 values
Schedule of Events *Synopsis* *Section 5.4.1*	Allowance of randomization on Day -1	Randomization to be performed on Day 1 only	Footnote 15: "Randomization may be performed on Day -1, if needed, with approval of the Medical Monitor. Administration of the first dose of Study Drug will continue to define Study Day 1."	Accommodate site logistical needs
Appendix D	Addition of calcium and phosphate to the chemistry laboratory panel	None	Calcium and phosphate added	Correction of an inadvertent omission

Protocol Section	**Description of Change**	**Old**	**New**	**Rationale for Change**
Appendix D	Revision of Special RBC indices	red cell size factor and low hemoglobin density parameters present	red cell size factor and low hemoglobin density parameters removed	Change to a different laboratory analyzer platform which does not measure these
Multiple	Correction of typographical errors, updating of protocol dates, formatting, and table of contents			Improve readability

Amendment 3 Summary of Changes

Protocol Section	**Description of Change**	**Old**	**New**	**Rationale for Change**
Synopsis, Section 4.2	*Exclusion Criterion #2*	"Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary."	"Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary. Oral prednisone up to 5 mg per day is (or equivalent) is permitted."	To clarify working definition of allowable use of glucocorticoids
Synopsis, Section 4.2	*Exclusion Criterion #5*	"Inability to undergo a non-contrast magnetic resonance imaging (MRI) scan (e.g., weight over the limits for MRI machine, claustrophobia that cannot be managed, certain metallic indwelling foreign bodies)."	"Inability to undergo a non-contrast magnetic resonance imaging (MRI) scan (e.g., weight over the limits for MRI machine, claustrophobia that cannot be managed, certain metallic indwelling foreign bodies). Requirement for MRI may exempted by the medical monitor due to practical considerations. In such situations, patients may be enrolled even if they are unable to undergo MRI."	To allow for practical constraints with obtaining MRIs in all patients

Synopsis, Section 4.2	*Exclusion Criterion #12*	"Absolute neutrophil count < 2.0 x 10^9/L at Initial or Full Screening."	"Absolute neutrophil count < 2.0 x10^9/L at Initial and Full Screening."	To allow for enrollment of patients with fluctuations in counts at baseline
Synopsis, Section 4.2	*Exclusion Criterion #13*	"Platelet count < 100 x 10^9/L at Initial or Full Screening."	"Platelet count < 100 x 10^9/L at Initial and Full Screening."	To allow for enrollment of patients with fluctuations in counts at baseline
Synopsis, Section 4.2	*Exclusion Criterion #25*	"iPTH at Screening > 1000 pg/mL"	"iPTH at Screening > 2500 pg/mL"	To increase cut off for patients with otherwise good evidence of marrow function based on other eligibility criteria
Section 5.4.1, Appendix A footnotes	*Day -1 randomization*	Randomization may be performed on Day -1 (with medical monitor approval)	Randomization may be performed on Day -1 (no medical monitor approval needed)	To facilitate site logistics
Synopsis, Section 11.4.4	*Free IL-6*	Primary PD endpoint	Exploratory PD endpoint	Technical limitations of assay
Appendix A and Appendix D	Additional time points for serum albumin added (pre-albumin removed from these same time points)	Week -2, Days 1, 36, 78, 162	Week -2, Days 1, 36, 64, 78, 92, 120, 162	To better define the time course of changes in albumin without increasing blood volume taken from patients
Appendix A	Screening Period window	-	Allowance of the Medical Monitor to approve an increase in the Screening Period window by up to 12 days	To facilitate site logistics and central MRI readings

Synopsis and Sections 3.1.3 and 11.4.4	Definition of baseline for secondary pharmacodynamic endpoints	Baseline defined as the mean of Week -1 and Day 1 for TSAT, CHr, and hsCRp and as mean of Screening and Day 1 for SAA and albumin	Baseline defined as the mean of Screening and Day 1 for TSAT, CHr, hsCRP, SAA, and albumin	Make uniform the definition of baseline for secondary pharmacodynamic endpoints lab parameters
Synopsis and Sections 11.3.2 and 11.4.1	Per protocol population	-	Per protocol population added	To add a sensitivity analysis
Section 2	Objectives		Addition of objectives related to handgrip strength and fatigue	Alignment of objectives between synopsis and protocol body
Section 4.4	Addition of relatedness category to DLT definition	"unlikely", "possibly", and "probably" mentioned as relatedness categories	"definitely" related added as a relatedness category	To align AE relatedness categories with this section
Synopsis and Section 3.5.4	Addition of actual doses used for completed and ongoing cohorts	Planned doses	Planned doses and actual doses for Cohorts 1 - 5	To update protocol information based on actual cohort dose escalation
Synopsis (EC #2) and Section 7.2				Clarification that up to 5 mg per day of prednisone is allowable during the study
Multiple				Correction of typographical errors, minor inconsistencies, and formatting issues

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PROTOCOL SYNOPSIS

Title	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
Study Number	COR-001-01
Study Phase	1/2
Objectives	In a genotype-positive population of maintenance hemodialysis patients with elevated IL-6 levels, the objectives are as follows: Primary objective: • To evaluate the safety of multiple doses of COR-001 Secondary objectives: • To model the relationship of COR-001 pharmacokinetics and primary pharmacodynamics as assessed by free and total serum 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: o Systemic iron availability (transferrin saturation, TSAT, reticulocyte hemoglobin, CHr) and absolute reticulocyte count o Systemic iron stores (serum ferritin and supplemental iron dose requirements) o Erythropoiesis stimulating agent (ESA) resistance index (ERI) o Malnutrition-inflammation (pre-albumin, albumin) o Serum cardiac biomarkers (Troponin T and N-terminal pro-B-natriuretic peptide [NT-proBNP]) o Left ventricular mass index (LVMI) by non-contrast MRI o Physical function by handgrip strength and symptoms of fatigue • To investigate the immunogenicity of COR-001
Study Design	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. Ten hemodialysis patients will be randomized to COR-001 or placebo within each dosing cohort. When a higher dose than studied in a prior cohort is being initiated, the first 2 (sentinel) patients in that cohort (randomized 1:1 to COR-001 or placebo) will be randomized first and the remaining patients will be randomized at least 48 hours later, in a 7:1 ratio of COR-001 to placebo. The final ratio of patients treated with COR-001 vs. placebo will be 8:2 in each cohort of 10 patients. Prior to dose escalation (i.e., higher total dose than studied in the preceding cohorts), there will be a formal safety review by the Safety Review Committee (SRC), which will include at least one nephrologist. The SRC will specifically determine whether the maximum tolerated dose (MTD) has been exceeded based on protocol-defined dose-

	limiting toxicities occurring through Study Day 21 in the 8 actively treated patients in the current cohort (see Figure 2). 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. Patients will undergo an up to 4-week Screening Period during which the ESA dose and parenteral iron doses must have been stable, as defined in the inclusion and exclusion criteria. All patients randomized will be continued on ESA and parenteral iron (if being given). Patients meeting the entry criteria will generally be randomized on Day 1. The first dose of Study Drug will be administered during dialysis. Administration of the first dose of Study Drug will define Study Day 1. Additional visits will follow the schedule of events (see Appendix A: Schedule of Events). All subsequent Study Drug infusions will also be administered during dialysis and study visits will coincide with regularly scheduled dialysis treatments. Patients dropping out (i.e., prematurely discontinuing Study Drug treatment) for reasons unrelated to safety may be replaced in order to maintain the randomization ratio within each cohort. Following the 12-week Treatment Period, patients will be followed for an additional 12 weeks for safety in the Safety Follow-Up Period. Patients will have completed their primary study participation at Week 24 (end of the Safety Follow-Up Period). Limited blood sampling will occur on Week 35 for anti-drug antibodies, pharmacokinetics, and IL-6 measurements as part of an Extended Follow-Up Period.
Study Periods:	The total study duration for an individual patient will be approximately 9 months, excluding the Screening Period. Initial Screening Period: up to 2 weeks [Days -28 to -15] • Starts with the first date that Initial Screening procedures were performed. The first procedure also defines the initial screening visit date. Full Screening Period: up to 2 weeks [Days -14 through Day -1] • Starts with the date of the Week -2 Visit Treatment Period: 12 weeks [Week 1, Day 1 through Week 12] Safety Follow-Up Period: 12 weeks [Weeks 13 through 24] Extended Follow-Up Period: 10 weeks [Weeks 25 through 35]
Inclusion Criteria:	To be eligible, potential study patients must meet all of the following criteria: 1. Age ≥18 years at the time of signing of the ICF. 2. Receiving chronic hemodialysis for at least three (3) months prior to Screening via an arteriovenous fistula or arteriovenous graft. *Note: Every effort will be made to recruit patients who have a well- functioning arteriovenous fistula or graft to minimize the chance of requiring a central venous catheter during the Treatment Period.* 3. The patient agrees to comply with the contraception and reproduction restrictions of the study: Women of childbearing potential must be using a method of contraception, that is "highly effective" (i.e., < 1% failure rate, see Appendix F)

	OR Postmenopausal women must have had no menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma follicle-stimulating hormone (FSH) level (i.e., > 40 mIU/mL) at Screening; AND All female patients of childbearing potential must have a documented negative pregnancy test result at Screening. Patients with elevated β-HCG levels believed to be due to end-stage renal disease may be enrolled if documented to not be pregnant. 4. The patient is able to give written informed consent and has signed a consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IEC). 5. At least one documented spKt/V > 1.2 within 8 weeks prior to the Full Screening Period. 6. "Genotype positive" (genotype GG or AG, as defined by the Central Lab via genetic testing developed by the Sponsor) at Screening. 7. Two serum IL-6 levels ≥ 4 pg/mL measured at least 1 week apart during the Screening Period. 8. Receiving one of the following IV or SC ESA drugs continuously prescribed for a minimum of 8 weeks prior to Full Screening: epoetin alfa, darbepoetin alfa, or methoxypolyethylene glycol-epoetin beta. • Epoetin alfa must not have had more than one dose missed or held during Week -3 prior to Randomization. • Darbepoetin alfa must not have had any doses missed or held during the 4 weeks prior to Randomization. • Methoxypolyethylene glycol-epoetin beta must not have had any doses missed or held during the 6 weeks prior to Randomization. 9. Stable ESA doses prior to randomization, defined as follows: ***For ESAs dosed weekly or more frequently***: No change in the total weekly dose during Week -1 compared with Week -2. ***For ESAs dosed less often than weekly:*** Any dose given during Full Screening Week -2 and Week -1 is unchanged from the immediately preceding dose. Note: If a dose was given on both Week -2 and Week -1, then both doses are the same. (These 2 doses may be different than earlier doses). 10. Has been receiving intravenous (IV) or dialysate iron regularly and continuously (e.g., with each dialysis or each week) during the 3 weeks prior to randomization OR has received no IV or dialysate iron during this time frame and use of IV or dialysate iron is not anticipated through Study Week 24. If parenteral iron has been administered during the 3 weeks prior to randomization,

	the regimen has been stable (same elemental iron dose, same frequency, and same iron product) with no more than 2 missed or held doses if dosed with each dialysis and no missed or held doses (if dosed weekly or less frequently) during this time frame. 11. If receiving oral ferric citrate, the patient has been prescribed it for at least 2 weeks prior to Full Screening and the dose is not anticipated to be changed through Study Week 24. 12. At least 2 ferritin values during Screening > 300 ng/mL. 13. At least 2 TSAT values during Screening between 15% and 50% (inclusive). 14. ESA resistance index (confirmed by the Sponsor) during the 2 weeks prior to randomization: **For patient receiving epoetin alfa**: $\frac{\text{Total weekly dose of epoetin alfa (units)}}{\text{(hemoglobin [g/dL]) * target dry body weight [kg])}}$ > 8 units/kg per g/dL **For patients receiving darbepoetin alfa:** $\frac{\text{Total weekly dose of darbepoetin alfa (mcg) * 300}}{\text{(hemoglobin [g/dL]) * target dry body weight [kg])}}$ > 8 units/kg per g/dL **For patients receiving methoxy polyethylene glycol-epoetin beta**: $\frac{\text{Weekly dose of methoxy polyethylene glycol-epoetin beta (mcg) *300}}{\text{(hemoglobin [g/dL]) * target dry body weight [kg])}}$ > 8 units /kg per g/dL If the ESA is dosed less often than once a week, divide the dose by the dosing interval to determine the weekly dose. For example, Weekly dose = dose given every two weeks ÷ 2. The first day of each week used for calculations is defined as the first dialysis day of the Week (i.e., Monday or Tuesday). 15. During the 4 weeks prior to randomization, the mean of 3 consecutive hemoglobins between ≥ 8.5 and ≤ 11.0 g/dL, with the difference between the first and last measurements being < 1.2 g/dL. Note: Qualifying hemoglobins must be drawn 2 or more days apart pre-dialysis, with no more than 2 measurements within a calendar week. There must be at least 9 days between the first and last of the 3 qualifying hemoglobin values. 16. Investigator anticipates no change to ESA, parenteral, or oral iron products, doses, or dosing regimen during Study Weeks 1 through 4 and that following the protocol guidance for ESA and iron dose changes (Appendix C) will be clinically appropriate for the patient. 17. Serum Vitamin B-12 and folate levels above the laboratory lower normal range during Full Screening.

Exclusion Criteria:	To be eligible for study enrollment, potential study patients must not meet any of the following exclusion criteria: 1. Any indwelling vascular catheter (including that used for dialysis) or anticipated of use of an indwelling catheter anytime during the study (including the Initial Screening and Full Screening Periods). 2. Patients for whom a central venous catheter is used within 2 weeks prior to Step 2 of the Initial Screening Period (blood draw for IL-6, see Section 5.2) will be also be considered screening failures. Use of systemic immunosuppressive drugs during the Full Screening Period or anticipated use of such drugs any time during the study. Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary. Oral prednisone up to 5 mg per day is (or equivalent) is permitted. 3. Clinical evidence or suspicion of active or smoldering infection (e.g., diabetic foot ulcer) or use of systemic antibiotics, systemic antivirals, or systemic antifungals within 2 weeks prior to Step 2 of the Initial Screening Period (blood draw for IL-6, see Section 5.2), during the Initial Screening Period, or the Full Screening Period. ("Systemic" is defined as oral or intravenous drugs that are absorbed into the circulation.) 4. Hospitalization or outpatient procedures within 2 weeks prior to Step 2 of the Initial Screening Period (blood draw for IL-6, see Section 5.2) , during the Initial Screening Period, or the Full Screening Period unless approved by the Medical Monitor. Note: Please contact the Medical Monitor for approval and determination of timing of IL-6 measurements if considering enrolling patients with hospitalizations or outpatient procedures during this time frame. 5. Inability to undergo a non-contrast magnetic resonance imaging (MRI) scan (e.g., weight over the limits for MRI machine, claustrophobia that cannot be managed, certain metallic indwelling foreign bodies). Requirement for MRI may exempted by the medical monitor due to practical considerations. In such situations, patients may be enrolled even if they are unable to undergo MRI. 6. Positive tuberculosis blood test at Screening 7. Evidence of HIV-1 or HIV-2 infection by serology at Screening. 8. Hepatitis B or C by serology (i.e. Hepatitis B Surface Antigen or Hepatitis C antibody positive) at Screening. 9. AST or ALT > 2.5x ULN at Screening. 10. History of liver cirrhosis or home oxygen use (other than nocturnal-only oxygen for those with sleep apnea). 11. History of gastrointestinal ulceration or active diverticulitis in the 1 year prior to Initial Screening. 12. Absolute neutrophil count < 2.0 x 10^9/L at Initial and Full Screening. 13. Platelet count < 100 x 10^9/L and Initial or Full Screening.

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14. Expected to receive any investigational drug or any of the exclusionary drugs listed in Appendix B during the Treatment Period or Safety Follow-Up Period.
15. Received an investigational drug within 30 days prior to the start of the Full Screening Period.
16. Known allergy to the Study Drug or any of its ingredients.
17. Currently breastfeeding.
18. Any condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or interpretation of the study results, or that would in the opinion of the Investigator increase the risk of the patient's participation in the study. This would include but is not limited to alcoholism, drug dependency or abuse, psychiatric disease, epilepsy, anemia attributable to a primary hematologic disease (e.g., sickle cell anemia), or any unexplained blackouts.
19. Actively treated or active malignancy (other than non-melanoma skin cancers or cervical carcinoma in situ considered cured at the time of Full Screening) during the 1 year prior to Full Screening.
20. Myocardial infarction during the 2 months prior to Full Screening or during Screening.
21. Known or suspected occult or active bleeding other than that related to the hemodialysis procedure.
22. Received a red blood cell or whole blood transfusion within 2 months prior to Full Screening or anticipated to receive a blood transfusion at any time during the study.
23. Have inflammatory bowel disease that has been clinically active during the 3 months prior to Full Screening or bone marrow or organ transplant.
Note: Patients with a previously explanted kidney transplant are eligible as are those who have an implanted kidney transplant, but have not received immunosuppression for at least 6 months prior to Full Screening.
24. Anticipated to receive an organ transplant during the time frame of the study.
25. iPTH at Screening > 2500 pg/mL.
</td></tr>
<tr><td>Test Product, Dose and Mode of Administration</td><td>
COR-001 will be administered as an intravenous infusion, started any time before the last 1 hour of the dialysis treatment.
The COR-001 dose regimens planned are itemized below. The planned doses may be substituted for lower doses (including previously studied doses) based on accruing data. The highest dose that will be studied is a cumulative dose of 360 mg
<table>
<tr><th>Dose Cohort</th><th>Dose Regimen</th><th>Number of Doses</th><th>Total Cumulative Dose</th></tr>
<tr><td>1</td><td>2 mg every 14 days</td><td>6</td><td>12 mg</td></tr>
<tr><td>2</td><td>6 mg every 14 days</td><td>6</td><td>36 mg</td></tr>
<tr><td>3</td><td>20 mg every 14 days</td><td>6</td><td>120 mg</td></tr>
<tr><td>4</td><td>60 mg every 14 days</td><td>6</td><td>360 mg</td></tr>
</table>
As of Amendment 3, the actual doses (all given every 14 days) were 2 mg (Cohorts 1 and 4); 6 mg (Cohorts 2 and 3); 20 mg (Cohort 5).
</td></tr>
<tr><td>Reference Therapy, Dose, and Mode of Administration</td><td>
The reference dose regimens to be examined in this study are:
• Matched placebo intravenously administered at the same frequency as the active
</td></tr>
</table>

	treatment in a given cohort

Pharmacokinetic and PK-PD Modeling:	• Serum COR-001 concentrations will be subjected to PK modeling and secondary PK parameters such as maximum serum drug concentrations (C_{max}), area under the serum drug concentration-time curve (AUC) and terminal elimination half-life ($t_{1/2}$) will be calculated. • The free (unbound to COR-001) and total (free + bound) IL-6 AUC will be described • The change in plasma concentration of COR-001 from pre-dialysis to post-dialysis will be described • The relationship between COR-001 pharmacokinetics and primary pharmacodynamic endpoints, specifically free and total serum IL-6, high-sensitivity C-reactive protein (hsCRP) and serum amyloid A (SAA) will be described.
Safety Endpoints:	**Primary** 1. Characterization of the MTD or to establish that the highest dose examined did not exceed the MTD **Secondary** 1. Description of the frequency of DLTs (defined in Section 4.4) by treatment group and dose 2. Description of the frequency of the events of interest by treatment group and dose (defined in Section 9.3) 3. Description of additional safety assessments by treatment group and dose: adverse events, vital signs, ECG, clinical laboratory, and anti-drug antibodies (binding and neutralizing)
Primary Pharmacodynamic Endpoints	• Change from baseline (mean of Screening and Day 1) in the SAA and hsCRP to Week 4 between treatment groups
Secondary Pharmacodynamic Endpoints	Mean differences between placebo and COR-001-treated patients will be determined for the following parameters: • Change from baseline (mean of Screening and Day 1 values) in TSAT to Week • Change from baseline (mean of Screening and Day 1 values) in the CHr to Week 4 • Change from baseline (mean of Screening and Day 1 values) in hsCRP to the mean of Weeks 10-12. • Change from baseline (mean of Screening Period and Day 1 values) in SAA to the to the mean of Weeks 10-12 • Change from baseline (mean of Screening Period 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 Exploratory pharmacodynamics endpoints are described in Section 11.4.4
Sample Size	Approximately 60 (i.e., up to 6 cohorts, including expansion cohorts)

Study Centers	Approximately 15 study sites
Statistical Methods Analysis	The following analysis Populations are defined for the different types of data analysis: • Intent-to-treat (ITT) analysis population, the primary population for the disposition and baseline data summaries. • Pharmacodynamic analysis population, the population for the pharmacodynamic analyses. • Pharmacokinetics analysis population for PK analysis. • Per-protocol analysis population for pharmacodynamics analyses • Safety analysis population for the safety analyses. All study-collected data will be summarized by treatment group for the appropriate analysis population, using descriptive statistics. 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 percentages. 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.

LIST OF ABBREVIATIONS, DEFINITIONS, AND TERMS

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
β-hCG	β -Human chorionic gonadotropin hormone
BMP	Bone morphogenic protein
BMPR	Bone morphogenic protein receptor
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CHr	Reticulocyte hemoglobin concentration
CFR	Code of Federal Regulations
COR-001	Monoclonal antibody to IL-6
$C_{max/min}$	Maximum/minimum observed concentration
CRF	Case report forms
CRO	Contract research organization
DLT	Dose-Limiting Toxicity
Dialysis Start Time	The start time of dialysis is defined by the earliest time point recorded on the dialysis flow sheet (or equivalent) with a blood flow rate > 0
Dialysis End Time	Dialysis is considered completed when the dialysis machine shows 0 minutes remaining for the treatment. The end time of dialysis is defined by the latest time point recorded on the dialysis flow sheet (or equivalent) with a blood flow rate = 0 or last recorded blood flow rate, whichever is later.
ECG	Electrocardiogram
ERI	ESA resistance index (ESA weekly dose/targeted dry weight in Kg*hemoglobin in g/dL)
ESA	Erythropoiesis-stimulating agent
FACIT-F [questionnaire]	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
FPN	Ferroportin
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HAMP	Hepcidin gene
HDL	High density lipoprotein
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus

Term	Definition
HR	Heart rate
hsCRP	High sensitivity C-Reactive Protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IL-6R	IL-6 receptor
IND	Investigational new drug
INR	International normalized ratio
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
IV	Intravenous
IVBP	IV Bag Protectant
IWRS	Interactive Web-Response System
kg	Kilogram
Kt/V	Measure of dialysis clearance and adequacy where K = dialyzer clearance of urea, t = dialysis time, and V – volume of distribution of urea
LDL	Low density Lipoprotein
LHD	Low Hemoglobin density
LLN	Lower Limit of Normal
LVMI	Left Ventricular Mass Index
MCV	Mean corpuscular hemoglobin
mg	Milligram
min	Minute
mL	Milliliter
mITT	Modified Intent-to-Treat
MRI	Myocardial Resonance Imaging
MTD	Maximally Tolerated Dose
NOAEL	No observed adverse effect level
NT-proBNP	N-terminal pro-B-natriuretic peptide
PD	Pharmacodynamic
PK	Pharmacokinetic
PI	Principal Investigator
PPD	Purified Protein Derivative
PT	Prothrombin Time
PTH	Parathyroid Hormone
RBC	Red Blood Cell
RDW	Red cell distribution width
RSf	Red cell size factor

Term	Definition
RR	Respiratory Rate
SAA	Serum amyloid A
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SRC	Safety Review Committee
SOP	Standard Operating Procedure
spKT/V	Single-pool Kt/V
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-life
TB	tuberculosis
TBD	To be determined
TIBC	Total iron binding capacity
TMP	Transmembrane Pressure
TSAT	Transferrin saturation
UFR	Ultrafiltration Rate
ULN	Upper limit of normal
WBC	White blood cells

1 INTRODUCTION

1.1 Background

Nearly all (> 90%) dialysis patients in the United States are treated with erythropoiesis stimulating agents (ESAs) and supplemental iron for management of chronic anemia and transfusion avoidance. However, the requirement for supra-physiologic ESA doses to maintain clinical guideline and FDA-specified target hemoglobin levels suggests some degree of erythropoietic inefficiency in these "hyporesponsive" patients (MacDougall 2005, Sun 2012). In the healthy state, serum erythropoietin levels are approximately 12-15 U/L. After a 2-unit phlebotomy and decline in hemoglobin from 15 g/dL to 12 g/dL, erythropoietin levels increase over 10-fold to approximately 200 U/L transiently. In contrast, a moderate-for-dialysis patient intravenous dose of erythropoietin of 3000 U results in a peak erythropoietin level of approximately 1000 U/L, levels not achieved with native erythropoietin production until the hemoglobin levels reach 5 g/dL (Fishbane 2007).

Erythropoiesis stimulating agent trials randomizing patients to higher vs. lower hemoglobin targets have shown an increase in cardiovascular events among those treated to higher hemoglobin targets in both dialysis-dependent and non-dialysis dependent chronic kidney disease patients (Besarab 1998 and Singh 2006). Analyses of these trials and others have shown that patients at greatest risk for cardiovascular events were those randomized to the higher hemoglobin target who failed to achieve said target (i.e. hyporesponders) and, per protocol, were treated with higher ESA doses (Fishbane 2007 and Kilpatrick 2008).
A number of potential, non-mutually exclusive mechanisms have been suggested to explain these observations (e.g., potential direct toxic effects of non-biologic ESAs and/or iron, increased platelet activity, hyperviscosity, and endothelial damage) and all of these mechanisms are superimposed upon individual ESA responsiveness. ESA hyporesponsiveness is also a manifestation of the malnutrition-inflammation complex in which inflammation is associated with reductions in pre-albumin and albumin (Kalantar-Zadeh 2003) and treatment of inflammation has been shown to improve nutritional markers (Hung 2011).

Patients with the most marked ESA hyporesponsiveness are characterized by lower hemoglobin levels, lower transferrin saturation levels, and normal or high ferritin levels (Kharagjitsingh 2005). Together, these parameters point to a functional blockade in release of iron for erythropoiesis from bodily stores. One important mechanism for this blockade is inflammation-induced expression of the "master iron regulator" hepcidin, a protein which prohibits cellular iron transport via degradation of ferroportin, the only known iron export channel in humans (Hentze et al 2004, Hentze et al 2010 and Sun 2012). Use of high doses of intravenous iron can partially overcome this blockade, but higher doses (> 400 mg/month) are associated with higher cardiovascular mortality and all cause mortality in the context of inflammation (Kalantar-Zadeh 2005). Current anemia treatments do not reduce inflammation and, therefore, fail to address an important mechanism of anemia in this population.

These observations form the basis for targeting inflammation as a means to treat anemia in the dialysis population. Inhibiting inflammation and thereby improving functional iron

deficiency would be expected to reduce the required ESA and iron supplementation at any level of targeted hemoglobin and potentially alleviate associated iatrogenic complications.

1.2 Description of COR-001

Additional information about the mechanism and structure of COR-001 can be found in the COR-001 Investigator's Brochure.

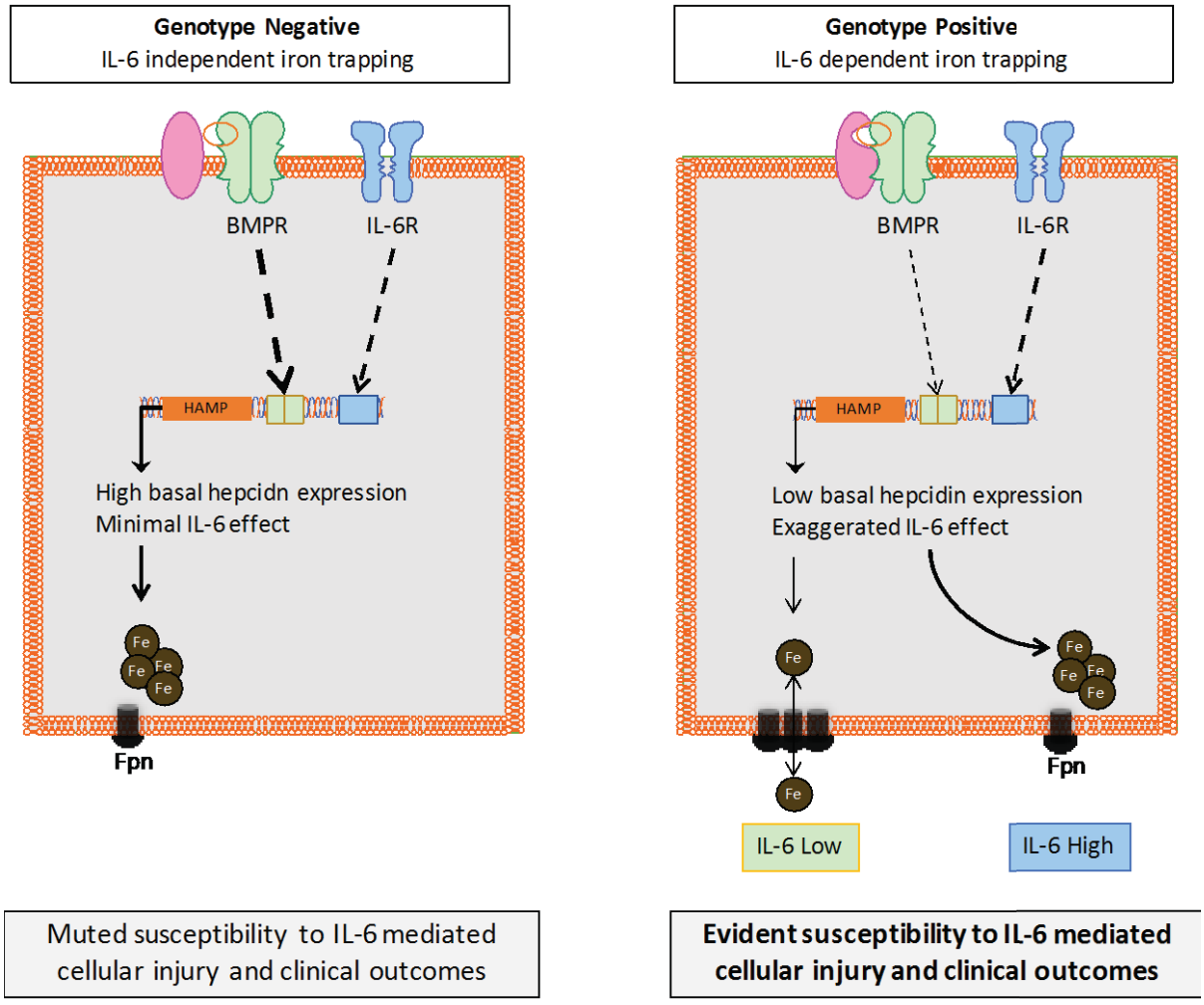
COR-001 is a human IgG1, kappa antibody directed against interleukin-6 (IL-6), containing a "YTE" mutation in its Fc region which affords the potential for extended half life. COR-001 is being developed for the treatment of anemia in genotype positive patients with chronic kidney disease on hemodialysis.

Alleviation of inflammatory anemia with anti-IL-6 therapy comes from published work regarding the use of said therapy in humans in non-renal inflammatory conditions. Tocilizumab (Roche) and clazakizumab (Alder Biopharmaceuticals) have both shown ability to raise hemoglobin in rheumatoid arthritis, Castleman's disease and advanced malignancy (Song 2010, Song et al 2013, Bayliss 2011). By example, the administration of tocilizumab (anti-IL-6 receptor antibody) reverses signs of inflammation, improves iron availability, and increases hemoglobin in Castleman's patients.

Although anti-IL-6 therapies have not been tested in dialysis patients to date, published and Sponsor's unpublished data in a large prevalent dialysis population documents a correlation between serum IL-6 levels and the degree of ESA hypo-responsiveness (i.e., erythropoietin dose requirement divided by achieved serum hemoglobin) (Won 2012 and see Section 2 of the COR-001 Investigator's Brochure).

However, the influence of IL-6 is not universal, and appears over-represented in a specific, genotypically defined dialysis subpopulation. Based on non-clinical study and retrospective review of dialysis populations (Sponsor's unpublished data), it appears a genotypic variation in the iron-control system of mammalian cells can render tissues more or less susceptible to IL-6 based inflammation, and dictate the influence of this inflammation on clinical outcomes (see Figure 1 and Section 2 of the COR-001 Investigator's Brochure).

Figure 1 **A model for the influence of genetic variation on IL-6 –mediated cellular iron handling**



BMPR = BMP receptor
IL-6R = IL-6 receptor
HAMP =hepcidin gene
FPN = ferroportin
Fe = iron

1.3 Summary of Relevant Nonclinical Experience with COR-001

1.3.1 Non-Clinical Pharmacology

In vitro studies were conducted to determine the affinity, potency and specificity of COR-001. These studies confirm COR-001 is highly (sub-pico-molar) potent and outcompetes cell bound or soluble IL-6 receptors, thus effectively preventing circulating IL-6 from binding to its receptors and eliciting effects via classical or trans-signaling A preclinical proof of concept study in a cardio-renal rodent model was conducted to expand on published data and the rationale for the intended indication. Further preclinical studies elucidated the direct and indirect mechanisms of IL-6 mediated inflammatory cardiac injury.

1.3.2 Pharmacokinetics in animals

Cynomolgus monkey was selected as the pharmacologically relevant animal model to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of COR-001 and conduct nonclinical safety assessment studies. One single-dose non-GLP study and one multiple-dose GLP study was conducted.

The elimination half-life of COR-001 was extended by approximately 3-fold and the clearance was reduced by approximately 4-fold compared to the parent molecule lacking the YTE Fc region mutations. The average half-life of COR-001 ranged from 27.2 to 28.8 days and clearance from 2.76 to 3.88 mL/day/kg.

1.3.3 Non-Clinical Toxicology and Safety

The nonclinical toxicology data for COR-001 include two studies in cynomolgus monkeys: a non-GLP single IV or SC dose PK and pharmacodynamics study, and a GLP repeat IV or SC administration toxicology study (every other week administration for 13-weeks with a 16-week recovery). In the non-GLP single-dose study, although there was no control group comparator, there were no adverse findings attributed to single COR-001 administration of 5 mg/kg IV or 50 mg/kg SC injections, the highest doses tested.

In the GLP repeat-dose study, the NOAEL was 100 mg/kg for animals dosed IV and 50 mg/kg for animals dosed SC, the highest doses tested. In addition, GLP tissue cross-reactivity studies in a full panel of human and cynomolgus monkey tissues showed staining judged as expected.

1.4 Summary of Relevant Clinical Experience

1.4.1 Phase 1 Study of COR-001 in Rheumatoid Arthritis Patients

The clinical program to date consists of a single Phase 1, double blind, placebo controlled single ascending dose study in rheumatoid arthritis patients (Study D4430C00001) conducted by MedImmune from 21 May 2012 to 25 February 2014. Dose escalation was to begin at 30 mg, with provisional doses of 90, 270, and 600 mg thereafter. After 4 patients were enrolled (3 receiving COR-001 30 mg IV (single dose) and 1 receiving placebo), the study was terminated due to difficulties with recruitment.

1.4.2 Summary of Safety from Clinical Studies (D4430C00001)

No patients died during the study. No patients reported any serious adverse events (SAEs) or discontinued investigational product administration due to an AE. All of the AEs were considered to be of mild to moderate intensity by the Investigator. The following AEs were considered related to the investigational product by the Investigator, and were of moderate intensity: Productive cough, influenza. The following AEs were considered related to the investigational product by the Investigator, and were of mild intensity: Nausea (placebo), diarrhea, vomiting, headache, and nasopharyngitis (COR-001).

No specific trends were observed in laboratory values, with the exception of changes in the white blood cell (WBC) and neutrophil counts. Whereas the patient who received placebo had no abnormal WBC or neutrophil counts, changes were observed in all 3 patients who received COR-001. One patient who received COR-001 had normal WBC and neutrophil counts at baseline, but neutrophil counts below normal during Weeks [redacted] to [redacted]. A second patient who received COR-001 had normal WBC and neutrophil counts at baseline, which decreased between Week [redacted] to Week [redacted], reaching a low WBC count of [redacted] and a low neutrophil count of [redacted]. The third patient who received COR-001 had a normal WBC and low neutrophil count ([redacted] at baseline, which further decreased between Day [redacted] and Week [redacted], reaching a low WBC count of [redacted] and a low neutrophil count of [redacted]. For all three patients who received COR-001, WBC and neutrophil counts returned to normal by the end of the study.

No other notable changes in laboratory parameters (including liver function), vital signs, or physical assessments as related to safety were noted.

2 STUDY OBJECTIVES

In a genotype positive population of maintenance hemodialysis patients with elevated IL-6 levels, the objectives are as follows:

Primary objective:

- To evaluate the safety of multiple doses of COR-001

Secondary objectives:

- To model the relationship of COR-001 pharmacokinetics and primary pharmacodynamics as assessed by free and total serum 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:
  - Systemic iron availability (transferrin saturation, TSAT, reticulocyte hemoglobin, CHr) and reticulocyte count
  - Systemic iron stores (serum ferritin and supplemental iron dose requirements)
  - Erythropoiesis stimulating agent resistance index (ERI)
  - 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 MRI
  - Physical function by handgrip strength and symptoms of fatigue
- To investigate the immunogenicity of COR-001

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan: Description

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.

Ten hemodialysis patients will be randomized to COR-001 or placebo within each dosing cohort. When a higher dose than studied in a prior cohort is being initiated, the first 2 (sentinel) patients in that cohort will be randomized 1:1 to COR-001 or placebo; the remaining patients will be randomized at least 48 hours later in a 7:1 ratio of COR-001 to placebo.

Prior to dose escalation (i.e., higher total dose than studied in the preceding cohorts), there will be a formal safety review by the Safety Review Committee (SRC), which will include at least one nephrologist. The SRC will specifically determine whether the maximum tolerated dose (MTD) has been exceeded based on protocol-defined dose-limiting toxicities occurring through Study Day 21 in the 8 actively-treated patients in the current cohort (see Figure 2). In addition, PK and PD 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 2. 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 (described in Section 11.5) is planned to enable future program planning.

Patients will undergo a Screening Period during which the ESA dose and parenteral iron doses must have been stable, as defined in the inclusion and exclusion criteria. Patients randomized to both COR-001 and placebo will be continued on ESA and parenteral iron (if being given).

Patients meeting the entry criteria will be randomized on Day 1 (a dialysis day), following which they will receive the first dose of Study Drug during dialysis. Additional visits will follow the schedule of events (Appendix A). All subsequent Study Drug infusions will also be administered during dialysis and study visits will coincide with regularly scheduled dialysis treatments. Patients dropping out (i.e., prematurely discontinuing Study Drug treatment) 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 in the Safety Follow-Up Period. The patient's 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.

3.1.1 Pharmacokinetic and PK-PD Modeling

- Serum COR-001 concentrations will be subjected to PK modeling and secondary PK parameters such as maximum serum drug concentrations (C_{max}), area under the serum drug concentration-time curve (AUC) and terminal elimination half-life ($t_{1/2}$) will be calculated.
- The free (unbound to COR-001) and total (free + bound) IL-6 AUC will be described
- The change in serum concentration of COR-001 from pre-dialysis to post-dialysis will be described
- The relationship between COR-001 pharmacokinetics and primary pharmacodynamic endpoints, specifically free and total serum IL-6, high-sensitivity C-reactive protein (hsCRP) and serum amyloid A (SAA) will be described.

3.1.2 Safety Endpoints

Primary

- Characterization of the MTD or to establish that the highest dose examined did not exceed the MTD

Secondary

- Description of the frequency of DLTs (defined in Section 4.4) by treatment group and dose
- Description of the frequency of the events of interest by treatment group and dose (defined in Section 9.3)
- Description of additional safety assessments by treatment group and dose: adverse events, vital signs, ECG, clinical laboratory, and anti-drug antibodies (binding and neutralizing)

3.1.3 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.

Primary

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

Secondary

- Mean differences between placebo and COR-001-treated patients will be determined for the following parameters:
- 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 Screening and Day 1 values) in hsCRP to the mean of Weeks 10 – 12
- Change from baseline (mean of Screening and Day 1 values) in SAA to the mean of Weeks 10 – 12
- Change from baseline (mean of 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 among patients
- Change from baseline (weekly mean of Screening) in ERI to the mean of Weeks 8 – 12

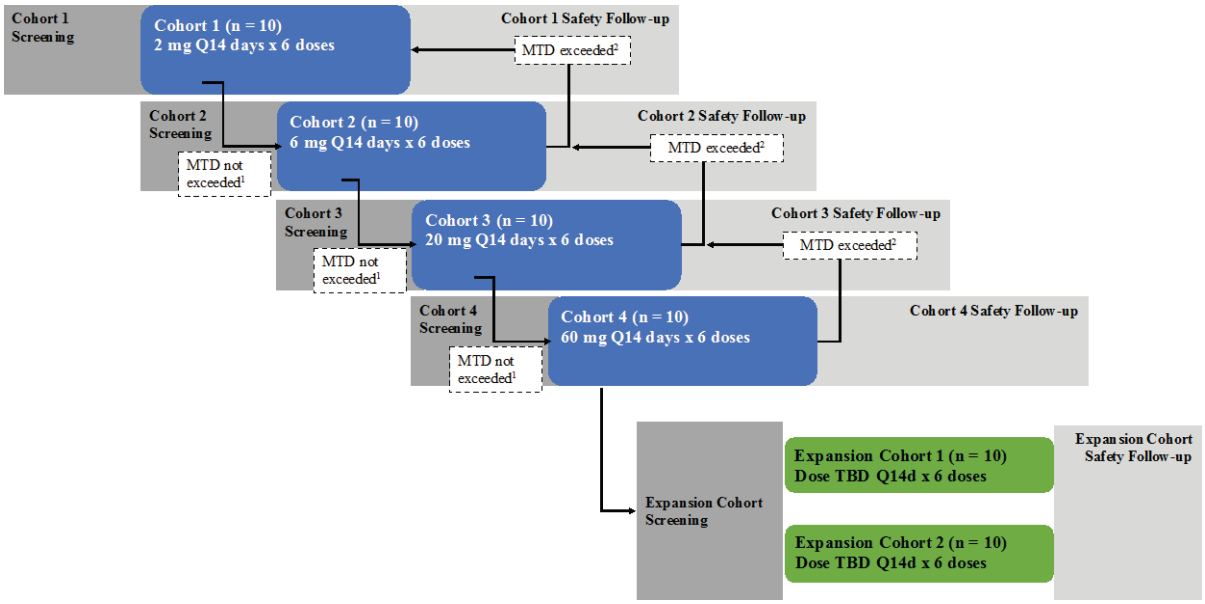
Exploratory

- 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

3.2 Study Schematic

Figure 2 Dose Escalation Schematic



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 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.

The planned doses shown here may be adjusted based on accruing PK, PD, and safety 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.

The randomization ratio within each cohort will be 8:2 (COR-001 to placebo).

3.3 Blinding and Randomization

3.3.1 Randomization

Randomized treatments will be assigned via an interactive web-response system (IWRS). Ten hemodialysis patients will be randomized to COR-001 or placebo within each dosing cohort. When a higher dose than studied in a prior cohort is being initiated, the first 2 (sentinel) patients in that cohort (randomized 1:1 to COR-001 or placebo) will be randomized first and the remaining patients will be randomized at least 48 hours later, in a 7:1 ratio of COR-001 to placebo. For cohorts in which doses are less than the dose that exceeded the MTD (determined from earlier cohorts), randomization of all 10 patients will proceed in parallel to achieve an 8:2 ratio of COR-001 to placebo.

3.3.2 Blinding

This study is double-blind. The patients, investigators, site personnel (not including site personnel responsible for drug versus placebo preparation), site monitors and Sponsor clinical operational personnel will be blinded to the treatment assignment. The Sponsor representative(s) on the SRC will become unblinded for the safety reviews of each cohort in order to select doses for the next cohort. The SRC will be unblinded. In addition, contract research organization (CRO) personnel analyzing the PK samples and performing the PK, target engagement, and analysis of PK/pharmacodynamic relationships and those responsible for interactive web-response system (IWRS) will have access to the randomization list. The randomization list will be generated by a CRO statistician not otherwise involved in the study or the SRC unblinded statistician.

3.3.3 Unblinding

In case of a medical emergency or medical situation in which the treatment assignment is necessary for proper patient management, the Investigator may obtain the treatment assignment from the IWRS. The Investigator should make every reasonable attempt to contact the Medical Monitor before unblinding a patient. In all cases, the Investigator must submit a written report, including all pertinent details, to the Medical Monitor within 24 hours of the unblinding.

3.4 Duration of the Study

The total study duration for an individual patient will be approximately 9 months, excluding the Screening Period. The study periods are as follows:

- Initial Screening Period: Up to 2 weeks [Days -28 to -15]
  - Starts with the first date that Initial Screening procedures were performed. The first procedure also defines the Initial Screening visit date.
- Full Screening Period: up to 2 weeks [Days -14 through Day -1]
  - Starts with the date of the Week -2 Visit

- Treatment Period: 12 weeks [Week 1, Day 1 through Week 12]
  - Safety Follow-Up Period: 12 weeks [Weeks 13 through 24]
- Extended Follow-Up Period: 10 weeks [Weeks 25 through 35]

3.5 Discussion of Study Design, Including Choice of Control Arm

The study is a randomized (within cohort), double-blind, placebo-controlled trial. Randomization and double-blinding are being used to minimize bias. The treatment duration (12 weeks) was chosen as the shortest duration needed to evaluate the pharmacodynamic effect of said doses on the proposed inflammatory, hematologic and cardiovascular endpoints. Sample size calculations were performed for several pharmacodynamics endpoints and these are presented in Section 11.1.

3.5.1 Study Population and Control Arm

Because the Study Drug is being administered in addition to current treatments for anemia, a placebo-control is justifiable. As there are no currently approved treatments that improve functional iron deficiency, there are no options for an active comparator.

The study is being conducted in the target population because the pharmacodynamic endpoints (inflammation, functional iron deficiency, and left ventricular hypertrophy and strain) cannot be evaluated in healthy volunteers.

Further, as human pharmacokinetic data to date are available only from a non-chronic kidney disease population, it is one aim of the study to obtain PK data in the hemodialysis population.

3.5.2 Rationale for Dosing and Length of Safety Evaluation

Inhibition of free IL-6 greater than 90% is needed to achieve biologic effect, because growth factors and soluble cytokines in general are able to elicit signaling with receptor occupancies of less than 10%. A basic logarithmic dose escalation scheme was used after modeling of IL-6 binding and the PK-PD (hsCRP) relationship from the concluded Phase 1 trial in RA patients (Study D4430C00001). Based on the clearance of COR-001 (dictated by the "YTE" Fc mutation), the duration of safety monitoring for 24 weeks following the last dose and extended follow-up for PK, IL-6, and antibody testing to 35 weeks is planned.

3.5.3 Rationale for the Pharmacodynamic Endpoints

The inflammatory pharmacodynamic endpoints of hsCRP and Serum Amyloid A reduction are chosen as they are a direct measures of IL-6 function (specifically their genes are induced by IL-6). Additionally, hsCRP is a clinically relevant measure of inflammation that may be used in future trials. Serum albumin and pre-albumin are also closely negatively correlated with inflammation in the dialysis population as is therefore also being analyzed as a marker of inflammation.

The hematologic pharmacodynamic endpoints chosen are as follows: TSAT, hemoglobin, reticulocyte count, CHr, ESA and iron dose requirements, and erythropoietin resistance index, defined as the epoetin alfa-equivalent dose (weight-based per week in U/kg) divided by the serum hemoglobin (in g/dL). These endpoints are intended to evaluate the effects of reducing inflammation on functional iron deficiency anemia as well as on ESA and iron requirements to maintain hemoglobin at a given (guideline-driven) level. It is hypothesized that CHr will increase as iron is released from tissue stores and that ERI will decrease as hemoglobin rises and/or ESA dose requirements fall assuming administered iron is maintained. The reticulocyte count is expected to transiently increase. TSAT to also expected to increase over time as more iron is mobilized, until iron is utilized for erythropoiesis (reflected in rising hemoglobin), assuming ESA and iron doses remain stable.

Supportive cardiovascular pharmacodynamic endpoints include serum biomarkers (Troponin and NT-proBNP) and left ventricular mass index via MRI. These are chosen based on the documented detrimental effects of IL-6, and beneficial effects of anti-IL-6 therapies, on cardiac structure and function in inflammatory conditions.

Finally, inflammation is known to affect systemic symptoms, notably fatigue and skeletal muscle strength.

3.5.4 Rationale for the Dose Regimens

The main goal of COR-001 dosing in the planned Phase 1/2 hemodialysis patient study is to attain and maintain serum COR-001 concentrations sufficient for ≥ 90% IL-6 binding over the 3-month Treatment Period, with a secondary goal of reducing hsCRP to below 5 mg/L while keeping the highest planned dose more than 20-fold below the no adverse effect level (NOAEL) observed in primates.

Effects on IL-6 and hsCRP

Pharmacokinetic and PD models were created based on data from the Phase 1 trial in RA patients (Study D4430C00001) and used to simulate dosing regimens that achieve the above goals (Section 3.5.4). Based on these models, lower doses were needed to maintain serum COR-001 concentrations above the target value (i.e., that value required to achieve > 90% IL-6 binding) compared to those needed to normalize hsCRP (defined as hsCRP < 5mg/L) in a hypothetical hemodialysis population whose baseline hsCRP is at median and serum IL-6 level is above the median. hsCRP normalization in at least 1/3 patients is predicted for cumulative COR-001 dose of ≥ 12 mg, and is not predicted for all patients until cumulative doses of 60 mg or greater are achieved. The COR-001 dose regimens planned are itemized below. Lower doses (including previously studied doses) may be substituted for the planned doses in the table below based on accruing data. In addition, PK and PD 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.

Dose Cohort	*Dose Regimen*	*Number of Doses*	*Total Cumulative Dose*
1	2 mg every 14 days	6	12 mg
2	6 mg every 14 days	6	36 mg
3	20 mg every 14 days	6	120 mg
4	60 mg every 14 days	6	360 mg

The planned doses all provide plasma IL-6 binding in excess of 90% for the duration of the study, while hsCRP normalization is expected to be attained in 1/3 of patients at the lowest dose, and in 3/3 patients at the highest dose. Full suppression of hsCRP is not believed to be required for beneficial effect on hematologic or iron parameters given the linear correlation between CRP and the degree of erythropoietic inefficiency (Bárány 1997).

As of Amendment 3, the actual doses (all given every 14 days) were 2 mg (Cohorts 1 and 4); 6 mg (Cohorts 2 and 3); 20 mg (Cohort 5).

Safety Margins

The predicted maximum serum COR-001 concentration within a dosing interval (C_{max}), minimum serum COR-001 concentration within a dosing interval (C_{min}), and the cumulative area under the curve from time 0 to infinite time ($AUC_{0-\infty}$) for the planned doses in this study are summarized in Table 1. Table 1 also provides the exposures obtained for the highest dose in the cynomolgus monkey repeat-dose toxicology study (Study 20004916). The exposures for all cohorts in this study have safety margins of ≥ 20-fold (based on AUC), relative to the no observed adverse effect level (NOAEL) exposures in cynomolgus monkeys.

Table 1 Exposures for Planned Doses and Safety Margins Relative to Toxicology Study

Human						*Cynomolgus Monkey*
Dosing Schedule		***2 mg q14days***	***6 mg q14days***	***20 mg q14days***	***60 mg q14days***	***100 mg/kg***
C_{max} *(ng/mL)*[a]	***1st dose***	***712***	***2138***	***7126***	***21379***	***2420000***
	last dose	***1640***	***4920***	***16399***	***49197***	***3230000***
C_{min} *(ng/mL)*[b]	***1st dose***	***268***	***803***	***2678***	***8032***	
	last dose	***1042***	***3125***	***10417***	***31251***	
Cumulative $AUC_{0-\infty}$ *(ng·day/mL)*[c]		***167447***	***502372***	***1674472***	***5023416***	***111642743***
Safety Margins						
C_{max} *(ng/mL)*[a]	***1st dose***	***3399***	***1132***	***340***	***113***	
	last dose	***1970***	***657***	***197***	***66***	
Cumulative $AUC_{0-\infty}$ *(ng·day/mL)*[c]		***667***	***222***	***67***	***22***	

[a] Defined as the mean end of infusion concentration for the simulated subjects.

[b] Defined as the mean concentration at the end of the dosing interval for the simulated subjects.

[c] Calculated based on the mean clearance for the simulated subjects.

3.6 Safety Plan and Monitoring

The study design, including entry criteria, planned interim safety data reviews, and planned conduct includes a number of elements intended to minimize risk, intended to better monitor for or to mitigate risk to study patients:

- All Study Drug doses will be administered in either a hemodialysis unit or Phase 1 research unit with hemodialysis capabilities in the presence of trained healthcare professionals and resuscitative equipment.
- Patients will be in contact with healthcare professionals three (3) times per week during their hemodialysis treatments, actively observed by study staff for adverse events such as infections, and undergo regular safety monitoring (i.e., vital signs, ECG, physical examination, laboratory evaluations).

- All principal investigators will be nephrologists and therefore skilled in the management of dialysis patients.
- Dose escalation will occur by cohort upon formal safety review as described above An every-other week dose administration paradigm was chosen based on formal PK/PD modeling to allow for timely withdrawal of investigative therapy if required. The dose escalation decision will also take into account accrued PK/PD data from the study, so that the planned doses can be adjusted, if necessary.
- Dose-Limiting Toxicity criteria and rules for MTD will be pre-defined. Because of the high background frequency of Grade 2 and 3 adverse events in hemodialysis patients (not dissimilar from cancer populations), the DLT threshold will be defined using a threshold of ≥ Grade 3 events.
- Initial dosing in each cohort examining a higher dose than studied in a prior cohort will be in two sentinel patients who will be observed for at least 48 hours for early adverse effects before additional patients are dosed.
- Patients will be required to have an absolute neutrophil count of > 2 x 109/L during screening, and decrease in neutrophil count will be treated as a safety event of interest.
- Patients at high risk for infection such as those with temporary hemodialysis catheters, recent or current active infections, smoldering infections, serologic evidence of Hepatitis B or C or HIV, history of tuberculosis (or positive interferon gamma release testing), and baseline neutropenia will be excluded.

Please see the Guidance to Investigators section of the Investigator's Brochure for a description of safety findings from other IL-6 monoclonal antibodies and guidance for clinical monitoring.

3.7 Benefit and Risk Assessment

Inflammatory functional iron deficiency anemia is a common clinical feature in hemodialysis populations. This condition represents an inefficiency of erythropoiesis, as evident by the need for elevated and escalating doses of ESAs or parenteral iron (or both), in order to maintain serum hemoglobin at an acceptable value. These high doses of ESAs and the maintenance of a high ferritin level are associated with increased risk of cardiovascular complications, the former of which is highlighted by the Agency's boxed warning on ESA product labeling advising conservative serum hemoglobin targets and avoidance of continued ESA dose escalation in hyporesponsive patients.

Despite the fact that the concept of inflammatory risk in renal patients has been in the public domain for decades, with an active basic research and clinical investigational community focused on its remediation, no therapy has been specifically designed or developed to address it. The advancement of an anti-inflammatory therapy which improve iron utilization and ultimately reduces the need for escalating doses of ESAs and / or parenteral iron would be a paradigm shift in the care of these patients.

As for the risks associated with administration of COR-001, nonclinical toxicology studies (See Investigator's Brochure) established the no-observed adverse effect level by the maximal dose administered. Both in terms of local and systemic effects, COR-001 was well tolerated, with no apparent adverse findings. Of note, the highest COR-001 dose planned for study allows an over 20-fold margin to NOAEL in the non-clinical toxicology program.

In Study D4430C00001 (AstraZeneca IND 114,712), COR-001 was well-tolerated in the three patients who received a single 30 mg dose. No patients died, no patients reported SAEs, and no patients discontinued the investigational product or from the study due to an AE. All AEs were considered to be mild to moderate in intensity. Overall, the most commonly reported AE was vomiting followed by diarrhea, reported by patients on COR-001 only. Although high and low laboratory values were reported for all 4 patients, no specific trends could be observed, with the exception of changes in the WBC and neutrophil counts. No other notable changes in laboratory parameters (including liver function), vital signs, or physical assessments as related to safety were noted.

Available data for anti-IL6R (tocilizumab) and anti-IL6 (siltuximab) therapies suggest neutralization of IL-6 have acceptable safety and tolerability profiles for the indications studied. Infusion-related and life-threatening hypersensitivity reactions are rare with these agents. Anti-inflammatory therapies in general run the risk of inducing immune suppression and promoting the emergence of infections, sometimes serious in nature. Although anti-IL-6 therapies lower neutrophil counts and may induce frank neutropenia, their rates of infectious complications appear to be similar to other immune-modulatory biologic agents when accounting for patient-specific factors (Sakai 2015, Sanofi 2016). Gastrointestinal perforation has been associated with anti-IL-6 therapy, however data suggests proper exclusion criteria may mitigate these risks (Tanaka 2014).

The inclusion and exclusion criteria and monitoring schema employed in the planned clinical studies are designed to minimize and manage the potential risks of COR-001 therapy as inferred from other anti-IL-6 therapies. The exclusion of patients with known infection, the use of absolute-neutrophil count stopping rules, prohibition of the use of live vaccines and certain concomitant medications which are metabolized by the CYP system and display narrow therapeutic windows, exclusion of patients with a history of diverticulosis, as well as the use of the CTCAE system of adverse event reporting and maximum tolerated dose definition are designed to minimize the drug-associated risks to study patients.

COR-001 will be administered in a monitored setting (the hemodialysis unit) where frequent laboratory measurements (to ascertain for effects such as altered liver function and elevation in serum cholesterol) and close contact with dialysis staff will allow for prudent monitoring and early treatment of complications should they occur.

Finally, the use of a mechanistically-derived genotype patient selection strategy is intended to enrich the enrolled cohort for patients with the greatest likelihood of response to anti-IL-6 therapy. Therefore, the treatment is precisely targeted to the population who might benefit the most.

On balance then, the Sponsor proposes the potential risks to patients in this study are justifiable and the benefit-to-risk ratio positive. Patients will be consented as to the potential risks and will be required to sign an ICF documenting their understanding of these risks and willingness to participate in the study.

4 SELECTION OF STUDY POPULATION AND CRITERIA FOR WITHDRAWAL

4.1 Inclusion Criteria

To be eligible, potential study patients must meet all of the following criteria:

1. Age ≥ 18 years at the time of signing of the ICF.
2. Receiving chronic hemodialysis for at least three (3) months prior to Screening via an arteriovenous fistula or arteriovenous graft.

   Note: Every effort will be made to recruit patients who have a well- functioning arteriovenous fistula or graft to minimize the chance of requiring a central venous catheter during the Treatment Period.
3. The patient agrees to comply with the contraception and reproduction restrictions of the study:

   Women of childbearing potential must be using a method of contraception, that is "highly effective" (i.e., < 1% failure rate, see Appendix F)

   OR

   Postmenopausal women must have had no menstrual bleeding for at least 1 year before initial dosing and either be over the age of 60 years or have an elevated plasma follicle-stimulating hormone (FSH) level (i.e., > 40 mIU/mL) at Screening;

   AND

   All female patients of childbearing potential must have a documented negative pregnancy test result at Screening. Patients with elevated β-HCG levels believed to be due to end-stage renal disease may be enrolled if documented to not be pregnant.
4. The patient is able to give written informed consent and has signed a consent form approved by the Investigator's Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
5. At least one documented spKt/V > 1.2 within 8 weeks prior to the Full Screening Period.
6. "Genotype positive" (genotype GG or AG, as defined by the Central Lab via genetic testing developed by the Sponsor) at Screening.
7. Two serum IL-6 levels ≥ 4 pg/mL measured at least 1 week apart during the Screening Period.

8. Receiving one of the following IV or SC ESA drugs continuously prescribed for a minimum of 8 weeks prior to Full Screening: epoetin alfa, darbepoetin alfa, or methoxypolyethylene glycol-epoetin beta.

- Epoetin alfa must not have had more than one dose missed or held during Week -3 weeks prior to Randomization.
- Darbepoetin alfa must not have had any doses missed or held during the 4 weeks prior to Randomization.
- Methoxypolyethylene glycol-epoetin beta must not have had any doses missed or held during the 6 weeks prior to Randomization.

9. Stable ESA doses prior to randomization, defined as follows:

   For ESAs dosed weekly or more frequently:

   No change in the total weekly dose during Week -1 compared with Week -2.

   For ESAs dosed less often than weekly:

   Any dose given during Full Screening Week -2 and Week -1 is unchanged from the immediately preceding dose.

   Note: If a dose was given on both Week -2 and Week -1, then both doses are the same. (These 2 doses may be different than earlier doses).

10. Has been receiving intravenous (IV) or dialysate iron regularly and continuously (e.g., with each dialysis or each week) during the 3 weeks prior to randomization OR has received no IV or dialysate iron during this time frame and use of IV or dialysate iron is not anticipated through Study Week 24.

    If parenteral iron has been administered during the 3 weeks prior to randomization, the regimen has been stable (same elemental iron dose, same frequency, and same iron product) with no more than 2 missed or held doses if dosed with each dialysis and no missed or held doses (if dosed weekly or less frequently) during this time frame.

11. If receiving oral ferric citrate, the patient has been prescribed it for at least 2 weeks prior to Full Screening and the dose is not anticipated to be changed through Study Week 24.

12. At least 2 ferritin values during Screening > 300 ng/mL.

13. At least 2 TSAT values during Screening between 15% and 50% (inclusive).

14. ESA resistance index (confirmed by the Sponsor) during the 2 weeks prior to randomization:

For patient receiving epoetin alfa:

$$\frac{\text{Total weekly dose of epoetin alfa (units)}}{\text{(hemoglobin [g/dL]) * target dry body weight [kg])}} > 8 \text{ units/kg per g/dL}$$

For patients receiving darbepoetin alfa:

$$\frac{\text{Total weekly dose of darbepoetin alfa (mcg) * 300}}{\text{(hemoglobin [g/dL]) * target dry body weight [kg])}} > 8 \text{ units/kg per g/dL}$$

For patients receiving methoxy polyethylene glycol-epoetin beta:

$$\frac{\text{Weekly dose of methoxy polyethylene glycol-epoetin beta (mcg) * 300}}{\text{(hemoglobin [g/dL]) * target dry body weight [kg])}} > 8 \text{ units/kg per g/dL}$$

If the ESA is dosed less often than once a week, divide the dose by the dosing interval to determine the weekly dose. For example, Weekly dose = dose given every two weeks ÷ 2.

The first day of each week used for calculations is defined as the first dialysis day of the Week (i.e., Monday or Tuesday).

15. During the 4 weeks prior to randomization, the mean of 3 consecutive hemoglobins between ≥ 8.5 and ≤ 11.0 g/dL, with the difference between the first and last measurements being < 1.2 g/dL.

    Note: Qualifying hemoglobins must be drawn 2 or more days apart pre-dialysis, with no more than 2 measurements within a calendar week. There must be at least 9 days between the first and last of the 3 qualifying hemoglobin values.

16. Investigator anticipates no change to ESA, parenteral, or oral iron products, doses, or dosing regimen during Study Weeks 1 through 4 and that following the protocol guidance for ESA and iron dose changes (Appendix C) will be clinically appropriate for the patient.

17. Serum Vitamin B-12 and folate levels above the laboratory lower normal range during Full Screening.

4.2 Exclusion Criteria

To be eligible for study enrollment, potential study patients must not meet any of the following exclusion criteria:

1. Any indwelling vascular catheter (including that used for dialysis) or anticipated of use of an indwelling catheter anytime during the study (including the Initial Screening and Full Screening Periods).

   Patients for whom a central venous catheter is used within 2 weeks prior to Step 2 of the Initial Screening Period (blood draw for IL-6, see Section 5.2) will be also be considered screening failures.

2. Use of systemic immunosuppressive drugs during the Full Screening Period or anticipated use of such drugs any time during the study.

   Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary. Oral prednisone up to 5 mg per day (or equivalent) is permitted.

3. Clinical evidence or suspicion of active or smoldering infection (e.g., diabetic foot ulcer) or use of systemic antibiotics, systemic antivirals, or systemic antifungals within 2 weeks prior to Step 2 of the Initial Screening Period (blood draw for IL-6, see Section 5.2), during the Initial Screening Period, or the Full Screening Period.

   ("Systemic" is defined as oral or intravenous drugs that are absorbed into the circulation.)

4. Hospitalization or outpatient procedures within 2 weeks prior to Step 2 of the Initial Screening Period (blood draw for IL-6, see Section 5.2), during the Initial Screening Period, or the Full Screening Period unless approved by the Medical Monitor.

   Note: Please contact the Medical Monitor for approval and determination of timing of IL-6 measurements if considering enrolling patients with hospitalizations or outpatient procedures during this time frame.

5. Inability to undergo a non-contrast magnetic resonance imaging (MRI) scan (e.g., weight over the limits for MRI machine, claustrophobia that cannot be managed, certain metallic indwelling foreign bodies). Requirement for MRI may exempted by the medical monitor due to practical considerations. In such situations, patients may be enrolled even if they are unable to undergo MRI.

6. Positive tuberculosis blood test at Screening

7. Evidence of HIV-1 or HIV-2 infection by serology at Screening.

8. Hepatitis B or C by serology (i.e. Hepatitis B Surface Antigen or Hepatitis C antibody positive) at Screening.

9. AST or ALT > 2.5x ULN at Screening.

10. History of liver cirrhosis or home oxygen use (other than nocturnal-only oxygen for those with sleep apnea).

11. History of gastrointestinal ulceration or active diverticulitis in the 1 year prior to Initial Screening.

12. Absolute neutrophil count < 2.0 x 10^9/L at Initial and Full Screening.
13. Platelet count < 100 x 10^9/L at Initial and Full Screening.
14. Expected to receive any investigational drug or any of the exclusionary drugs listed in Appendix B during the Treatment Period or Safety Follow-Up Period.
15. Received an investigational drug within 30 days prior to the start of the Full Screening Period.
16. Known allergy to the Study Drug or any of its ingredients.
17. Currently breastfeeding
18. Any condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or interpretation of the study results, or that would in the opinion of the Investigator increase the risk of the patient's participation in the study. This would include but is not limited to alcoholism, drug dependency or abuse, psychiatric disease, epilepsy, anemia attributable to a primary hematologic disease (e.g., sickle cell anemia), or any unexplained blackouts.
19. Actively treated or active malignancy (other than non-melanoma skin cancers or cervical carcinoma in situ considered cured at the time of Full Screening) during the 1 year prior to Full Screening.
20. Myocardial infarction during the 2 months prior to Full Screening or during Screening.
21. Known or suspected occult or active bleeding other than that related to the hemodialysis procedure.
22. Received a red blood cell or whole blood transfusion within 2 months prior to Full Screening or anticipated to receive a blood transfusion at any time during the study.
23. Have inflammatory bowel disease that has been clinically active during the 3 months prior to Full Screening or bone marrow or organ transplant.

    Note: Patients with a previously explanted kidney transplant are eligible as are those who have an implanted kidney transplant, but have not received immunosuppression for at least 6 months prior to Full Screening.
24. Anticipated to receive an organ transplant during the time frame of the study.
25. iPTH at Screening > 2500 pg/mL.

4.3 Criteria for Discontinuation of Study Drug

Study Drug may be prematurely discontinued for a number of reasons, including:

- An intercurrent illness
- Any intolerable AE that cannot be ameliorated by appropriate medical intervention or that in the opinion of the Medical Monitor or Investigator would lead to undue risk if the patient were to continue on treatment

- Implementation of stopping rules (see Section 4.4)
- Pregnancy
- Organ transplantation or development of another indication for chronic immunosuppression,
- Withdrawal of consent. A patient may elect to withdraw consent to treatment at any time.
  - Patients discontinuing Study Drug treatment after receiving any amount of Study Drug should undergo all follow-up study procedures unless the patient also explicitly withdraws consent for these procedures. The Study Drug has a long pharmacodynamic effect; therefore, continued monitoring for pharmacodynamic effects and safety is prudent. Patients withdrawing their consent for all study procedures must be given the option to continue to give consent for passive follow-up (i.e., by means of chart review) for adverse events through Study Week 24.

Reasons for all withdrawals/discontinuations of Study Drug will be recorded, and the Medical Monitor should be informed of all such cases as they occur.

4.4 Dose-Limiting Toxicities, Maximum Tolerated Dose, and Stopping Rules

Prior to dose escalation (i.e., higher total dose than studied in the preceding cohorts), there will be a formal safety review by the Safety Review Committee. The safety review required for dose escalation will include 21 days of treatment data from the preceding cohort(s).

Dose-Limiting Toxicities are defined as follows:

1. Confirmed Grade 3 neutropenia and representing a decline of > 25% from baseline
2. Serious adverse events of infection in the presence of confirmed Grade 2 or higher new onset lymphopenia or new onset neutropenia.
3. ≥ Grade 3 ALT or AST
4. ≥ Grade 4 hematologic toxicity
5. ≥ Grade 3 non-hematologic toxicity

DLT will be 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.

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

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

In addition, dose-escalation may be halted for any safety trend believed to be dose-related that would pose an unacceptable risk if dose were escalated.

If more than 2 of 8 COR-001-treated patients in a cohort experience a DLT, the MTD will be exceeded and stopping criteria for that dose will have been met.

In addition, if 1 of 8 COR-001-treated patients in a cohort experiences a Grade 4 or 5 DLT, the dose will not be escalated.

Stopping Rules for Individual Patients

Severe (i.e., ≥ Grade 3): infusion-related reactions, cardiopulmonary infusion reactions, anaphylaxis, or hypersensitivity (see Section 8.2)

Stopping Rules for the Entire Study

If ≥ 5 COR-001-treated patients develop anaphylaxis at any point during the entire study, enrollment and further dosing will be stopped.

4.5 Patient Replacement

Patients dropping out (i.e., prematurely discontinuing Study Drug treatment) for reasons unrelated to safety may be replaced at the Sponsor's discretion.

4.6 Study Completion

Primary study completion is defined as the completion of the Week 24 visit, even if one or more interim visits or procedures was/were missed.

Completion of the Extended Follow-Up is defined by the completion of the Week 35 visit even if one or more interim visits or procedures was/were missed.

5 ENROLLMENT AND STUDY PROCEDURES

5.1 Patient Identification Numbers

After signing the Short ICF, patients should be registered into the electronic data capture system to obtain a patient identification number for the study.

5.2 Screening Visit Procedures (Up to 2 weeks, Days -28 to -15) – Initial Screening

Screening will be conducted in a stepwise manner.

The Initial Screening procedures will be conducted under a Short ICF that will include a medical chart review (e.g., medical history, concomitant medication, laboratory data) for eligibility criteria that can be ascertained in this manner (**Step 1**). In addition, the Short ICF will include consent for adjusting or washing out medications as needed. Upon determining eligibility based on medical chart review, Central Laboratory tests including genotyping and Screening IL-6 tests should be submitted to the Central Laboratory (see Appendix A) (**Step 2**).

During Initial Screening period, patients should be monitored for prospective eligibility based on parameters to be assessed during Full Screening. Specifically, ERI, hemoglobin stability, and stability of ESA and iron dosing should be observed per the Schedule of Events and patients who in the judgment of the Investigator are likely to clear these inclusion criteria during Full Screening should be allowed to enter the 2-week Full Screening period.

Patients who are eligible following Initial Screening should proceed as soon as feasible into the full Screening Period, to ensure that the time from the first Screening IL-6 measurement and randomization does not exceed 6 weeks.

Tentatively schedule the Cardiac MRI to occur during Full Screening.

5.3 Screening Visit Procedures (Days -14 to -1) – Full Screening

Prior to conducting any procedures, informed consent for the full study should be obtained and the Long ICF signed. The Long ICF includes consent for all study procedures subsequent to the Initial Screening.

Every effort should be made to obtain the blood tests for each visit on the same day of the week (e.g. on Wednesdays).

Important: Please note that ESA, IV iron, and dialysate iron dosing should be monitored carefully during this period as it is required to be stable (as defined in the inclusion criteria #8 and #9, Section 4) in order for patients to be eligible. Update standing orders for these medications as needed.

The following sections summarize the procedures for Week -2 and Week -1. Please see Appendix A for full details.

Week -2

- Dispense 3 fecal occult blood tests collection materials and review instructions for stool collection with the patient to avoid false positives (see Laboratory Manual for instructions). Request return of the samples within 1 week to allow sufficient time for analyses of these at the Central Laboratory. If necessary, stool occult blood testing may be performed locally if materials have not been returned in a timely manner.

Week -2 and Week -1

- On each of these weeks, obtain, before and after a single dialysis session: pre-dialysis and post-dialysis Central Laboratory tests, pre-dialysis and post-dialysis vital signs and weights, and record the net ultrafiltration (i.e. fluid removed minus fluid administered during dialysis) from the same dialysis session around which above procedures were performed.
  - At any time during these 2 weeks, perform a limited physical examination (see Section 10.2.3), obtain a 12-lead ECG (see Section 10.2.2), measure the handgrip strength, and have the patient complete the FACIT-F questionnaire.
  - Instructions for performing the handgrip strength and the FACIT-F questionnaire can be found in the Study Reference Manual
- Collect all 3 stool occult blood tests from patients and submit to the Central Laboratory. Locally performed stool testing may be substituted, if Central Laboratory results are not available prior to randomization.
- Record adverse events and any medication changes.
- Ascertain that the patient remains eligible before proceeding to the next visit
- Schedule the Day 1 visit to occur on a Monday, Tuesday, Thursday or Friday whenever possible.
- Obtain a non-contrast cardiac MRI (see MRI Technical Manual for instructions) in Week -1 or Week -2

5.3.1 Laboratory Re-Testing and Re-Screening

An individual laboratory value may be repeated once during Initial Screening or Full Screening for any reason (e.g., Investigator believes value to be erroneous). Any additional laboratory re-testing must be approved by the Medical Monitor.

Patients failing Screening may be allowed to re-enter Screening under some circumstances with approval from the Medical Monitor.

Patients who are re-screening may follow an abbreviated/modified set of Screening procedures as follows:

- Genotype testing: not required
- Cardiac MRI: not required if previously performed within 12 weeks prior to the re-screening Week -2 Visit date
- Initial Screening medical history: not required. Please note that confirmation of eligibility remains a procedure during Full Screening.
- TB testing: not required if previously performed within 12 weeks prior to the re-screening Week -2 Visit date
- Stool occult blood testing: not required if previously performed within 12 weeks prior to the re-screening Week -2 Visit date
- Short ICF and Long ICF: Re-sign prior to starting re-screening procedures

The following sections summarize the procedures for the Treatment Period. Please see Appendix A for full details.

5.4 Treatment Period (Study Weeks 1 - 12)

Important: Please note that ESA and IV and dialysate iron dosing should be controlled carefully during this period as they are required to be stable (as defined in Appendix C). Ensure processes and staff training are in place to avoid inadvertent changes in these medication.

Study Visits during which Study Drug infusions are required should be planned for the same day of the week so that Study Drug administration can occur on a schedule of every 7 days. See Section 6.1.1 for guidance on missed doses.

5.4.1 Week 1, Day 1 (First Dose)

- Randomize the patient
  - Randomization may be performed on Day -1, if needed. Administration of the first dose of Study Drug will continue to define Study Day 1.
- Prepare the Study Drug prior to the anticipated time of administration (see Section 6.1.1 and Pharmacy Manual)
- Perform the hand grip strength prior to the start of dialysis (see instructions in the Study Reference Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain an ECG prior to the start of dialysis (see Section 11.4.5.4)

- Have patient complete the FACIT-F questionnaire (see instructions in Study Reference Manual) prior to dialysis or during the first hour of dialysis
- Any time prior to the last one hour of dialysis, start the Study Drug infusion
- Obtain vital signs within 15 minutes prior to start of the Study Drug infusion, 15 ± 10 and 45 ± 10 minutes following the start of the Study Drug infusion and 0-15 minutes, 30-45 minutes, and 60-75 minutes following the end of the Study Drug infusion.
- Within 10 minutes after completing the Study Drug infusion, obtain blood samples
- Whenever feasible (e.g., first shift patients), obtain PK/PD blood samples 4 [+ 2] hours after completing the Study Drug infusion
- Record adverse events and any medication changes

5.4.2 Week 1, Days 3 and 5

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain Central Laboratory blood samples within 10 minutes after the end of dialysis
- Record adverse event and any medication changes

5.4.3 Week 2

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain vital signs within 15 minutes prior to the start of dialysis
- Obtain Central Laboratory blood samples within 10 minutes after the end of dialysis
- Record adverse event and any medication changes

5.4.4 Week 3

- Prepare the Study Drug prior to the anticipated time of administration (see Section 6.1.1 and Pharmacy Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Any time prior to the last one hour of dialysis, start the Study Drug infusion
- Within 10 minutes after completing the Study Drug infusion, obtain blood samples
- Obtain vital signs within 15 minutes prior to the start of the Study Drug infusion and 15 ± 10 and 45 ± 10 minutes following the start of the Study Drug infusion and 0-15 minutes and 30-45 minutes following the end of the Study Drug infusion
- Record adverse events and any medication changes

5.4.5 Week 4

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain vital signs within 15 minutes prior to the start of dialysis
- Record adverse event and any medication changes

5.4.6 Week 5

- Prepare the Study Drug prior to the anticipated time of administration (see Section 6.1.1 and Pharmacy Manual and Pharmacy Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Any time prior to the last one hour of dialysis, start the Study Drug infusion
- Obtain vital signs within 15 minutes prior to the start of the Study Drug infusion and 15±10 and 45±10 minutes following the start of the Study Drug infusion and 0-15 minutes and 30-45 minutes following the end of the Study Drug infusion
- Record adverse events and any medication changes

5.4.7 Week 6

- Perform the hand grip strength prior to the start of dialysis (see instructions in the Study Reference Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain an ECG prior to the start of dialysis (see Section 11.4.5.4)
- Have patient complete the FACIT-F questionnaire (see instructions in Study Reference Manual) prior to dialysis or during the first hour of dialysis
- Obtain vital signs within 15 minutes prior to the start of dialysis
- Perform a limited physical examination (see Section 11.4.5.5)
- Record adverse events and any medication changes
- If not previously done, Schedule Cardiac MRI to occur on Week 12 [+ 2 weeks].

5.4.8 Week 7

- Prepare the Study Drug prior to the anticipated time of administration (see Section 6.1.1 and Pharmacy Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Any time prior to the last one hour of dialysis, start the Study Drug infusion

- Obtain vital signs within 15 minutes prior to the start of the Study Drug infusion and 15±10 and 45±10 minutes following the start of the Study Drug infusion and 0-15 minutes and 30-45 minutes following the end of the Study Drug infusion
- Record adverse events and any medication changes

5.4.9 Week 8

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain vital signs within 15 minutes prior to the start of dialysis
- Obtain Central Laboratory blood samples within 10 minutes after the end of dialysis
- Record adverse event and any medication changes

5.4.10 Week 9

- Prepare the Study Drug prior to the anticipated time of administration (see Section 6.1.1 and Pharmacy Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Any time prior to the last one hour of dialysis, start the Study Drug infusion
- Obtain vital signs within 15 minutes prior to the start of the Study Drug infusion and 15±10 and 45±10 minutes following the start of the Study Drug infusion and 0-15 minutes and 30-45 minutes following the end of the Study Drug infusion
- Record adverse events and any medication changes

5.4.11 Week 10

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain vital signs within 15 minutes prior to the start of dialysis
- Record adverse event and any medication changes

5.4.12 Week 11, Day 71

- Prepare the Study Drug prior to the anticipated time of administration (see Section 6.1.1 and Pharmacy Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain weight within 30 minutes prior to the start of the dialysis
- Obtain vital signs within 30minutes prior to the start of dialysis
- Any time prior to the last one hour of dialysis, start the Study Drug infusion
- Obtain vital signs within 15 minutes prior to the infusion, 15 ± 10 and 45 ± 10 minutes following the start of the Study Drug infusion and 0-15 minutes and 30-45 minutes following the end of the Study Drug infusion.
- Obtain blood samples within 10 minutes after completing infusion
- Obtain blood samples within 10 minutes after completing dialysis
- Obtain vital signs within 30 minutes after dialysis
- Obtain weight post-dialysis within 30 minutes after completing dialysis
- Whenever feasible (e.g., first shift patients), obtain PK blood samples 4 [+2] hours after completing the Study Drug infusion
- Record net ultrafiltration for the dialysis session
- Record adverse events and any medication changes

5.4.13 Week 11, Day 75

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain weight within 30 minutes prior to the start of the dialysis
- Obtain vital signs within 30 minutes prior to starting dialysis
- Obtain blood samples within 10 minutes after completing dialysis
- Obtain vital signs within 30 minutes after dialysis
- Obtain weight post-dialysis within 30 minutes after completing dialysis
- Record net ultrafiltration for the dialysis session
- Record adverse events and any medication changes

5.4.14 Week 12/ET-1

- Perform the hand grip strength prior to the start of dialysis (see instructions in the Study Reference Manual)
- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain a weight within 30 minutes prior to the start of dialysis
- Obtain vital signs within 30 minutes prior to the start of dialysis
- Obtain an ECG prior to the start of dialysis (see Section 11.4.5.4)
- Have patient complete the FACIT-F questionnaire (see instructions in Study Reference Manual) prior to dialysis or during the first hour of dialysis
- Obtain blood samples within 10 minutes after completing dialysis
- Obtain vital signs within 30 minutes after dialysis
- Obtain weight post-dialysis within 30 minutes after completing dialysis
- Record net ultrafiltration for the dialysis session
- Perform a limited physical examination (see Section 11.4.5.5)
- Record adverse events and any medication changes
- Obtain a non-contrast cardiac MRI (see MRI Technical Manual for instructions)

5.5 Safety Follow-Up Period Procedures (Study Weeks 13 – 24)

5.5.1 Weeks 14, 16, and 20

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)
- Obtain vital signs within 30 minutes prior to the start of dialysis
- Record adverse events and any medication changes

5.5.2 Weeks 18 and 24/ET-2

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis
- Obtain a Local Laboratory (or point of care) INR (only for patients on warfarin)

- Obtain an ECG prior to the start of dialysis (see Section 11.4.5.4)
- Obtain vital signs within 30 minutes prior to the start of dialysis
- Perform a limited physical examination (see Section 11.4.5.5)
- Record adverse events and any medication changes

5.6 Extended Follow-Up Procedures (Study Week 35)

5.6.1 Week 35

- Obtain Central Laboratory blood samples within 15 minutes prior to the start of dialysis

5.7 Unscheduled Visit

Additional clinical visits may be scheduled at the Investigators' discretion in order to follow or evaluate AEs. The reason for a given unscheduled visit will be recorded.

The following must be performed at any unscheduled visit occurring prior to Week 24:

- Record adverse events and any medication changes

5.8 Early Termination Visit

There are two possible types of Early Termination visits:

Early Termination Visit 1 (ET-1): Randomized patients terminating from the study prematurely prior to Study Week 12 should undergo an Early Termination Visit during which Week 12 procedures are performed. Patients terminating the study prior to Week 4 should not undergo the Week 12 cardiac MRI.

Early Termination Visit 2 (ET-2): Randomized patients terminating from the study prematurely after Study Week 12 visit, but before Week 24 should undergo an early termination visit during which Week 24 procedures are performed.

5.8.1 Early Withdrawal from the Study

Criteria for discontinuation of Study Drug can be found in Section 4.3.

Patients may be withdrawn from the study for a number of reasons, including those outlined below.

- Withdrawal of consent for all study procedures
  - Patients withdrawing their consent for all study procedures must be given the option to continue to give consent for passive follow-up (i.e. by means of chart review) for adverse events through Study Week 24.
- Discontinuation of the study by the Sponsor

6 DRUG SUPPLIES AND DOSING

6.1.1 Dosing and Administration

The dose of COR-001 for intravenous (IV) administration must be prepared using aseptic techniques. Drug Product is presented as a single use vial and any unused portion must be discarded.

COR-001 is supplied as a lyophilised cake. Reconstitution with 1.2 mL Sterile Water for Injection gives a 1.0 mL nominal volume containing 50 mg of COR-001 (50mg/mL COR-001 stock solution) in 25 mM L-histidine/L-histidine hydrochloride monohydrate, 225 mM (8.5% [w/v]) trehalose dihydrate, 0.05 % (w/v) polysorbate 80, pH 6.0.

The planned doses for the study are described in Section 3.5.4 and in Table 2. The actual doses will be based on a review of safety and in-life pharmacokinetic data (to the extent available) during the study. The reconstituted COR-001 stock solution will require serial dilution in IV Bag Protectant (IVBP) to obtain concentrations which permit manageable volumes of drug to be handled. Please see Table 2 and Figure 3. Personnel responsible for study drug preparation should have an appropriate background (i.e., physician, pharmacist, pharmacy technician, nurse, or other personnel approved by the Sponsor) and has been appropriately trained. Please see Pharmacy Manual for full details.

The final required volume of diluted COR-001 (1.6-18.mL) plus IV Bag Protectant (1.8 mL) is added to 100 mL 0.9% saline for IV infusion (Figure 3).

Each dose of COR-001 or placebo will be administered via IV infusion with a 0.2 micron in-line filter over approximately 60 minutes, starting any time prior to the last 1 hour of dialysis. Study Visits during which Study Drug infusions are required should be planned on the same day of the week so that Study Drug administration can occur on a schedule of every 14 days. Please see the Pharmacy Manual for instructions on preparing and administering the Study Drug and storage of prepared Study Drug.

Special Situations

- If the dialysis treatment is ended earlier than planned, continue the Study Drug infusion until the infusion is completed.
- If the infusion is interrupted or flow rate slowed (e.g., due to an adverse event) and dialysis is completed before the Study Drug infusion has ended, continue the Study Drug infusion until the infusion is completed.
- Patients who require slower flow rates (e.g., due to prior intolerance with the normal flow rates), the Study Drug administration may be started earlier in the dialysis session to allow the Study Drug infusion end to coincide with the end of dialysis or prior to the end of dialysis.

- Patients who miss a dose of Study Drug (e.g., due to a missed dialysis visit) may receive the missed Study Drug up to 96 hours later (on a dialysis day). If the missed dose cannot be administered within this time frame, the dose should be considered "missed" and the next dose administered at the next study visit as planned.

For patients for whom logistical considerations require minor adjustments to the Study Drug infusion timing (including administration of the Study Drug prior to or after dialysis), please contact the Medical Monitor.

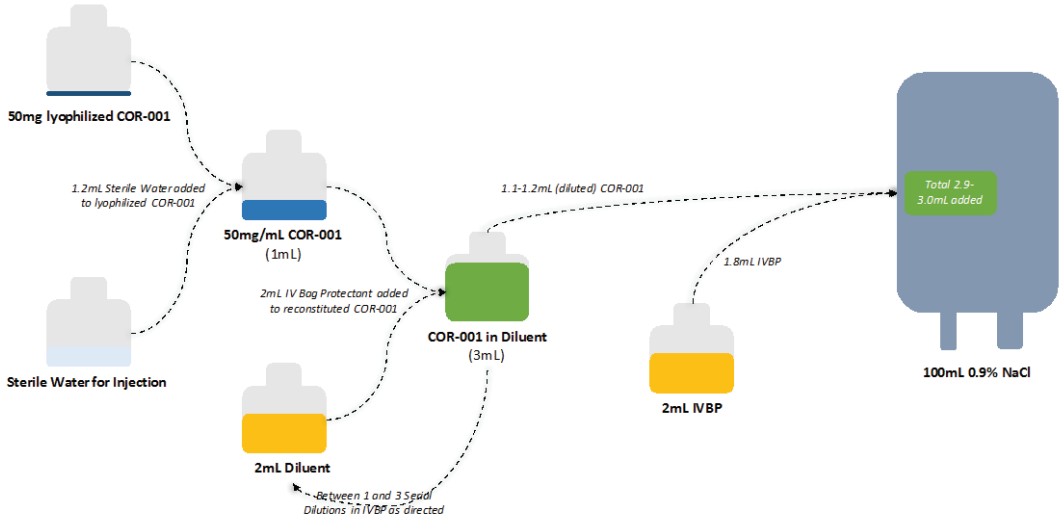
In the above special situations, please ensure that blood testing that is timed with the start and end of infusion are adhered to.

Table 2 Planned COR-001 Doses, Serial Dilutions and Administered Volumes

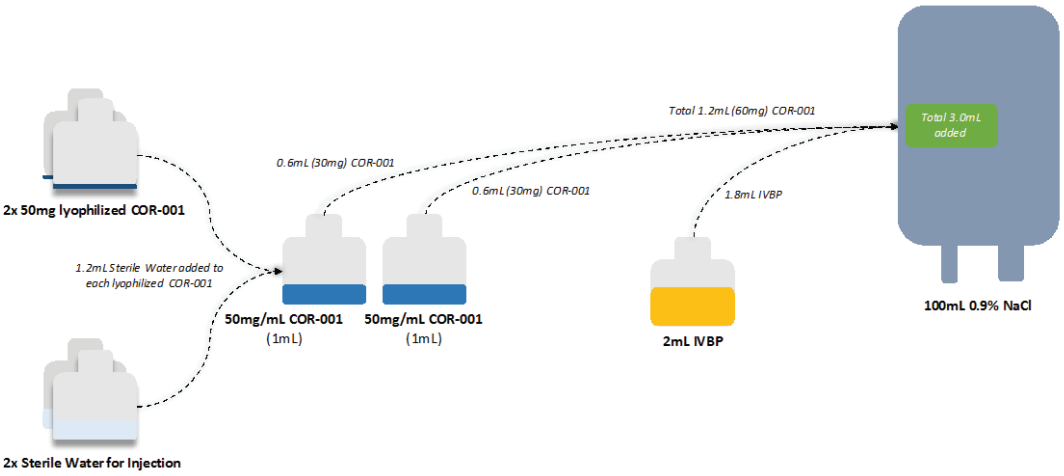
Dose Cohort	**Dosing Regimen**	**Drug Stock Concentration (mg/mL in sterile water)**	**# of serial dilutions (1 ml drug stock added to 2 ml from dilution vial for final volume of 3 ml)**	**Diluted Drug Volume to be Used (mL)**	**IVBP volume to be added to saline infusion bag (in 100 ml saline)**	**Total 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 (0.6 mL from 2 drug vials)	1.8	3.0
	As of Protocol Amendment 3, the actual doses (all given every 14 days) were 2 mg (Cohorts 1 and 4); 6 mg (Cohorts 2 and 3); 20 mg (Cohort 5).					

Figure 3 **A and B: Reconstitution and Serial Dilution of COR-001 for Administration**

3A: Reconstitution of COR-001 for Administration for Cohorts 1-3



3B: Reconstitution of COR-001 for Administration for Cohort 4



The date and time of administration of Study Drug must be recorded in the appropriate sections of the CRFs. Any interruptions in the investigational product infusion (date and time infusion was stopped and date and time infusion was restarted) and any changes in flow rate should also be documented in the CRF with an appropriate explanation.

6.1.2 Storage

COR-001, placebo, diluent, and the IV bag protectant must be stored at 2 to 8°C in the original container and must not be frozen.

6.1.3 Formulation and Packaging

Table 3 Composition for COR-001 for Injection, 50 mg/Vial

Ingredients	**Quantity per vial**
COR-001	**50 mg**
L-Histidine	**1.9 mg**
L-Histidine hydrochloride monohydrate	**2.6 mg**
Trehalose dehydrate	**85.0 mg**
Polysorbate 80	**0.5 mg**
Water for Injection	**1.2 mL reconstitution volume**

Table 4 Composition for Placebo for Injection (3 mL vial)

Ingredients	**Quantity per vial**
L-Histidine	***1.9 mg***
L-Histidine hydrochloride monohydrate	**2.6 mg**
Trehalose dehydrate	**85.0 mg**
Polysorbate 80	**0.5 mg**

Table 5 Composition IV Bag Protectant and Diluent (3 mL vial)

Ingredients	**Quantity per vial**
Sodium citrate	**11.3 mg**
Citric acid	**1.2 mg**
Polysorbate 80	**139.1 mg**

6.2 Drug Accountability and Compliance

The dispensing pharmacist or designated qualified individual will write the date dispensed, dose dispensed, and the patient's identification number, and initials on the Drug Accountability Source Documents. All medication supplied will be accounted for on the

Drug Accountability Record. All partially used or unused drug supplies will be destroyed at the site in accordance with approved written site procedures, or returned to Corvidia Therapeutics only after written authorization is obtained from Corvidia Therapeutics. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Corvidia Therapeutics. All records will be retained as noted in Section 13.5.

7 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

7.1 Prior Medications and Treatments

See Section 4.1 and Section 4.2 for restrictions on prior medications and treatments.

7.2 Concomitant Medications and Treatments

Patients may receive concomitant medications as clinically indicated with the following restrictions:

- Parenteral iron: For patients receiving IV or intradialytic iron, doses and frequency must be maintained during Study Weeks 1 through 24 (see Appendix D)
- ESAs: Restrictions on dose adjustment during Study Weeks 1-4 and dose adjustments during Study Weeks 5 through 24 should be made in agreement with the protocol requirements and guidelines (see Appendix D)
- Oral ferric citrate: For patients receiving this drug during Screening, maintain the dose during Study Weeks 1 through 24
- Systemic immunosuppressive drugs (i.e., such as cyclosporine, tacrolimus, sirolimus, mycophenolate, oral and intravenous glucocorticoids other than prednisone [or equivalent] up to a dose of 5 mg per day) may not be prescribed at any time during Study Weeks 1-24. Topical use (e.g., cyclosporine eye drops) is not restricted

  Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not restricted. Short-term systemic glucocorticoid use (e.g., less than 5 consecutive days) for managing acute illnesses is also not restricted.
- Narrow therapeutic window medications that are influenced by CYP enzymatic pathways (See list in Appendix B) may not be prescribed at any time during Study Weeks 1-24.
  - Warfarin is permitted, but the INR must be monitored closely and, at minimum, according to the protocol Schedule of Events (see Appendix A)

8 MANAGEMENT OF SPECIFIC ADVERSE EVENTS

8.1 Serious Infections

Study drug treatments should be withheld if patients experience a serious infection until the infection is believed to have completely resolved. The Investigator should contact the Medical Monitor to discuss whether the patient should return to Study Drug treatment.

8.2 Infusion-Related Reactions, Hypersensitivity, and Anaphylaxis

Signs of a possible infusion-related reactions include fever, chills, pruritus, urticaria. Cardiopulmonary reactions including, but not limited to, chest pain, dyspnea, hypotension or hypertension may also be indicative of an infusion reaction, but some, such as hypotension may be difficult to distinguish from symptoms related to the dialysis procedure-related signs and symptoms. In these situations, Investigators must determine whether or not the symptom(s) represent an infusion-related reaction (e.g., by considering symptoms and symptom severity are typical for that patient, etc.).

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, such as an investigational product.

For the purposes of this study, a hypersensitivity reaction is defined as an acute onset of an illness with involvement of the skin, mucosal tissue, or both during infusion of the Study Drug (but does not meet the definition of anaphylaxis described above).

If signs and symptoms of infusion-related reactions are observed during the infusion and the patient's cardiovascular status is stable:

- Reduce the flow rate of the infusion by at least half, and increase the infusion time.
- If the patient continues to show signs and symptoms of hypersensitivity, administer an IV dose of antihistamine, if the Investigator believes this is appropriate. The infusion may also be interrupted, if needed, and restarted at a flow rate that is at least 50% reduced.
- In patients who have experienced mild or moderate infusion reactions during prior Study Drug administrations, antihistamines and/or acetaminophen may be administered prophylactically prior to subsequent infusions, at the discretion of the Investigator.

In patients who experience severe (i.e., ≥ Grade 3): infusion-related reactions, cardiopulmonary infusion reactions, anaphylaxis, or hypersensitivity (see definition and grading below):

- Permanently discontinue the Study Drug
- Treat the patients as for an anaphylactic reaction with IV antihistamines, corticosteroids, epinephrine, inhaled bronchodilators, and other measures as necessary

- Obtain a blood sample for the presence of anti-drug antibodies
- The patient should remain in the study for continued follow-up, but should receive no further Study Drug

CTCAE Grading for Infusion-Related Reactions

- Grade 1: Mild, transient reaction; infusion interruption not indicated; intervention not indicated
- Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamine, non-steroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours
- Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

CTCAE Grading for anaphylaxis

- Grade 3: Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death

9 ADVERSE EVENT REPORTING

9.1 Adverse Event Definitions

An AE is any undesirable event or any untoward medical occurrence that occurs to a participant during the course of a study, or the protocol-defined time after study termination, whether or not that event is considered Study Drug-related.

Examples include:

- Any treatment emergent signs and symptoms (events that are marked by a change from the patient's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder]);
- All reactions from Study Drug, abuse of drug, withdrawal phenomena, sensitivity or toxicity to Study Drug;
- Apparently unrelated illnesses;
- Injuries or accidents (e.g., for a fall secondary to dizziness, record "dizziness" as the event and include the information about the fall in the comment/narrative section and information about any injury secondary to the fall as part of the "outcome");
- Exacerbations (increase in frequency or severity) of symptomatology, subjective patient-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing or physical examination;
- Abnormal laboratory findings considered by the Investigator to be clinically significant. In general, an abnormal laboratory value should not be recorded as an adverse event unless:
  - It is associated with clinical signs or symptoms,
  - Requires an intervention, results in a serious adverse event, or
  - Results in study termination or interruption/discontinuation of study treatment.

However, if none of the above apply, but the laboratory abnormality is considered clinically significantly worsened, it should be reported as a laboratory AE (e.g., "increased white blood cell count"). When recording an adverse event resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

9.2 Serious Adverse Event Definition

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Results in death;
- Is life-threatening. Life-threatening means that in the opinion of the Investigator or Study Sponsor, the patient was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form);
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned before the signing for the ICF, are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned);
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions;
- Is a congenital anomaly/birth defect;
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A distinction should be made between the terms "serious" and "severe" since they **are not** synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted serious criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.3 Adverse Events of Special Interest

The following adverse events of special interest must be reported to the Sponsor within 24 hours of the Investigator's awareness, even if not meeting the definition of a serious adverse event:

- Severe infusion-related reactions (see Section 8.2).
- Hypersensitivity reaction during the Study Drug infusion (see Section 8.2).
- Anaphylaxis (see Section 8.2) occurring at any time, even if considered unrelated to the Study Drug

A CRF for the collection of the details of such reactions will be available in the EDC.

Neutropenia, Grade 2 or higher [i.e., absolute neutrophil count < 1500/mm^3 and decline by at least 25% from Baseline] are also events of interest and these will be separately summarized by treatment group and dose.

9.4 Assessment of Causal Relationship

The causal association of AEs to Study Drug administration should be determined as follows:

The following categories should be used in the causality assessment of suspected adverse reactions:

Probable

The AE:

- follows a reasonable temporal sequence from the time of Study Drug administration; and/or
- follows a known response pattern to the Study Drug; and
- was unlikely to have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Possible

The AE:

- follows a reasonable temporal sequence from the time of Study Drug administration; and/or
- follows a known response pattern to the Study Drug; but
- could have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Unlikely

The AE:

- does not follow a reasonable temporal sequence from the time of Study Drug administration; and
- was most likely produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Unrelated

This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (the patient's clinical state, therapeutic intervention or concomitant therapy) and do not meet the criteria for Study Drug relationship listed under Probable, Possible, or Unlikely.

An AE with causal relationship not initially determined will require follow-up to assign causality.

9.5 Assessment of Severity

The Investigator must determine the severity of the event according to CTCAE version 4.03. Severity describes the intensity of the adverse event.

For events not covered by the CTCAE, will be qualitatively described as below and mapped as Grade 1 through 5 as shown for analysis purposes.

Mild (Grade 1)	Awareness of sign or symptom, but easily tolerated
Moderate (Grade 2)	Discomfort enough to cause interference with normal daily activities
Severe (Grade 3)	Inability to perform normal daily activities
Life Threatening (Grade 4)	Immediate risk of death from the reaction as it occurred
Fatal (Grade 5)	Event resulted in death

9.6 Adverse Event Reporting

The AE reporting period starts with the signing of the Long ICF and continues through the Week 24 study visit, other than for AEs believed to be related to study procedures, which should be recorded starting with the signing of the Short ICF. Patients in this study who experience a drug-related AE or SAE will be followed until the AE or SAE is resolved or stabilizes per the Investigator's judgment, even if this occurs after the final study visit. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded and reported on the appropriate CRF. When a unifying diagnosis has been made that accounts for several possible signs and/or symptoms, the unifying diagnosis should be selected as the AE term. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as "upper respiratory syndrome" if this diagnosis has been made, rather than reporting the individual symptoms as separate events.

If any laboratory test is newly abnormal during the course of the study, it will be followed at the discretion of the Investigator. Abnormalities of laboratory tests which are, in the opinion of the Investigator, clinically significantly worse compared to prior to the signing of the Long ICF, or for which a medical intervention is initiated, should be reported as AEs on the AE CRF.

9.7 Reporting of Serious Adverse Events and Adverse Events of Special Interest

The SAE reporting period is the same as the AE reporting period. All SAEs that occur during the reporting period and regardless of causality, must be reported by the Investigator to [redacted] by completing the SAE Form in the electronic data capture (EDC) system. Any pertinent source documents should also be submitted as soon as they are available. Do not withhold submission of an SAE even if complete information about the event is not available at the time of the initial report. Follow-up information on the SAE should be sent promptly by the Investigator when any additional relevant information about the event becomes known to the Investigator, or as requested by [redacted] or Corvidia Therapeutics.

SAE and Pregnancy Reporting Contact Information

[redacted]

Hypersensitivity reactions (see Section 8.2) occurring during the Study Drug infusion and anaphylaxis occurring anytime during Weeks 1 – 24 of the study should be reported as adverse or serious adverse events within the EDC AE and SAE CRFs within 24 hours of the site's awareness of the event. A supplemental CRF will also be completed for such events. Please submit as much information as is available with the initial report.

Corvidia Therapeutics will immediately notify the Investigator about important safety or toxicology information as it becomes available. It is the responsibility of the Investigator to promptly notify the IRB/ IEC about new and relevant safety information regarding the Study Drug, including serious adverse drug reactions involving risk to human subjects, in accordance with the applicable policies. An unexpected event is one that is not listed by nature or severity in the Investigator's Brochure.

9.8 Pregnancy Reporting

If a woman who is a study patient becomes pregnant or a woman suspects she is pregnant from a male study patient, the Investigator should be informed immediately. The Sponsor must, in turn, also be notified by the Investigator immediately by completing a Pregnancy Form and faxing or emailing it to [redacted] (see Section 9.7). The pregnancy must be followed up through delivery or other fetal outcome. For any abnormal fetal outcome, including congenital anomaly or birth defect, spontaneous or therapeutic abortion, still birth, pre-mature birth, or other outcome other than live normal birth, the Investigator should promptly report to the Sponsor the abnormal fetal outcome on an SAE form.

10 STUDY ASSESSMENTS

10.1 Pharmacodynamic Assessments

10.1.1 Cardiac Magnetic Resonance Imaging for LV Mass Index

Magnetic resonance imaging will be used to characterize cardiac left ventricular mass index. Methodology for this assessment will be specified via a separate imaging protocol and MRI Technical Manual.

10.1.2 Handgrip Test

The handgrip test is a measure of strength. The methodology is described in the Study Reference Manual.

10.2 Safety Assessments (other than Adverse Events)

10.2.1 Vital Signs

Vital signs include temperature, respiratory rate, heart rate, and blood pressure. Whenever possible, vital signs will be obtained after at least 5 minutes in the sitting position or, when necessary, in a semi-recumbent position.

10.2.2 12-lead ECG

At specified time points, standard 12-lead ECG will be recorded in the supine position (or with the patient as flat as possible). The ECG will be locally read by the Investigator.

10.2.3 Physical Examination

Scheduled (limited) physical exams must include at a minimum an examination of the skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection.

10.2.4 Stool Occult Blood Testing

Stool fecal occult blood testing will be performed at Screening and analyzed by the central lab. If needed to meet Screening timelines, one or more stool tests may be performed locally.

10.2.5 Clinical Laboratory Testing

Details on the collection, processing, storage, and shipment of central lab samples are contained in the Laboratory Manual. The list of laboratory parameters can be found in Appendix E, Local Laboratory assessments are described below.

The following tests will be performed at the Local Laboratory:

- Coagulation: INR (only for patients on warfarin)
- Stool occult blood (if needed)

11 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

The study design and objectives are described in Sections 2.0 and 3.0, respectively.

11.1 Sample Size

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 $\alpha = 0.05$.

11.2 Randomization

To maximize the chance of at least one placebo patient in a cohort considering that cohort may stop enrollment early, the first 2 (sentinel) patients in that cohort will be randomized 1:1 to COR-001 or placebo. The remaining patients will be randomized at least 48 hours later in a 7:1 ratio of COR-001 to placebo, with a total of 10 (8:2) patients planned for each cohort.

11.3 General Statistical Considerations and Definitions

11.3.1 General Statistical Methods

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.

11.3.2 Analysis Populations

Intent-to-treat (ITT) analysis population: The ITT 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 received their assigned Study Drug, had any pharmacodynamic assessments, and did not have major protocol violations. This will be the population for the pharmacodynamic analyses.

Per-protocol analysis population: The subset of the pharmacodynamics population that did not have a major protocol deviation, as defined in the SAP. The Per-Protocol analysis population will be used to perform the sensitivity analysis for the pharmacodynamics endpoints.

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.

MTD analysis Population: The MTD analysis population will be defined as a subset of safety analysis population by excluding subjects replaced due to a non-safety reason. Treatment classification will be based on the actual treatment received This population will be used for MTD and DLT analyses.

Safety analysis population: The safety 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

11.3.3 Analysis Windows and Baseline

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.

The observational period for the study will start from informed consent and end with study completion (see Section 4.6) 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 planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the patient data listings.

For evaluations that are collected at multiple occasions prior to initiation of Study Drug, the latest evaluation will be considered the "Baseline" evaluation for analysis, unless otherwise specified.

11.3.4 Missing Data Handling

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

11.4 Statistical Analyses

11.4.1 Demographic and Background Characteristics

Patient demographics and baseline characteristics will be summarized by treatment group using the mITT, pharmacodynamics, per-protocol, and safety populations

11.4.2 Study Drug and Concomitant Medications

Summaries of prior (pre-baseline) medications and concomitant (baseline or later) medications will be provided by treatment group using the safety population. Medications will be coded with World Health Organization (WHO) Drug Dictionary. Patients will be counted only once by medication class or name.

11.4.3 Efficacy Analysis

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.

11.4.4 Efficacy Variables

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

- 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 Screening and Day 1 values) in hsCRP to the mean of Weeks 10-12
- change from baseline (mean of Screening and Day 1 values) in SAA to the to the mean of Weeks 10-12
- change from baseline (mean of 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 (mean of Screening) in ERI to the mean of Weeks 8 – 12
- change from baseline (mean of Screening and Day1) in the free IL-6 to Week 4 between treatment groups

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

- systemic iron availability (TSAT, absolute reticulocyte count, hemoglobin, CHr, hypochromic RBC) over time
- markers of malnutrition-inflammation (pre-albumin and albumin) over time
- systemic iron stores (serum ferritin, hepatic and splenic iron content, and supplemental iron dose requirements) over time
- ERI change from baseline (weekly mean during the Screening Period) through Week 24
- ESA and parenteral irondose requirements from baseline (weekly mean during the Screening Period) to Evaluation Period (Weeks 8 – 12) and through Week 24
- 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 11 – 12
- Handgrip over time
- FACIT fatigue score over time

For the above efficacy variables, the observed values and changes from baseline will be summarized by treatment group using descriptive statistics using mITT and PP populations.

11.4.5 Safety Analysis

11.4.5.1 Adverse Events

The MedDRA dictionary will be used for coding adverse events (AEs). An AE (classified as preferred term) occurring during the double-blind treatment period will be counted as a treatment emergent AE (TEAE) if it is not present at baseline.

The number (percentage) of patients reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to Study Drug. 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.

Safety events of special interest will be summarized by dose group and treatment assignment.

11.4.5.2 Laboratory Tests

Laboratory values (excluding efficacy lab) will be summarized by treatment group, including changes from baseline at each visit.

11.4.5.3 Vital Signs

Vital signs and change from baseline in vital signs will be summarized descriptively at each visit by treatment group. The percentage of patients exceeding pre-defined absolute and relative threshold values will be summarized.

11.4.5.4 12-lead ECG

ECG interpretation (normal vs. abnormal) will be summarized using frequency and percentage at each visit by treatment group. ECG intervals (PR, QT, HR, and QTcF) will be summarized descriptively at each visit. The percentage of patients exceeding pre-defined absolute and relative threshold values will be summarized.

11.4.5.5 Physical Examination

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

11.4.5.6 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). 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.

11.4.6 Pharmacokinetic Analysis and Pharmacokinetic/Pharmacodynamic Analysis

11.4.6.1 Pharmacokinetic Data

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A patient listing of all serum concentration-time data for each dose group will be presented. COR-001 serum concentrations will be summarized by dose group and nominal time point, using appropriate descriptive statistics (eg, n, arithmetic mean, standard deviation (SD), coefficient of variation (CV), minimum, median, maximum, geometric mean, and geometric CV (GCV).

Results of PK parameters such as C_{max}, AUC, and $T_{1/2}$ will be summarized by dose group.

Individual and mean concentration-time profiles will be presented graphically.

The data from this study may be used in combination with data from other studies to develop a population PK model. If performed, the plan for and results of such analysis will be documented separately.

11.4.6.2 Pharmacokinetic/Pharmacodynamic Analysis

PK-PD model parameters will be derived using plasma IL-6 levels to describe target engagement, with clinically meaningful PD variables that may include one or more of the following: C-reactive protein, serum amyloid A, transferrin saturation, hemoglobin, reticulocyte hemoglobin content, or reticulocyte count. The specific model parameters to be estimated will be determined based on review of the observed data. The PD endpoints to be included in the PD analysis will be determined following review of the study data.

A listing of PD blood sample collection times as well as derived sampling time deviations will be provided. A patient listing of all PD results and their corresponding change from baseline value for each dose group will be presented. The observed and change from baseline serum results will be summarized using descriptive statistics by dose group.

Graphical presentations, as appropriate for PD variables, may include: individual observed and percent change from baseline serum concentration-time curves for each patient on linear scale; arithmetic mean serum concentration-time curves by dose group on linear scale.

11.5 Interim Analyses

A single interim analysis will be conducted the purpose of which is to guide future COR-001 clinical program activities. There are no stopping rules associated with the interim analysis. The interim analysis will be conducted, at earliest, once all cohorts below that which exceeded the MTD, excluding any expansion cohorts, have completed the study through Week 4 (or final visit, if prematurely discontinued). The Sponsor personnel will only receive the treatment group-level information and have no access to subject-level treatment information Specifics of interim analysis will be described in the statistical analysis plan.

12 STUDY COMMITTEES AND COMMUNICATIONS

After all patients in a cohort have completed 21 days of treatment (or last visit, if prematurely discontinued), the SRC will evaluate the safety and tolerability of COR-001 and recommend the next dose. The SRC may not be convened if the next cohort is expected to be the last cohort in the study. Pharmacokinetic data, as it becomes available, will also be made available to the SRC. The Safety Review Committee will apply its judgment to the conduct of this study in order to ensure the safety of study participants.

The SRC will consist of the following core members:

- Two or more clinicians, at least one of whom is a nephrologist with expertise in clinical trial safety data review
- A statistician (non-voting member)

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

13 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

13.1 Institutional Review Board or Independent Ethics Committee

The protocol and informed consent for this study must be reviewed and approved by an appropriate IRB or IEC before patients are enrolled in the study. It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and Local Regulations, International Conference on Harmonisation (ICH), GCP, and the Declaration of Helsinki. A letter, documenting the approval that specifically identifies the protocol by number and title as well as the Investigator, must be received by Corvidia Therapeutics before initiation of the study. Amendments to the protocol will be patient to the same requirements as the original protocol.

After the completion or termination of the study, the Investigator will submit a report to the IRB or IEC.

13.2 Informed Consent

Each patient must be provided with oral and written information describing the nature and duration of the study, and must sign a written ICF in a language in which the patient is fluent before study specific procedures are conducted. In this study, patients will sign both a Short and Long ICF for procedures to be completed during the Initial and Full Screening Periods, respectively. The signed and dated ICF will be retained with the study records. Each patient will also be given a copy of their signed ICF.

13.3 Supplementary Documentation

Before initiation of the study, the Investigator must provide Corvidia Therapeutics. with the following documents (copies of which must be maintained by the Investigator):

1. Curriculum vitae of the Investigator and any sub-Investigators listed on the 1572 form;
2. A signed copy of the IRB or IEC approval notice for protocol and informed consent;
3. A copy of the IRB or IEC approved ICF;
4. Laboratory certification with a list of normal values for laboratory tests that will be conducted at local laboratories;
5. Completed financial disclosure form for the Investigator and any sub Investigators listed on the 1572 form.

13.4 Data Reporting and Case Report Forms

Data for each patient will be entered into the CRF and verified by the Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient's clinical status.

The Investigator or designated representative should complete the CRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. CRF data will be processed in a US 21 Code of Federal Regulations (CFR) Part 11-compliant system.

13.5 Retention of Data

U.S. Federal regulations require that a copy of records (e.g., laboratory data slips, source documents, test article disbursement records), which support case records of this study, must be retained in the files of the responsible Investigator for a minimum of 2 years after notification by the Sponsor that the FDA has approved a marketing application for the drug and indication being investigated, or the investigation has been terminated.

13.6 Deviation from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, and then notify the Corvidia Therapeutics Medical Monitor and the IRB or IEC immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate CRF. Any other changes or deviations in the protocol will be made as an amendment to the protocol and must be approved by Corvidia Therapeutics and the IRB or IEC — before the changes or deviations are implemented. Corvidia Therapeutics will not assume any responsibility or liability for any deviation or change.

13.7 Study Monitoring

The Investigator will allow representatives of Corvidia Therapeutics to periodically audit (at mutually convenient times before, during, and after the study has been completed) all CRFs and relevant portions of office, clinical, and laboratory records for each patient. Appropriate source documents such as a record of the patient's medical history and concomitant medications from the patient's physician must be available to confirm eligibility for the study. The monitoring visits provide Corvidia Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of CRFs; assure that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

13.8 Drug Accountability

The Investigator must maintain accurate records of the amounts and dates Study Drugs were received from Corvidia Therapeutics and dispensed to the patients, including the volume and concentration of stock solution prepared and remaining stock solution volume after dose preparation. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies will be destroyed at the site, in accordance with approved written procedures, or returned to Corvidia Therapeutics after written authorization is obtained from Corvidia Therapeutics. The Investigator will maintain a record of the amount and dates when unused

supplies were either destroyed or returned. All records will be retained as noted in Section 13.5.

13.9 Disclosure of Data

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the U.S. FDA and the study sponsor, Corvidia Therapeutics, and its agents will need to review patient medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the patient's identity will remain confidential.

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15 APPENDICES

Appendix A Schedule of Events

Schedule of Events for the Screening Period

	Initial Screening	Full Screening	
Study Week(s)	-3 (-1)	-2	-1
Study Day(s) [1]	-28 to -15	-14 to -8	-7 to -1
Short ICF signed	X		
Medical History	X		
Concomitant and Prior Medications	X		
Genotype	X		
Determine/Confirm Eligibility	X		
	Keep ESA and Parenteral Iron Doses Stable [2]		
Long ICF signed		X	
Fecal Occult Blood [3]		X	
Lab Panels 9 [INFEC] and 13 [BVIT], iPTH		X[a]	
Screening IL-6 (total), hsCRP	X[a]	X[a]	
Serum Pregnancy, FSH [4]		X[a]	
Label Panel 1 [CHEM]		X[a]	
Lab Panel 6 [IRON]	X[a]	X[a]	X[a]
Lab Panel 5 [HEME]	X[a]	X[a]	X[a]
Lab Panel 4 [SPRBC]			X[a]
Lab Panels 11 [INFL2]		X[a]	X[a]
Lab Panel 3 [INFL1], pre-albumin, hsCRP		X[a]	X[a]
Lab Panel 8 [CARD]		X[a,d]	X[a,d]
Vital Signs [5]		X	X
Weight (pre-dialysis and post-dialysis) [6]		X	X
Record net ultrafiltration during dialysis [7]		X	X
Record height		X	
12-lead ECG pre-dialysis		X	
Limited Physical Examination [9]		X	
Cardiac MRI		X	
Hand Grip Strength [10]		X	
FACIT-F [8]		X	
Adverse Events	X[11]	X [12]	

Laboratory test panels are defined in Appendix D

Every effort should be made to conduct the weekly study visits on the same day of the week (e.g. on Wednesdays)

For patients who are re-screening please refer to Section 5.3.1 for allowable modifications to Screening Procedures.

M = Monday, W = Wednesday, Th = Thursday, F = Friday

[a], [b], [c], [d] Please see Footnote i

[1] Every effort should be made to obtain the blood tests for each visit on the same day of the week (e.g. on Wednesdays). The Screening Period may be increased by up to 12 days with approval from the Medical Monitor.

[2] See Inclusion Criteria #8 and #9 for definition of stability (Section 4.1)

[3] Three stool tests should be distributed during Week -2 and sent to the Central Laboratory within a timeframe that ensures results are returned prior to randomization. Locally performed stool testing may be substituted, if needed, if Central Laboratory results are not available prior to randomization (Day 1).

[4] Pregnancy in women of childbearing potential only. FSH only in postmenopausal women below 60 years who have had no menses for 1 year.

[5] Obtain blood pressure, heart rate, respiratory rate, and temperature: within 30 minutes prior to the start of dialysis and within 30 minutes after dialysis.

[6] Obtain weight within 30 minutes prior to the start of dialysis and within 30 minutes after the end of dialysis for the **same** dialysis session during which Lab Panel 8 [CARD] was collected.

[7] Net ultrafiltration volume should be recorded for the **same** dialysis session during which Lab Panel 8 [CARD] data were collected.

[8] Have patient complete the FACIT-F questionnaire (see instructions in Study Reference Manual) prior to dialysis or during the first hour of dialysis

[9] Limited physical exam to include skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection. May be performed by a physician-investigator or mid-level provider. Record abnormal findings in the source documents.

[10] Perform any time prior to starting dialysis.

[11] Only adverse events considered related to study procedures.

[12] All adverse events are collected starting with the signing of the Long ICF.

Schedule of Events for the Treatment Period – Weeks 1 through 6

Treatment Period							
Study Week(s)	1		2	3	4	5	6
Visit Window		+1	±2	±2[14]	±2	±2[14]	±2
Study Day(s)	1 [M-Th, if possible]	3 5	8	15	22	29	36
	ESA and iron dosing per Appendix C						
Randomization	X [15]						
Study Drug Administration [1]	X			X		X	
Lab Panel 1 [CHEM]	X [a]						X [a]
Lab Panel 2 [LIP], Lp(a), serum pregnancy [2]	X [a]						X [a]
Lab Panel 3 [INFL1]	X [a]			X [a]	X [a]		
Pre-Albumin, hsCRP	X [a]	X[a,d]	X [a,d]	X [a,b]	X [a]	X [a]	X [a]
Lab Panel 4 [SPRBC]	X [a]		X [a]	X [a]	X [a]	X [a]	X [a]
Lab Panel 5 [HEME]	X [a]		X [a]	X [a]	X [a]	X [a]	X [a]
Lab Panel 6 [IRON]	X [a]		X [a]	X [a]	X [a]	X [a]	X [a]
Lab Panel 7 [PK]	X [a,b,c]	X[a,d]	X [d]	X [a,b]		X[a]	
Lab Panel 8 [CARD]							
Lab Panel 10 [ADA]	X [a]			X [a]		X [a]	
Lab Panel 11 [INFL2]	X[a,b,c]	X[a,d]	X [d]	X [a,b]		X[a]	
Lab Panel 12 [BIO]	X [a]						
Serum pregnancy [2]	X [a]						
Local Lab INR [3]	X [a]		X [a]	X [a]	X [a]	X [a]	X [a]
12-lead ECG pre-dialysis	X						X
FACIT-F [13]	X						X
Limited Physical Examination [5]							X
Vital Signs	X[7]		X[6]	X[7]	X[6]	X[7]	X[6]
Weight (pre-dialysis)							
Weight (post-dialysis)							
Record net ultrafiltration during dialysis							
Cardiac MRI							
Hand grip strength	X [11]						X [11]
Adverse Events	X						
Concomitant Medications	X						

Schedule of Events for the Treatment Period – Weeks 7 through 12/ET-1

Treatment Period (continued)							
Study Week(s)	7	8	9	10	11		12/ET-1
Visit Window	±2[14]	±2	±2[14]	±2	±2[14]		±2
Study Day(s)	43	50	57	64	71	75	78
	ESA and iron dosing per Appendix C						
Study Drug Administration [1]	X		X		X		
Lab Panel 1 [CHEM]							X [a]
Albumin				X			
Lab Panel 2 [LIP], Lp(a),							X [a]
Lab Panel 3 [INFL1]	X [a]		X [a]	X [a]	X [a]		X [a]
hsCRP	X [a]	X [d]	X [a]	X [a]	X [a,b,c]	X[a,d]	X [a]
Pre-Albumin	X [a]	X [d]	X [a]		X [a,b,c]	X[a,d]	X [a]
Lab Panel 4 [SPRBC]	X [a]	X [a]	X [a]	X [a]	X [a]		X [a]
Lab Panel 5 [HEME]	X [a]	X [a]	X [a]	X [a]	X [a]		X [a]
Lab Panel 6 [IRON]	X [a]	X [a]	X [a]	X [a]	X [a]		X [a]
Lab Panel 7 [PK]	X [a]	X [d]	X[a]		X [a,b,c]	X[a,d]	
Lab Panel 8 [CARD]					X[a,d]	X[a,d]	X [a,d]
Lab Panel 10 [ADA]	X [a]		X [a]		X [a]		
Lab Panel 11 [INFL2]	X [a]	X [d]	X [a]		X [a,b,c]	X[a,d]	X [a]
Lab Panel 12 [BIO]							X [a]
Serum pregnancy [2]							X [a]
Local Lab INR [3]	X [a]	X [a]	X [a]	X [a]	X [a]		X [a]
12-lead ECG pre-dialysis							X
FACIT-F [13]							X
Limited Physical Examination [5]							X
Vital Signs	X[7]	X[6]	X[7]	X[6]	X[7, 12]	X[12]	X[12]
Weight (pre-dialysis)					X[4]	X[4]	X[4]
Weight (post-dialysis)					X[8]	X[8]	X[8]
Record net ultrafiltration during dialysis					X[9]	X[9]	X[9]
Cardiac MRI							X[10]
Hand grip strength							X [11]
Adverse Events	X						
Concomitant Medications	X						

Laboratory test panels are defined in Appendix D

Every effort should be made to conduct the weekly study visits on the same day of the week (e.g. on Wednesdays)

ET-1 = Early Termination Visit 1 (see Section 5.8)

[a], [b], [c], [d] Please see Footnote i

[1] The Study Drug is to be administered during dialysis over approximately 1 hour, starting any time prior to the last 1 hour of dialysis (see Section 6.1.1)

- Study Visits during which Study Drug infusions are required should be planned on the same day of the week so that Study Drug administration can occur on a schedule of every 14 days.

- Whenever possible, keep the timing of the start of study drug relative to the start of dialysis constant (e.g., study drug is always started ~15 minutes after dialysis is started)
- Patients who miss a dose of Study Drug (e.g., due to a missed dialysis visit) may receive the missed Study Drug up to 96 hours (or 4 days) later. If the missed dose cannot be administered within this time frame, the dose should be considered "missed" and the next dose administered at the next study visit as planned.

[2] Serum pregnancy in women of childbearing potential only.

[3] Patients receiving warfarin only. May also be done using a point of care device.

[4] Obtain weight within 30 minutes prior to the start of dialysis. On Weeks 11 and 12, should be recorded for the same dialysis session during which Lab Panel 8 [CARD] data were collected.

[5] Limited physical exam to include skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection. May be performed by a physician-investigator or mid-level provider. Record abnormal findings in the source documents.

[6] Obtain blood pressure, heart rate, respiratory rate, and temperature: within 15 minutes prior to starting dialysis.

[7] On Day 1: Obtain blood pressure, heart rate, respiratory rate, and temperature: within 15 minutes prior to starting the infusion; 15±10 and 45±10 minutes following the start of the infusion and 0-15 minutes, 30-45 minutes, and 60-75 minutes following the end of the infusion.

After Day 1: Obtain blood pressure, heart rate, respiratory rate, and temperature: within 15 minutes prior to starting the infusion, 15 ± 10 and 45 ± 10 minutes following the start of the infusion; 0-15 minutes and 30-45 minutes following the end of the infusion.

[8] Within 30 minutes after the end of dialysis. Should be recorded for the **same** dialysis session during which Lab Panel 8 [CARD] was collected.

[9] Net ultrafiltration volume should be recorded for the **same** dialysis session during which Lab Panel 8 [CARD] data were collected.

[10] Obtain during Week 12 (+ 2 weeks).

[11] Perform handgrip strength any time prior to starting dialysis.

[12] Obtain blood pressure, heart rate, respiratory rate, and temperature: within 30 minutes prior to starting dialysis and within 30 minutes after dialysis.

[13] Have patient complete the FACIT-F questionnaire (see instructions in Study Reference Manual) prior to dialysis or during the first hour of dialysis. On Day 1, must be completed before the start of the Study Drug infusion.

[14] Visit window may be extended to +4 days only in instances when the study drug was missed on the targeted visit day and also could not be given during the dialysis visit after the missed dose.

[15] Randomization may be performed on Day -1, if needed. Administration of the first dose of Study Drug will continue to define Study Day 1.

Schedule of Events for the Safety Follow-Up and Extended Follow-Up Periods

	Safety Follow-Up Period					Extended F/U
Study Week	14	16	18	20	24/ET-2	35
Visit Window	± 3	± 3	± 3	± 3	± 3	± 7
Study Day	92	106	120	134	162	239
	ESA and iron dosing per Appendix C					
Lab Panel 1 [CHEM]					X[a]	
Albumin	X		X			
Lab Panel 2 [LIP], Lp(a), serum pregnancy [1]					X[a]	
Lab Panel 3 [INFL1]	X[a]		X[a]		X[a]	
hsCRP	X[a]		X[a]		X[a]	X[a]
Pre-Albumin					X[a]	
Lab Panel 4 [SPRBC]	X[a]	X[a]	X[a]	X[a]	X[a]	
Lab Panel 5 [HEME]	X[a]	X[a]	X[a]	X[a]	X[a]	
Lab Panel 6 [IRON]	X[a]	X[a]	X[a]	X[a]	X[a]	
Lab Panel 7 [PK]	X[a]		X[a]			X[a]
Lab Panel 10 [ADA]					X[a]	X[a]
Lab Panel 11 [INFL2]	X[a]		X[a]		X[a]	X[a]
Local Lab INR [2]	X[a]	X[a]	X[a]	X[a]	X[a]	
12-lead ECG (pre-dialysis)			X		X	
Limited Physical Examination [3]			X		X	
Vital Signs (pre-dialysis) [4]	X	X	X	X	X	
Adverse Events	X					
Concomitant Medications	X					

[1] Serum pregnancy in women of childbearing potential only.

[2] Patients receiving warfarin only. May also be done using a point of care device.

[3] Limited physical exam to include skin, oropharynx, lungs, heart, abdomen, extremities (including feet), and any areas suggested by symptoms, with particular attention to signs of infection. May be performed by a physician-investigator or mid-level provider. Record abnormal findings in the source documents.

[4] Obtain blood pressure, heart rate, respiratory rate, and temperature: within 30 minutes prior to dialysis.

Every effort should be made to conduct the study visits on the same day of the week (e.g. on Wednesdays)

Laboratory test panels are defined in Appendix D.

ET-2 = Early Termination Visit 2 (see Section 5.8)

[a], [b], [c], [d] Please see Footnote i

Footnote i: Footnotes **Common to All Schedule of Events' Tables**

[a] Within 15 minutes prior to dialysis. Draw blood through either a peripheral needle stick or the arterial dialysis needle before connecting the arterial blood tubing or flushing the needle. Be sure that no saline or heparin is in the arterial needle or tubing prior to drawing the sample.

[b] Within 10 minutes after completing the infusion

If dialysis has ended, draw the sample after the machine has been turned off, either through a peripheral needle stick or from the arterial needle tubing prior to taking out the needle or arterial blood line/sample port.

If dialysis is still ongoing and the sample is being drawn through the arterial blood line/sample port, obtain the sample in a manner that minimizes possible recirculation in the dialysis access. See Study Reference Manual for recommendations. Alternatively, the sample may be drawn through a peripheral needle stick.

[c] 4 [+ 2] hours after completing the infusion, whenever feasible (e.g., first shift patients)

[d] Within 10 minutes after completing dialysis. Please see recommendations for blood drawing in section (b) above.

Appendix B Exclusionary Drugs

The following medications are metabolized by CYP450 enzymatic pathways and have a narrow therapeutic window. The use of these medications from one day prior to Randomization (Day -1) through Study Week 24 is prohibited.

- digoxin
- theophylline
- terfenadine
- tizanidine
- quinidine
- phenytoin and its derivatives
- taxane chemotherapeutic agents
- cyclosporine
- mTOR inhibitors (sirolimus, tacrolimus)
- ergot alkaloids
- antipsychotic medications (specifically pimozide, thioridazine)
- fentanyl and derivatives (e.g., alfentanil and sufentanil)

Appendix C ESA and Parenteral Iron Dose-Adjustments

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

Appendix D Laboratory Measurements

Laboratory	Panel Name	Tests Included
Central	Panel 1: Chemistry [CHEM]	Sodium, potassium, chloride, bicarbonate (or CO2), calcium, phosphate, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) creatinine, total bilirubin, direct bilirubin, alkaline phosphatase, albumin, glucose
Central	Panel 2: Lipids [LIP]	Total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL), triglycerides
Central	Panel 3: Inflammation 1 [INFL1]	serum amyloid A, hepcidin
Central	Panel 4: Special RBC Indices [SPRBC]	reticulocyte hemoglobin concentration (CHr), % hypochromic red cells (%HRC)
Central	Panel 5: Hematology [HEME]	Hemoglobin, hematocrit, reticulocyte count, red blood count (RBC) indices (e.g., mean corpuscular volume (MCV), red cell distribution width (RDW), platelets, white blood count (WBC), WBC differential
Central	Panel 6: Iron Indices [IRON]	TSAT, ferritin, iron, total iron binding capacity (TIBC)
Central	Panel 7: PK [PK]	COR-001
Central	Panel 8: Cardiac Markers [CARD]	Troponin T, NT-proBNP
Central	Panel 9: Infection Screen [INFEC]	HIV 1 and 2, Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis C antibody, mycobacterium tuberculosis blood test (i.e., interferon gamma release assay)
Central	Panel 10: Anti-Drug Antibodies [ADA]	Anti-COR-001 binding antibodies and neutralizing antibodies (if binding antibodies are detected)
Central	Panel 11: Inflammation 2 [INFL2]	Total and free IL-6
Central	Panel 12: Future biomarkers [BIO]	Future cardiac, renal, and hematologic markers, including gene variations, ribonucleic acid, or protein markers
Central	Panel 13: B-Vitamins [BVIT]	B-12, folate
Central	Other individual tests	Screening (total) IL-6, genotype, intact parathyroid hormone [PTH], lipoprotein a [Lp(a)], pregnancy [β-hCG in women of childbearing potential only], follicle-stimulating hormone (FSH), stool occult blood, pre-albumin, hsCRP
Local	Coagulation	International normalized ratio (INR) (warfarin-treated patients only)

Appendix E FACIT-F

FACIT-F (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACIT-F (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACIT-F (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix F Guidance on Contraception

For the purposes of the proposed study, **"highly effective" contraceptive methods** are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, and include the following:

- Surgical sterilization at least 6 months before Study Drug administration
- Implants
- LNG and Copper T IUDs
- Sexual abstinence

Patients who prefer methods which evidence a higher (6-9%) failure rate with typical use will be required to employ at least two methods of contraception concurrently. These methods include the following:

- Injectable hormone depots
- Oral contraceptive pill
- Hormone patch
- Vaginal ring

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.

http://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/contraceptive_methods_508.pdf for a list of contraceptive methods and effectiveness.

Investigators may contact the Medical Monitor to discuss questions regarding appropriate contraception.. The guidance will follow that described in the document http://www.covance.com/content/dam/covance/assetLibrary/posters/KamACCP15.pdf and will comply with FDA M3(R2).