Anti-Cytokine Therapy for Hemodialysis InflammatION (ACTION)

A phase II multi-center study to evaluate the safety and tolerability of anakinra, an IL-1 receptor antagonist, for patients treated with maintenance hemodialysis

Funding Sponsor: *National Institutes of Diabetes and Digestive and Kidney Diseases*
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Study Product: Anakinra

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List of Abbreviations

AE	adverse event
ANC	absolute neutrophil count
BDI-II	Beck Depression Index II
CBC	complete blood count
CKD	chronic kidney disease
CRF	case report form
CRP	C-reactive protein
CVD	cardiovascular disease
DCC	Data Coordinating Center
DMS	data management system
DSMB	Data and Safety Monitoring Board
ESRD	end stage renal disease
FACIT	Functional Assessment of Chronic Illness Therapy
FTP	File Transfer Protocol
HD	hemodialysis
HIPAA	Health Insurance Portability and Accounting Act
hsCRP	high-sensitivity C-reactive protein
IDS	Investigational Drug Service
IL	Interleukin
IL-1ra	Interleukin 1 receptor antagonist
IRB	Institutional Review Board
IV	Intravenous
KDQOL SF12	Kidney Disease Quality of Life Short Form 12
MOP	Manual of Procedures
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
PHI	protected health information
SAE	serious adverse event
SAP	statistical analysis plan
TNF-α	tumor necrosis factor-alpha
UAE	unanticipated adverse event

Study Summary

Title	Anti-Cytokine Therapy for Hemodialysis Inflammation (ACTION)
Short Title	ACTION
Protocol Number	
Phase	Phase II
Methodology	Randomized, double-blind, placebo-controlled trial
Study Duration	3 years
Study Centers	Brigham and Women's Hospital George Washington University University of Washington Vanderbilt University University of Pennsylvania (Data Coordinating Center)
Objectives	1. To evaluate the safety and tolerability of the interleukin-1 receptor antagonist, anakinra, for patients receiving maintenance hemodialysis during a 24- week treatment period and a 24-week post-treatment period during which participants will not be enrolled in any other interventional research study 2. To assess the efficacy of anakinra for reducing CRP during 24 weeks of treatment for patients receiving maintenance hemodialysis 3. To explore the effects of anakinra on markers of inflammation, cardiovascular risk, nutrition and metabolism, and patient reported outcomes for patients receiving maintenance hemodialysis
Number of Participants	80
Condition / Main Inclusion Criteria	End-stage renal disease / treatment with maintenance hemodialysis
Study Product, Dose, Route	Anakinra; 100 mg administered intravenously 3X per week at the end of hemodialysis
Duration of administration	24 weeks
Reference therapy	Placebo
Major Outcomes	<u>Safety Outcomes</u> • Adverse events • Infections • Cytopenias <u>Feasibility Outcomes</u> • Recruitment rate, retention, dosing completeness <u>Efficacy Outcomes</u> • Reduction in CRP over 24 weeks • Change in markers of inflammation, cardiovascular disease, nutrition, and metabolism • Change in patient reported indicators of fatigue, depression, symptoms, and quality of life • Change in hand grip strength

Statistical Methodology	Efficacy: Mixed effects linear regression models will be used to assess the direction and time averaged magnitude of change in efficacy parameters, with and without controlling for baseline covariates. Safety: Generalized linear mixed effects models (logistic and/or Poisson regression) will be used to compare incidence and incidence rate of safety parameters, adjusting for stratification factors and baseline covariates.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations, and the research policies and procedures in effect at the institutions where the study is implemented.

1.1 Inflammation as a Target to Improve Outcomes in ESRD

The mortality of patients undergoing maintenance hemodialysis in the United States is unacceptably high[1]. A majority of the deaths are due to cardiovascular diseases, followed by infectious complications and protein-energy wasting[2]. Strategies to reduce the mortality of these patients, including those directed at traditional cardiovascular risk factors such as statins, have largely been ineffective[3-5]. Biomarkers of the inflammatory state, such as C-reactive protein (CRP), interleukin-1 (IL-1), and interleukin-6 (IL-6), are elevated in maintenance hemodialysis patients and are also robust predictors of cardiovascular disease and mortality in this patient population[6,7,8]. In addition to its predictive ability, inflammation has been implicated in the pathogenesis of atherosclerotic cardiovascular disease and protein-energy wasting. There is ample evidence showing that atherosclerosis is an inflammatory process and pro-inflammatory cytokines play a crucial role in its development[9]. There are also data supporting an intimate link between systemic inflammation and vascular calcification, another important component of cardiovascular disease in end stage renal disease (ESRD) [10]. Pro-inflammatory cytokines also cause anorexia and skeletal muscle breakdown, leading to protein-energy wasting, a condition with significant morbidity and mortality risk in ESRD[11]. Elevations in IL-6 and TNF-alpha have been associated with increased symptom burden and reduced quality of life in chronic kidney disease (CKD)[12]. Taken together, the available data indicate a causal relationship between inflammation and morbidity in ESRD patients rendering inflammation a critically important target to improve outcomes in this high risk patient population (Figure 1).

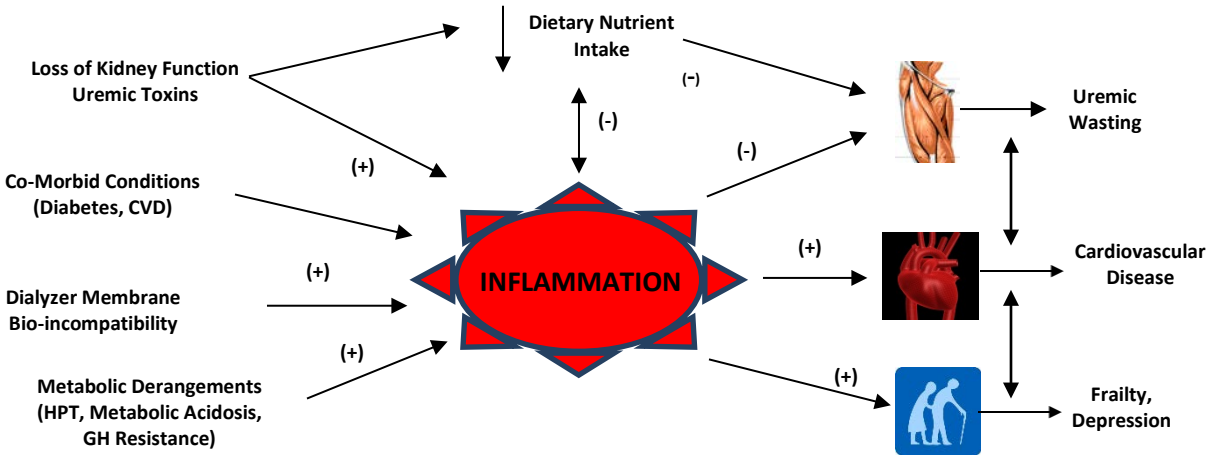

Figure 1: Conceptual model for etiology of systemic inflammation and its adverse effects in advanced kidney disease. HPT: Hyperparathyroidism; GH: Growth hormone; CVD: Cardiovascular Disease

1.2 IL-1 as a Specific Target to Improve Outcomes in ESRD

IL-1 plays a key role in the development and progression of atherosclerosis. Elevated levels of IL-1 result in secretion of chemokines and other cytokines (eg, IL-6)[13], increased levels of CRP[14], increased expression of adhesion molecules, activation of endothelial and smooth muscle cell proliferation, macrophage activation, and increased vascular permeability. IL-1 stimulates release of endothelin-1[15], a potent vasoconstrictor, and also stimulates inducible nitric oxide synthase, which increases the formation of reactive oxygen species and reactive nitrogen species which leads to oxidative stress and endothelial dysfunction[16]. IL-1 is also implicated in the proposed link between vascular calcification and systemic inflammation. TNF-α induces mineralization of calcifying vascular cells *in vitro*, and co-culture of these cells with monocyte⁄macrophages accelerates mineralization[17]. IL-1 down-regulates the synthesis and release of fetuin-A, a circulating inhibitor of calcification. Vascular calcification, via the deposition of basic calcium-phosphate crystals in the arterial intima, activates human monocyte-derived macrophages, inducing a pro-inflammatory state[18].

These observations, together with the strong relationship between pro-inflammatory cytokine levels and risk of cardiovascular events and death in ESRD, have motivated the current protocol which evaluates the safety, feasibility, and efficacy of treatment with anakinra, an IL-1 receptor antagonist (IL1ra), in patients with ESRD receiving maintenance hemodialysis, through a 24-week single dose, placebo-controlled, double blind trial.

1.3 Anti-Inflammatory Interventions in ESRD

While anti-inflammatory interventions, especially specific anti-cytokine therapies, have been used successfully to treat patients with inflammatory bowel disease[19], psoriasis, rheumatoid arthritis[20], and auto-inflammatory syndromes[21], and while encouraging results such as improvement in glycemic control and beta cell function have been reported with their use in type 2 diabetes mellitus[22], there are only limited studies using these interventions in patients undergoing maintenance hemodialysis. Etanercept, a TNF-receptor antagonist, was tested in a small number of maintenance hemodialysis patients over a 44-week period [23]. Although there were encouraging positive effects on serum albumin and prealbumin levels compared to the placebo group and no adverse events, etanercept treatment did not result in significant reductions in serum CRP or IL-6 concentrations.

1.3.1 IL-1Ra as an anti-inflammatory agent in ESRD

In comparison with other specific anti-cytokine agents, there is more precedence for the use of IL-1ra as anti-cytokine therapy. In addition to significant amelioration of the systemic inflammatory response in multiple chronic disease states such as rheumatologic diseases and diabetes mellitus, short-term inhibition of IL-1 with the IL-1ra anakinra has been shown to reduce circulating markers of oxidative stress and improve brachial artery flow-mediated dilation (an indicator of endothelial function) in patients with rheumatoid arthritis[24]. There are also intriguing preliminary data for IL-1 blockade in patients with ESRD. In a placebo-controlled pilot study that evaluated IL-1 inhibition in 22 maintenance hemodialysis patients, 14 of whom completed the trial, the active treatment group had a 53% reduction

in mean hsCRP compared with 1% in the placebo arm (P = 0.008), and a 40% reduction in mean IL-6 levels compared with a 20% increase in the placebo arm (P = 0.03) [25]. In a subgroup of these patients who underwent metabolic studies using stable isotopes, anakinra resulted in a significant decrease in skeletal muscle breakdown compared to placebo (Hung et al, ASN abstract presentation 2014). These improvements were associated with an increase in serum adiponectin concentrations, suggesting significant metabolic and nutritional benefit in response to IL1-ra administration in maintenance hemodialysis patients.

In addition to studies in ESRD patients, IL-1 antagonism has been studied in non-dialysis dependent chronic kidney disease. A recently completed two-site pilot randomized clinical trial evaluated rilonacept, an interleukin-1 (IL-1) trap, for 12 weeks in 42 patients with stage 3-4 chronic kidney disease. This study found significant improvements in markers of inflammation (hsCRP, IL-6) and vascular health (brachial artery flow-mediated dilation) in the active drug group compared with the placebo group. The medication was very well tolerated without any significant side-effects. (Novak et al and Hung et al ASN 2015, Oral Presentation, Late-Breaking Clinical Trials session).

1.4 Study Agent

1.4.1 Information obtained from FDA product label

Anakinra (Kineret®) is a therapeutic agent that blocks the effects of IL-1α and IL-1β by competitively binding to the interleukin-1 type I receptor (IL-1RI). Anakinra is a recombinant, non-glycosylated form of the naturally occurring human interleukin-1 receptor antagonist (IL-1Ra). It differs from native human IL-1Ra in that it has the addition of a single methionine residue at the amino terminus. Anakinra is produced using recombinant technology in an E. coli bacterial expression system. Anakinra is supplied commercially in single use 1 ml prefilled glass syringes as a sterile, clear, colorless-to-white, preservative free solution. Each 1 ml prefilled glass syringe contains: 0.67 ml (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg) and polysorbate 80 (0.70 mg) in Water for Injection, USP.

1.4.2 Intravenous administration of anakinra

Anakinra has FDA marketing approval for subcutaneous administration but was initially developed for intravenous administration for patients with sepsis, and can be administered intravenously. The formulation used for intravenous administration is identical to that used for subcutaneous administration, and, with the exception of injection site reactions that can occur with subcutaneous but not with intravenous administration, the adverse event profiles do not differ based on administration route. The ACTION trial will use intravenous administration of anakinra at a dose of 100 mg three times per week administered over 1 minute at the end of hemodialysis sessions. The rationale for using intravenous rather than subcutaneous administration is as follows:

1) Intravenous administration eliminates a) the risk of injection site reactions, the most common adverse event with anakinra, and b) the risk of injection-associated pain. Because these events are

caused by the vehicle (which would be used for the placebo to maintain blinding), the elimination of risk through the use of intravenous administration is relevant not only for participants receiving active drug but also for those randomized to placebo. Injection site reactions are often mild but can result in abscess formation and can necessitate discontinuation of study drug. Injection-associated pain is anticipated to be a deterrent to study participation. Thus, the use of intravenous rather than subcutaneous administration of anakinra for the ACTION trial is expected to decrease risk of important adverse events, increase enrollment rates, and increase participant retention.

2) Because anakinra can be administered through the hemodialysis extracorporeal blood circuit during regularly scheduled hemodialysis sessions, intravenous administration of anakinra does not require placement of venous access and should be highly feasible in the research setting and, if found to be beneficial, in the clinical setting.

1.4.3 Dosing of Anakinra in Renal Impairment

Renal excretion accounts for a substantial proportion of the elimination of anakinra. The half-life with subcutaneous administration is 4-6 hours in patients with rheumatoid arthritis. As reported in the FDA product label, in mild renal impairment (creatinine clearance 50-80 ml/min) and moderate renal impairment (creatinine clearance 30-49 ml/min), the mean plasma clearance was reduced by 16% and 50%, respectively. For patients with severe renal impairment (creatinine clearance less than 30 ml/min) and end-stage renal disease, the mean plasma clearance was decreased by 70% and 75%, respectively. The recommended dose of anakinra for patients receiving maintenance hemodialysis is 100 mg subcutaneous every other day (from FDA product label).

The pharmacokinetics of anakinra with intravenous administration have been studied in individuals with normal kidney function and various degrees of renal impairment[26]. Among individuals receiving maintenance hemodialysis, the mean plasma clearance of anakinra was 18.2 $\pm$3.2 ml/min compared with 137$\pm$21 ml/min in individuals with normal kidney function. The mean half-life of anakinra administered intravenously at a dose of 1 mg/kg was 7.15 hours in hemodialysis patients compared with 2.64 hours in those with normal kidney function. The plasma concentrations of anakinra at 24, 48, and 72 hours after drug administration were similar with intravenous and subcutaneous administration.

1.4.4 Dose Rationale for ACTION Trial

The recommended dose of anakinra for patients with rheumatoid arthritis is 100 mg per day administered subcutaneously. The recommended dose of anakinra for Cryopyrin-Associated Periodic Syndromes (CAPS) is 1 -2 mg/kg daily with a maximum dose of 8 mg/kg. For patients with severe renal impairment (creatinine clearance less than 30 ml/min) or ESRD, it is recommended that the prescribed dose be administered every other day. In the previous published trial of anakinra in hemodialysis patients, the dosing schedule was 100 mg three times per week. This is the schedule that will be used in the ACTION trial[25]. With dialysis schedules of Monday, Wednesday, and Friday or Tuesday, Thursday,

and Saturday, participants will receive anakinra every other day for 2 of the 3 doses each week, and every 3rd day for one of the 3 doses each week. As described in Section 1.4.3, pharmacokinetic studies suggest that for patients receiving hemodialysis, the same dosing schedule can be used for intravenous and subcutaneous administration of anakinra[26].

1.5 Clinical Efficacy Evaluations of Anakinra

Anakinra was approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis in 2002, and for (CAPS) in 2013. At the time of regulatory approval the efficacy of anakinra for rheumatoid arthritis had been evaluated in three randomized, double-blind, placebo-controlled clinical trials that enrolled a total of 1392 patients. In two of these studies, anakinra was administered in combination with other disease-modifying anti-rheumatic drugs other than TNF blocking agents[27,28], and in one study anakinra was used as monotherapy[29]. Efficacy was evaluated using the American College of Rheumatology (ACR) response criteria (ACR_{20}, ACR_{50}, and ACR_{70}). Patients receiving active treatment were more likely to achieve an ACR20 or higher magnitude of response than patients treated with placebo. Most of the responses occurred within 12 weeks. An additional fourth randomized, placebo-controlled trial in 1414 patients with rheumatoid arthritis was conducted to assess safety[30]. In this trial, patients received a variety of concurrent medications, other than TNF blocking agents, including methotrexate, sulfasalazine, hydrochloroquine, gold, penicillamine, leflunomide, and azathioprine, and the trial enrolled patients predisposed to infection based on comorbid conditions.

The FDA approval of anakinra for Cryopyrin-Associated Periodic Syndromes was based on a long-term, open label, uncontrolled study of 43 patients of 0.7 to 46 years of age with Neonatal-Onset Multisystem Inflammatory Disease (NOMID). Treatment was administered for up to 60 months[31]. Efficacy assessment was based on a disease specific Diary Symptom Sum score that included fever, rash, joint pain, vomiting and headache. Improvements occurred in all the individual symptoms as well as in circulating inflammatory markers. Among patients who underwent a treatment withdrawal phase, symptoms and inflammatory markers worsened after withdrawal and responded promptly to resumption of the treatment.

1.6 Risks

The following adverse events have been reported with the use of anakinra in non-ESRD populations:

1. Serious infections (2%) vs. placebo (<1%). In studies of rheumatoid arthritis the incidence of serious infections over 6 months was 2% in anakinra-treated patients and 1% in placebo-treated patients. Most of the infections were bacterial and included cellulitis, pneumonia and bone and joint infections. Opportunistic infections from fungal, mycobacterial and bacterial pathogens have occurred in clinical studies and post-marketing experience.
2. Neutropenia, particularly when used in combination with TNF blocking agents (8%) vs placebo (2%).
3. Injection-site reactions with subcutaneous administration are the most common adverse events. These are generally mild, typically last 14-28 days, and are characterized by erythema, ecchymosis, inflammation, and pain. In some studies, 71% of the subjects treated with anakinra experienced an injection-site reaction, compared to 28% of individuals receiving saline placebo. Injection site reactions are not a risk with intravenous administration as will be used in the ACTION study.

4. Other adverse events, with incidence compared to placebo, have included headache (12% vs. 9%), nausea (8% vs. 6%), diarrhea (7% vs. 5%), sinusitis (7% vs. 6%), influenza-like symptoms (6% vs. 5%), and abdominal pain (5% vs. 4%).
5. Hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with anakinra.

1.7 Benefits

There are no established benefits of anakinra in the dialysis population. It is hypothesized that anakinra will reduce inflammation and, as a result, have benefits on cardiovascular disease, protein-energy wasting, anemia, fatigue, quality of life, and, possibly, survival.

2 Study Objectives

The goals of this study are to evaluate the safety and tolerability of anakinra for patients receiving maintenance hemodialysis, and to explore in this patient population the efficacy of anakinra on a broad array of parameters. The findings from this early phase study will be used to assess the feasibility and inform the design of a subsequent efficacy trial.

2.1 Primary Objectives

- To evaluate the safety and tolerability of the interleukin-1b receptor antagonist, anakinra, for patients receiving maintenance hemodialysis during a 24-week treatment period and a 24-week post-treatment period during which participants will not be enrolled in any other interventional study
- To evaluate the efficacy of anakinra on reducing CRP after 24 weeks of treatment for patients receiving maintenance hemodialysis

2.2 Secondary Objectives

- To explore the efficacy of anakinra on improving markers of inflammation and cardiovascular disease risk after 24 weeks of treatment for patients receiving maintenance hemodialysis
- To explore the efficacy of anakinra on improving nutritional and metabolic markers after 24 weeks of treatment for patients receiving maintenance hemodialysis
- To explore the efficacy of anakinra on patient reported indicators of fatigue, depression, symptoms, and quality of life after 24 weeks of treatment for patients receiving maintenance hemodialysis

3 Study Design

3.1 General Design (Figure 2)

This is a randomized, placebo-controlled 2-arm trial that will compare anakinra 100 mg IV three times per week to placebo. Treatment assignment will be masked to participants and researchers. Treatment

duration will be 24 weeks and participants will be followed for safety assessment for an additional 24 weeks after treatment is completed.

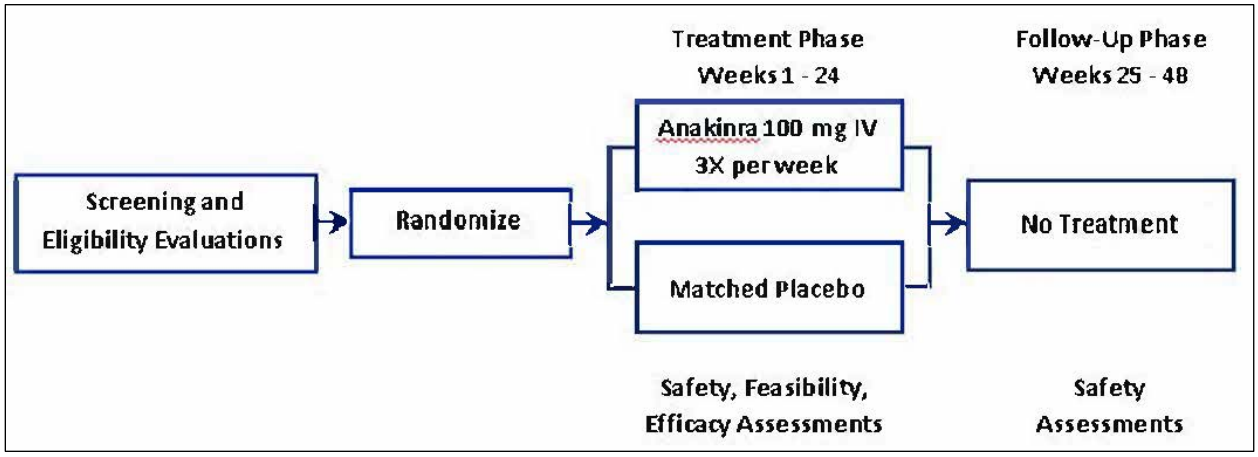

Figure 2. Trial Design

3.2 Study Endpoints

3.2.1 Safety Endpoints

The safety endpoints are:

1) adverse events
2) adverse events that preclude further treatment with the study agent
3) infections
    a. All infections – any infection regardless of severity, treatment, or distribution (i.e., localized versus systemic)
    b. Serious infections - defined as documented bacteremia, systemic fungal infection, central nervous system infection, pneumonia, infection-associated sepsis, infection requiring hospitalization for more than 2 calendar days, or infection-associated death
4) neutropenia defined as absolute neutrophil count <1000 cells/mm^3 (1.0 x 10^9 cells/L)
5) thrombocytopenia defined as platelets <75,000/mm^3 (75 x 10^9/L)
6) systemic hypersensitivity reactions

3.2.2 Tolerability Endpoint

The tolerability endpoint is:

1) the proportion of participants able to complete the full 24 weeks of treatment

3.2.3 Feasibility Endpoints

An objective of this study is to assess the feasibility of conducting a large-scale trial powered for clinical outcomes. Feasibility will be assessed based on rates of recruitment, withdrawal, and loss-to-follow-up, reasons for ineligibility, and adherence to the study drug administration schedule.

3.2.4 Efficacy Endpoints

1) The primary efficacy endpoint is the change in log-transformed circulating CRP concentration over the 24-week treatment period. The pre-treatment CRP will be the mean of the values from the two Screening and the Baseline CRP measurements, all performed at the same central laboratory as the CRPs obtained during the treatment period and Week 28 visit (see **Sections 6.1.2 and 6.1.3** for procedure for obtaining screening CRP measurements)
2) Secondary efficacy endpoints include:
    a. Change in circulating markers of inflammation and oxidative stress between baseline and end of treatment
        i. pro- and anti-inflammatory cytokines (e.g., IL-6, TNF-α, IL-10)
        ii. serum albumin concentration
        iii. F2-isoprostane/isofuran, sICAM, sVCAM levels
    b. Change in circulating markers of cardiac disease risk between baseline and end of treatment. Markers of cardiomyocyte injury, myocardial stretch, and cardiac fibrosis include troponin T, NT-pro-BNP, and galectin-3, respective
    c. Change in circulating nutritional and metabolic markers between baseline and end of treatment (e.g., adiponectin, insulin, leptin, resistin, cholesterol, and prealbumin levels)
    d. Change in patient reported outcomes using indicators of fatigue (FACIT), depression (Beck Depression Index II), symptoms (Dialysis Symptom Index, Illness Effects Questionnaire), and quality of life (KDQOL™ SF-12)
    e. Change in muscle strength (hand grip)

4 Participant Selection and Withdrawal

4.1 Inclusion Criteria

a) Maintenance hemodialysis therapy 3 times per week for end-stage renal disease
b) Age 18 – 85 years
c) ≥6 months since hemodialysis initiation
d) C-reactive protein measured by high sensitivity assay (hsCRP) ≥2.0 mg/L at screening and within 10 days prior to randomization (see **Section 4.1.1** for explanation of pre-specified plan for changing the hsCRP threshold while enrollment is underway, if necessary)
e) Most recent single pool Kt/V $\geq$ 1.2 within 30 days prior to first screening visit
f) Negative tuberculosis interferon gamma release assay (e.g. Quantiferon-TB Gold) for tuberculosis unless documented treatment for a) positive PPD, b) positive interferon gamma release assay, or c) tuberculosis.
g) Negative human immunodeficiency virus (HIV) antibody test, negative hepatitis C Ab test unless viral clearance following direct antiviral therapy is documented, and negative hepatitis B surface antigen positivity.
h) For women of childbearing potential, willingness to use a highly effective method of birth control for up to 4 weeks after the last dose of anakinra. See **Section 4.2.1** for definition of childbearing potential and acceptable methods of birth control.
i) Ability to provide informed consent

4.1.1 Change to CRP Eligibility Threshold

Version 1.0 of the protocol used a CRP threshold of >3 mg/L with the stipulation that the threshold could be decreased to ≥2.0 mg/L if needed to facilitate enrollment. In accordance with that stipulation, Version 1.3 of the protocol incorporates the new threshold of ≥2.0 mg/L. In addition to enhancing enrollment, using the lower threshold will increase the generalizability of the findings, both in terms of safety and efficacy.

4.2 Exclusion Criteria

a) Current or anticipated use of a hemodialysis central venous catheter
b) Acute bacterial infection, including vascular access infection, within 60 days prior to screening unless treated with antibiotics and resolved. Any chronic bacterial infection (e.g., osteomyelitis or bronchiectasis)
c) Hospitalization within 30 days unless for vascular access procedure
d) Cirrhosis
e) Malignancy within the past 5 years with exception of basal or squamous cell carcinoma
f) Use of an immunosuppressive drug within the past 3 months except low doses of oral corticosteroids (total daily dose ≤10 mg/day of prednisone or equivalent)
g) Receipt of live vaccine within the past 3 months. Live vaccines include Varicella zoster, measles, oral polio, rotavirus, yellow fever, and the nasal spray influenza vaccine
h) Absolute neutrophil count (ANC) <2,500 cells/mm^3 (2.5 x 10^9 cells/L)
i) Platelet count <100,000/mm^3 (100 x 10^9/L)
j) Known allergy to anakinra
k) Anticipated kidney transplantation, change to peritoneal dialysis, or transfer to another dialysis unit within 9 months
l) Expected survival less than 9 months
m) Pregnancy, anticipated pregnancy, or breastfeeding
n) Incarceration
o) Receipt of an investigational drug within the past 30 days
p) Current or anticipated participation in another intervention study

4.2.1 Women of Childbearing Potential

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as:

- Amenorrhea for ≥12 consecutive months without another cause, or
- Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL, or
- Women receiving hormone replacement therapy (HRT)

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or who are practicing

abstinence, or have a partner who is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

Acceptable methods of highly effective birth control include:

- Condom with spermicide
- Diaphragm and spermicide
- Cervical cap and spermicide
- Hormonal contraception

A serum pregnancy test will be done at the local laboratory for women of childbearing potential at the second screening visit, and at weeks 4, 8, 12, 16, 20, 24, and 28.

4.3 Recruitment

Participants at dialysis units affiliated with the practices of a Clinical Center will be screened for eligibility. In addition to active screening of dialysis unit patient rosters by study personnel, informational handouts and brochures may be disseminated at affiliated dialysis units in order to allow potential participants to learn about the study and to contact investigators if interested. All study material must be approved by local IRBs before dissemination to potential study participants.

Dialysis unit laboratory studies, medical records at Clinical Centers, and treatment or history records at local dialysis units will be reviewed to assess eligibility for enrollment. Prior to enrollment, each participant's treating nephrologist will be contacted to assess suitability for enrollment.

Once preliminary eligibility is confirmed, written informed consent will be obtained by a qualified investigator or study site designee during an in-person visit. This visit may take place either at the dialysis unit or at the Clinical Center according to investigator and participant preferences.

Participants may be compensated for study participation. Each Clinical Center is responsible for developing a compensation plan and schedule, and distributing payment.

5 Study Drug

5.1 Description

Anakinra will be supplied in pre-filled syringes as a sterile, clear, colorless-to-white, preservative free solution. Each syringe will contain 100 mg in 0.67 ml solution (pH 6.5) containing disodium EDTA (0.12 mg), sodium chloride (5.48 mg), sodium citrate (1.29 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP. There will be no modification to the formulation of the manufacturer-supplied anakinra. Saline (0.9%) will be used as the placebo. The study drug will be refrigerated at 2 °C – 8 °C and will be kept away from light.

5.2 Administration of Study Drug

Study drug (100 mg) will be administered via a medication port in the extracorporeal dialysis blood circuit three times per week during the last 30 minutes of the hemodialysis session. The study drug will

be administered by a dialysis unit nurse over 1 minute. There must be at least one calendar day between successive doses, meaning that the drug will not be administered on consecutive days even if dialysis occurs on both days. The duration of treatment is 24 weeks. Participant-specific study drug administration logs documenting each dose administration as well as scheduled doses that are not administered, with the reason for non-administration, will be completed by the dialysis unit nurse administering drug, and provided to the Clinical Center research teams upon resupply visits. Receiving, Storing, Dispensing and Returning Study Drug

5.2.1 Receiving Study Drug

Study drug and placebo will be distributed by Sobi, the manufacturer of study drug, to the research pharmacy at each Clinical Center. Each Clinical Center research pharmacy will be responsible for maintaining detailed records regarding the receipt of study drug. General study drug accountability, participant-specific study drug accountability and, if necessary, Shipment Tracking Accountability logs will be maintained by the Clinical Center pharmacists. Documentation includes study drug receipt, storage, dispensing, and final disposition.

5.2.2 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of study agent shipped, study agent consumed, and study agent remaining. This reconciliation will be logged on the study agent reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented before the return or destruction of unused study agent. Study agent destroyed on site will be documented in the study files.

5.3 Concomitant Therapy

Information about medication use will be collected at baseline and throughout the course of the study. Appropriate sources for obtaining this information include the participant, the medical/dialysis unit record, and treating clinicians.

6 Study Procedures

6.1 Study Visits and Activities

A schedule of study visits and procedures is provided in the Study Procedures Table in **Section 15.1**.

All blood collections will be performed either on a non-dialysis day, or before the initiation of dialysis on a dialysis day. Post-randomization study visits can take place in the dialysis unit or via phone.

6.1.1 Pre-screening Activities

Patients at participating dialysis units will be screened for eligibility. Clinical Center study personnel will review dialysis unit records and other medical records to assess eligibility. The treating nephrologist for a potentially eligible patient will be contacted to further assess eligibility and obtain permission to contact the patient.

6.1.2 First Screening Visit (Day –30 to Day –14)

Patients who appear eligible based on pre-screening will be approached in person to determine interest in participation and confirm eligibility. Study personnel will discuss the study goals and procedures with the potential participant in detail. If the patient agrees to participate in the study, study personnel will review and assess understanding of the entire informed consent form before obtaining written informed consent from the participant. The consenting process will be performed by a qualified investigator or study site designee. Informed consent will be obtained and documented before any study procedures are performed.

The screening activities may take place over a single visit or multiple visits.

Screening Activities

- Obtain informed consent
- Collect baseline data including demographics, medical history, and medication use
- Obtain blood for hsCRP (local Clinical Center laboratory and central laboratory), and CBC with differential (local laboratory). The hsCRP result from the local laboratory will be used for eligibility determination and a batched measurement made by the central laboratory on a stored sample will be used for determining the pre-treatment hsCRP value used in efficacy assessments. The blood obtained for the central laboratory measurement will be processed, aliquoted and stored at -80 °C for future batched shipping. If blood is obtained on a dialysis day, blood should be drawn before dialysis.
- Testing for tuberculosis, hepatitis B, hepatitis C, and HIV if clinical results are not available (at research team's discretion, can occur at Screening Visit 1 or 2).
- Review eligibility criteria

6.1.3 Second Screening Visit (Day –10 to Day –1)

The second screening visit should be performed within 10 days prior to the baseline/randomization visit and far enough in advance of the baseline/randomization visit to be sure that the results of the hsCRP (performed at the local laboratory), CBC with differential, and, if applicable, serum pregnancy test, will be available prior to baseline.

- Obtain blood for hsCRP (local Clinical Center laboratory and central laboratory), and CBC with differential (local laboratory). The hsCRP result from the local laboratory will be used for eligibility determination and a batched measurement made by the central laboratory on a stored sample will be used for determining the pre-treatment hsCRP value used in efficacy assessments. The blood obtained for the central laboratory measurement will be processed, aliquoted and stored at -80 °C for future batched shipping. If blood is obtained on a dialysis day, blood should be drawn before dialysis.
- Testing for tuberculosis, hepatitis B, hepatitis C, and HIV if clinical results are not available (at research team's discretion, can occur at Screening Visit 1 or 2).
- Obtain blood for serum pregnancy test for women of childbearing potential (local laboratory)
- Review eligibility criteria

6.1.4 Baseline/Randomization Visit (Day 0)

At the baseline visit medication use, vital signs, physical examination and adverse events will be recorded, and eligibility will be confirmed. After eligibility has been confirmed, a call will be scheduled for the participant to complete five telephone questionnaires (see section 6.1.13). Hand grip strength will be measured using a dynamometer.

Blood will be collected for serum, plasma, and buffy coat isolation for future DNA extraction. Samples will be aliquoted and stored at -80 °C for future batched shipping. Blood collection will be performed prior to dialysis initiation if performed on a dialysis day. If blood is not collected on the day of the Baseline/Randomization visit (Day 0), it will be collected pre-dialysis at the next dialysis session and prior to initiation of the study drug. The batched samples will include blood for hsCRP.

Randomization to treatment group will be performed through the centralized Data Management System.

6.1.5 Initiation of Study Drug Administration

Study drug administration will begin at a dialysis session within 1 week after the Baseline/Randomization Visit and continue through Week 24 at a frequency of 3 times per week. The study drug administration log will be completed after each administration to document the administration and any symptoms or adverse events that occur during the dialysis session.

6.1.6 Weeks 1, 2, and 3

Week 1 begins on the day of the first drug administration. During Weeks 1, 2, and 3 there will be an in-person or telephone contact to perform the following:

- Review clinical events

6.1.7 Weeks 4, 8, 16, and 20

The following will be performed at in-person visits which may take place at the dialysis unit:

- Blood collection for CBC with differential that will be performed at the local Clinical Center laboratory
- Blood collection for hsCRP that will be performed at the central laboratory
- Obtain blood for serum pregnancy test for women of childbearing potential (local laboratory)
- Recording of concomitant medications, and adverse events

6.1.8 Weeks 12 and 24 (End of Treatment Visit)

The following will be performed at in-person visits which may take place at the dialysis unit:

- Blood collection for serum and plasma. Samples will be aliquoted and stored at -80 °C for future batched shipping. The batched samples will include blood for hsCRP.
- Blood collection for CBC with differential that will be performed at the local Clinical Center laboratory

- Obtain blood for serum pregnancy test for women of childbearing potential (local laboratory)
- Recording of dialysis unit laboratory studies, concomitant medications, and adverse events
- Hand grip strength measurement using a dynomometer

6.1.9 Early Withdrawal Visit

If a participant withdraws from the trial before the Week 24 end of treatment visit an Early Withdrawal visit will be scheduled to conduct the assessments that otherwise would be performed at Week 24. Participants who stop taking study drug are not considered early withdrawals and will be asked to continue to provide follow-up data on the study schedule and to participate in the assessment at Week 24.

6.1.10 Post-Treatment Period: Weeks 28 through 48

After the study drug treatment period, participants will be followed for an additional 24 weeks to collect additional information about safety. Visits will occur every 4 weeks. Participants who stop taking study drug before Week 24 will be followed for an additional 24 weeks following study drug discontinuation. Participants will be instructed that enrolling in another interventional study during this post-treatment period is not permitted.

Week 28

The following will be performed at in-person visits which may take place at the dialysis unit:

- Blood collection for serum and plasma. Samples will be aliquoted and stored at -80 °C for future batched shipping. The batched samples will include blood for hsCRP.
- Blood collection for CBC with differential that will be performed at the local Clinical Center laboratory
- Obtain blood for serum pregnancy test for women of childbearing potential (local laboratory)
- Recording of concomitant medications and adverse events
- Hand grip strength measurement using a dynomometer

Weeks 32, 36, 40, 44, and 48

Adverse events will be recorded.

6.1.11 Patient Reported Outcomes (PROs) Questionnaire Administration

The University of New Mexico Health Sciences Center Computer Assisted Telephone Interviewing (CATI) team will contact study participants at Baseline and Weeks 12, 24, and 28 to administer the following questionnaires via telephone:

- Beck Depression Index (BDI) II
- FACIT Fatigue Scale
- Illness Effects Questionnaire
- Dialysis Symptom Index
- KDQOL™ SF-12

The questionnaires will be administered on non-dialysis days. It is expected that completion of the questionnaires will take approximately 45 minutes. If participants are unable to complete the full battery of questionnaires at one time, they will be permitted to continue the interview on a subsequent day.

6.1.12 Pharmacokinetic and Pharmacodynamic Studies

Pharmacokinetic and pharmacodynamic studies will be performed on 12 participants. Blood will be collected for measurement of anakinra concentration and hsCRP assay according to the following schedule starting on the first day of study drug administration:

1. Sampling Day 1 (the first day of study drug administration and prior to a 48-hour interval between dialysis sessions): prior to dialysis initiation and at the end of the dialysis session
2. Sampling Day 2 (the non-dialysis day following the first day of study drug administration): at the same time as the Sampling Day 1 end-of-dialysis collection
3. Sampling Day 3 (the dialysis session approximately 48 hours after the Sampling Day 1 pre-dialysis blood draw): prior to dialysis initiation and at the end of the dialysis session
4. Sampling Day 4 (dialysis day, 4 weeks after the first day of study drug administration, and prior to a 48-hour interval between dialysis sessions): prior to dialysis initiation and at the end of the dialysis session
5. Sampling Day 5 (the non-dialysis day immediately following Sampling Day 4): at the same time as the Sampling Day 4 end-of-dialysis collection
6. Sampling Day 6 (the dialysis session approximately 48 hours after the Sampling Day 4 pre-dialysis blood draw): prior to dialysis initiation and at the end of the dialysis session

6.2 Temporary Discontinuation of Study Drug (see also Section 6.4)

Study drug will be temporarily discontinued by the research team for the following events but can be resumed after event:

- Non-serious Infection (see **Section 6.4.1**)
- Neutropenia with absolute neutrophil count (ANC) <1000/mm^3 but ≥500/mm^3
- Thrombocytopenia with platelet count <75,000/mm^3 but ≥25,000/mm^3
- Use of a tunneled or non-tunneled central venous dialysis catheter. If a central venous catheter is placed after trial enrollment, study drug will be discontinued until the catheter is removed.

Resumption of study drug must be approved by a Study Drug Management Committee comprised of Clinical Center and DCC investigators.

6.3 Permanent Discontinuation of Study Drug

Study drug will be permanently discontinued by the research team for the following events because of the potential for compromising patient safety:

- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that treatment with anakinra is not in the best interest of the subject
- Serious infection (see **Section 6.4.1**)

- Allergy to or documented intolerance of study drug
- New malignancy
- Initiation of immunosuppressive therapy
- Neutropenia with ANC <500/mm^3
- Thrombocytopenia with platelet count <25,000/mm^3
- Organ transplantation
- Change to a different dialysis modality
- Transfer to a non-participating dialysis unit

If study drug is discontinued study visits and procedures will continue to the extent possible unless the participant withdraws consent for follow-up.

6.4 Management of Clinical Events

6.4.1 Infection

Participants with clinically significant infections should be treated according to standard of care and the adverse event should be recorded. Study drug should be temporarily discontinued for non-serious infections until it is clear that the infection has resolved. Study drug should be permanently discontinued if there is a serious infection. Serious infections include documented bacteremia, systemic fungal infection, central nervous system infection, pneumonia, infection-associated sepsis, infection requiring hospitalization for more than 2 calendar days, or infection-associated death.

The Study Drug Management Committee must approve resumption of study drug after discontinuation for infection.

6.4.2 Neutropenia

Study drug will be temporarily discontinued if the ANC is <1000/mm^3 and ≥500/mm^3, and can be resumed once the ANC is ≥2000/mm^3. Study drug will be permanently discontinued if the ANC is <500/mm^3. A complete blood count will be obtained at least once per week until the ANC is ≥2000/mm^3.

6.4.3 Thrombocytopenia

Study drug will be temporarily discontinued if the platelet count is <75,000/mm^3 and ≥25,000/mm^3, and can be resumed once the platelet count is >120,000/mm^3. A complete blood count will be obtained at least once per week until the platelet count is >120,000/mm^3. Study drug will be permanently discontinued if the platelet count is <25,000/mm^3. A complete blood count will be obtained at least once per week until the platelet count is ≥75,000/mm^3.

6.4.4 Immunizations

Live vaccines should not be administered to subjects during the study (including the screening period). Live vaccines include Varicella zoster, measles, oral polio, rotavirus, yellow fever, and nasal spray (live

attenuated) influenza vaccine. Inactivated vaccines (e.g., influenza injection) are allowed; however, the efficacy may be attenuated.

6.4.5 Allergic / Acute Hypersensitivity Reactions to Anakinra

Signs of potential acute hypersensitivity reactions include hypotension; dyspnea; wheezing; acute pain in the chest, back, or extremities; chills, fever, or urticaria; or generalized erythema. These events should be recorded on the appropriate Case Report Form. In the case of discontinuation of study drug due to potential acute hypersensitivity reactions, the participant should not be rechallenged with the study drug. Management of potential acute hypersensitivity reaction should be determined by the investigator or clinician and might include intravenous fluid, epinephrine, glucocorticoids, antihistamines, and/or pressor agents.

Allergic / acute hypersensitivity reactions will be graded using the Common Terminology Toxicity Scale Version 4.0 shown in the Table below.

Grade					
Toxicity	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <39° C (<100.4° F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hrs	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	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis			Symptomatic bronchospasm with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death

CTC Toxicity Scale, Version 4.0, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

6.4.6 Management of Active Suicidal Intent

This trial is not specifically enrolling individuals who are at high risk for suicide. However, it is possible that suicidal ideation will be evident from responses to the Beck Depression Inventory-II (BDI-II) which is one of several patient reported outcome instruments used in this study. Participants will be considered

to have active suicidal intent if the answer to Question 9 of the BDI-II is either "I would like to kill myself" or "I would kill myself if I had the chance".

The personnel at the central PRO administration center (CATI Center) administering the BDI-II will have emergency telephone numbers for 3 members of the research team at each Clinical Center. If a participant indicates active suicidal intent by answering either "I would like to kill myself" or "I would kill myself if I had the chance" to question 9 on the BDI-II, the person administering the BDI-II will immediately stop administering that questionnaire. The CATI team member will inform the participant that the research team will follow up with them to provide follow-up and resources, and end the call. The CATI team will immediately contact the research team at the participant's Clinical Center to inform them of the participant's possible suicidal intent. A designated member of the Clinical Center research team will immediately contact the participant and provide appropriate support and resources, including arrangement for emergency care and/or referral to mental health specialists as needed.
The CATI team member will also notify the DCC electronically using the participant's study ID.

If a participant indicates active suicidal intent requiring follow up by the clinical center, the administration of the remaining ACTION questionnaires will be deferred until a later date after the management of suicidal intent protocol has been completed.

6.5 Early Withdrawal of Participants

Early withdrawals will be discouraged and participants who are not willing or able to continue study drug will be encouraged to remain in the study and continue study evaluations. In the case of withdrawal of consent, every attempt will be made to obtain consent to continue monitoring for the occurrence of mortality, hospitalizations and other safety signals via telephone or in-person contact with participants, relatives, and dialysis unit staff and records. As a last resort, the Social Security Death Index will be queried for mortality events on individuals otherwise lost to follow-up. If a patient becomes pregnant, she will be withdrawn from the study but will be followed for specific pregnancy outcomes.

7 Statistical Plan

7.1 Sample Size Determination

Sample size considerations were framed using standard study design parameters to ensure 80% power to detect pre-specified effect sizes utilizing intermediate outcomes. However, for this early phase pilot study, the primary focus is directed at assessing safety and feasibility, with no attempt to create critical test result regions for standard hypothesis testing.

From preliminary studies, we assumed estimated mean CRP at baseline to be 9.5 ± 4 mg/L and log-transformed mean CRP at baseline to be 2.14 ± 0.55 log(mg/L) [25]. Assuming a correlation of 0.6 between pre- and post-treatment CRP in the placebo group, and a 10% dropout rate of study participants by the end of the study, a sample size of 80 (40 patients for the placebo arm and 40 patients for the active

treatment arm) will provide 80% power to detect an effect size of 0.6SD (0.33 log(mg/L)) difference between treatment arms in the change from baseline to 24-week endpoint in log-transformed CRP.

7.2 Randomization and Stratification

A stratified randomization procedure, blocking on two strata (diabetes or no diabetes) within Clinical Centers will be implemented within a web-based randomization module deployed centrally within the DCC. Within each of these strata, participants will be randomly allocated to anakinra or placebo in a 1:1 distribution.

The treatment assignment code, corresponding to each treatment identifier number, will be known only to a single member of the DCC data management group and to the research pharmacist at the relevant Clinical Center, until the completion of treatment and data collection on all participants. At the end of a treatment, the participant and the treating physician will be asked to guess the assigned treatment group, and provide the basis for their judgments for analysis later, to determine whether the blinding has been broken. However, except in the case of emergency unmasking, the treatment codes will not be identified until the DSMB has approved unblinding in preparation for the public dissemination of results.

7.3 Analysis Populations and Missing Data

The analysis populations are defined as follows:

- All-randomized / intention-to-treat (ITT) population: Any participant randomized into the study, regardless of whether study drug was received.
- As-treated population: The as-treated population is the same as the ITT population (i.e., any participant randomized into the study regardless of whether study drug was received). However for the as-treated analysis, patients in the active drug group who did not receive at least one dose of study drug will be classified into the placebo arm.
- All-treated population: Any participant randomized into the study who received at least one dose of study drug.
- Per-protocol population: Any participant who was appropriately randomized, and received the protocol-dictated study drug exposure (≥75% of prescribed doses) and endpoint assessments through 24 ± 2 weeks.

An intent-to-treat analysis, in which all available data on all randomized participants are included, will be used for the primary comparison of treatments. All attempts will be made to keep missing data to a minimum, and participants who withdraw from treatment will be encouraged to continue on study in order to provide complete follow-up information. Thus, irrespective of withdrawal from treatment, all participants should continue to be followed with all scheduled outcome evaluations until the end of the study. However, it is expected that up to 10% of the randomized participants may withdraw prior to the final assessment of response at 24 weeks. These participants will be included in the denominator for evaluation of the response rates defined for the primary endpoint.

The characteristics at the time of randomization for those participants without complete

follow-up will be examined; however, there will be limited statistical power to detect any but major differences between these participants and those with complete follow-up. In addition, in order to assess the potential biases introduced by differential withdrawal among treatment arms, a comparison of withdrawal rates and/or time to withdrawal will be included as an ancillary analysis to the primary endpoint comparison.

Secondary analyses will examine the as-treated, per-protocol, and all-treated populations. Because dose-related efficacy and safety are primary questions of interest in this study, the ITT analysis will be supplemented with an analysis of the as-treated population. Although ITT approaches provide the least-biased analysis of treatment efficacy and safety, as-treated analyses provide important complementary information on biological effectiveness of therapy (e.g. theoretical efficacy if drug were tolerated by all participants) and on the effects of actual doses used that are not captured by ITT analyses in which the unit of analysis is a randomized therapy that may not have been used by individual participants[32]. For this reason, as-treated approaches provide important complementary information to ITT analyses and are typically mandated as an important secondary analyses of clinical trials by the FDA[32].

7.4 Statistical Methods

In addition to the analyses described subsequently, descriptive statistics will be used during the course of the study as part of data management procedures for monitoring data quality. A brief overview of some of the statistical methods that may be used at the time of analysis, both for descriptive purposes and in more comprehensive analysis of the primary research questions, is summarized in the following sections. It is recognized that these methods may be revised and additional ones considered as the details of the specific analyses are developed.

7.4.1 Descriptive Analyses and Primary Efficacy and Safety Analyses

Standard descriptive statistics will be used to summarize baseline characteristics and study outcome measures at each follow-up visit, both overall, and within each treatment group. Examination of baseline characteristics will include estimates of the distribution of age, race, and other demographic characteristics, lab measures and study center. Summary statistics such as means, medians, and interquartile ranges will be produced for all measured variables. Frequencies and percentages will be computed for all categorical and ordinal variables. Graphical methods including quantile-quantile plots and boxplots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations, if warranted. The balance of baseline measures across the three treatment groups will be compared using appropriate 2-sample tests, including Mann-Whitney tests and Fisher's exact tests.

For the analyses of the primary efficacy outcome, mean (± standard deviation) or median (interquartile ranges) of baseline and each of subsequent measurements in the primary endpoint, log-transformed CRP, will be presented. Change in log-transformed CRP at 24 weeks will be assessed and reported quantitatively, and descriptive statistics for absolute and % change will be provided. Linear mixed effects regression models with adjustment for stratification factors and baseline covariates will be used for assessment of treatment effects on repeated measurements of CRP. Model assumptions regarding

homoscedasticity and normality will be examined using standard techniques. With repeated measurements of CRP, the area under the time-log-transformed CRP curve[33] can be estimated from the linear mixed effects models and used to compare an aggregate efficacy between treatment and placebo arms over the 24-week period of the study.

For the safety endpoints, tables with percent incidence and incidence rate (for both adverse events and infections which can occur more than once throughout the course of study) will be prepared. Differences in incidence and incidence rate between arms will be assessed using generalized linear mixed effects models (logistic and/or Poisson regression) adjusting for stratification factors and baseline covariates.

The primary analysis will examine the intention to treat population. All analyses will be repeated in the as-treated, all-treated and per-protocol populations (see **Section 7.3**). Secondary endpoint analyses will be presented using analogous techniques. $P<0.05$ will be considered significant in all analyses.

7.4.2 Secondary Analyses

A number of secondary analyses will be conducted to evaluate the secondary efficacy outcomes. Secondary efficacy outcomes include change in markers of inflammation and oxidative stress (including pro- and anti-inflammatory cytokine, serum albumin, F2-isoprostane/isofuran levels, etc.), in circulating markers of cardiac disease risk, in nutritional and metabolic markers, and in patient reported outcomes (including indicators of fatigue, depression, symptoms, muscle strength, and quality of life) between baseline and 24 weeks. For markers measured repeatedly, (generalized) linear mixed effects models will be used to assess the effect of treatment. Analytical approaches for these secondary outcomes will be similar to that used for the primary outcome. Distribution of the secondary outcome parameters will be examined and appropriate transformation will be applied. For this early phase study, analyses of the secondary efficacy outcomes will be viewed as exploratory, and correction for multiple comparisons will not be performed.

7.4.3 Interim Analysis

The pharmacokinetic and pharmacodynamic data will be analyzed after 12 participants have completed the assessments in order to allow modification of dosing if indicated based on anakinra concentrations or CRP concentrations.

7.4.4 Missing Data

In general, missing data will not be imputed. Every effort will be made to use statistical methods that are robust to missingness, and the number of participants included with each analysis will be given with the results.

8 Safety and Adverse Events

8.1 Definitions

Definitions are per the January 2007 Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants or Others and Adverse Events, Office on Human Research Protection (OHRP) Guidance. http://www.hhs.gov/ohrp/policy/advevntguid.html

8.1.1 Adverse Event

An *adverse event (AE)* is any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (for example, abnormal physical examination or laboratory finding), symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to the participant's participation in the research.

8.1.2 Serious Adverse Event

A *serious adverse event* (SAE*)* is any AE that is:

- fatal or results in death
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- results in congenital anomalies or birth defects
- an important medical event*

*Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance.

8.1.3 Unanticipated Problem Involving Risk to Participants or Others

An Unanticipated Problem is any incident, experience, or outcome that meets **all** of the following criteria:

- it is unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the IRB-approved research protocol and informed consent document and the characteristics of the participant population being studied;
- it is related or possibly related to participation in the research; possibly related means that there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research, and
- it suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

8.1.4 Pre-Existing Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.2 Adverse Event Reporting Period

The study period during which adverse events must be tracked and reported is defined as the period from the initiation of study procedures to study completion. Participants who fail screening will no longer be followed for adverse events or serious adverse events. If a participant is rescreened in the future, he or she will once again be followed for those events once screening procedures resume.

8.2.1 Post-study Adverse Events

All unresolved adverse events will be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the Data Coordinating Center (DCC) of any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to the study.

8.3 Recording of Adverse Events

At each contact with the participant, the investigator or site designee will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on adverse events will be recorded in the source document, and also on the adverse event log case report form (CRF). All signs, symptoms, and abnormal diagnostic procedure results relating to the same event will be recorded under one diagnosis name.

8.3.1 Anticipated Adverse Events

The following adverse events are anticipated in the hemodialysis population and are not considered Unanticipated Problems. Note that the designation as "Anticipated" does not imply that the event is not an SAE but relates to the regulatory definition of Unanticipated Problems as provided in **Section 8.1.3**.

- Death
- Coronary Ischemia including:
    - Unstable angina
    - Acute MI
    - Coronary revascularization
- Heart failure hospitalization or exacerbation
- Cardiac arrest
- Cardiac arrhythmia (ventricular or atrial)
- Peripheral vascular revascularization
- Amputation
- Hypotension
- Vomiting
- Vascular Access Events Including:
    - Catheter exchange, removal or declotting
    - Arteriovenous graft or fistula complications

  - Clotting
  - Stenosis
  - Revascularization
  - Infection
- Infections Including:
  - Pneumonia
  - Bacteremia
  - Hemodialysis vascular access infection

8.3.2 Non-Reportable Events

The hemodialysis population is characterized by frequent laboratory testing and a high rate of peri-dialytic hypotensive events requiring change in the dialysis prescription, adjustment of dry weight or change in dialysis-related medications. Due to the unique nature of this population, the following events are considered routine aspects of chronic dialysis therapy and they will not be considered to meet the criteria of SAE in this study except as noted:

- Anemia—will be reported only when hemoglobin <8.0 mg/dL
- Hyperphosphatemia—will be reported only when phosphate >9.5 mg/dL
- Hypocalcemia—will be reported only when serum calcium <7.0 mg/dL
- Hypercalcemia—will be reported only when serum calcium >11.0 mg/dL
- Hyperparathyroidism—will be reported only when PTH>1000 pg/mL
- Hypotension—will be reported only when requiring emergency room visit or hospitalization

8.4 Reporting of Serious Adverse Events and Unanticipated Problems

Study sites are required to report SAEs to the DCC within 24 hours of first knowledge of the event. To report such events, an SAE form will be completed by the investigator and faxed or emailed to the DCC. The DCC will facilitate the timely medical review and reporting of the event, and provide reports to the NIDDK and the Data and Safety Monitoring Board (DSMB) in accordance with DSMB-approved study policies and regulatory requirements (see **Section 8.5.1** for details of the DSMB).

The investigator will keep a copy of the SAE form on file at the study site. At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study participation

Within the following 7 days, the investigator will provide further information on the SAE or the unanticipated problem in the form of a written narrative. This should include a copy of the completed SAE form, and any other diagnostic information that will assist in the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the DCC.

If a participant becomes pregnant while participating in the study it will be reported as an adverse event and will trigger the collection of additional documentation about the pregnancy. Pregnancy outcomes will be collected, including the outcome of the infant and if the pregnancy was terminated. This information will be submitted to the University of Pennsylvania IRB, and to the local site IRB as required.

SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

The DCC will report SAEs for any participant identified to be on active drug to Sobi at the end of the trial once unblinding has occurred.

8.4.1 Investigator Reporting to the IRB

Site investigators will report SAEs and Unanticipated problems to their IRB in accordance with the reporting requirements of the local IRB or with the Office of Human Research Protections (OHRP) guidelines, whichever is sooner. OHRP recommends that:

1) Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event; and

2) Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

Reporting Process

Unanticipated problems posing risks to participants or others as noted above will be reported using the appropriate IRB-designated form or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be maintained in the Clinical Center Investigator's study file.

Other Reportable Events:

- Any adverse event that would cause the study's Steering Committee to modify the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human participants.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency.
- Breach of confidentiality

- Change to the protocol made without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under 45 CFR part 46 subpart C and the investigator believes it is in the best interest of the participant to remain in the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of participants.

8.4.2 DCC Notification to Participating Investigators

The DCC will notify all Clinical Center principal investigators, in a written safety report, of any adverse event that meets the criteria of an unanticipated and related event as described in **Section 8.1.3**.

8.5 Medical Monitoring

Each Clinical Center Principal Investigator will be responsible for overseeing the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Independent Data and Safety Monitoring Board (DSMB)

The information provided in this section of the protocol is a general description of the DSMB responsibilities and processes. A DSMB charter for the Hemodialysis Novel Therapies Consortium includes additional detail. The NIDDK DSMB charter is provided as an attachment in **Section 15.**

A DSMB has been established by the NIDDK and provides input to the Institute. The DSMB is comprised of individuals with expertise in clinical trials design and methodology, biostatistics, clinical nephrology and other relevant medical specialties. The DSMB members are not affiliated with the study and are appointed by the NIDDK. DSMB members will be free of conflicts of interest that could be affected by the outcomes of the study. During the study, DSMB members who develop real or perceived conflicts of interest that impact objectivity will disclose them to NIDDK project officers, who will arrange for replacement of the member, if indicated.

The DSMB will review the protocol before initiation of the study. After initial approval during the course of the study, the primary responsibilities of the DSMB will be to:

- Review safety data and provide input to protect the safety of the study participants;
- Provide input on major changes to the research protocol and plans for data and safety monitoring;

- Provide input on the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study sites, and other factors that may affect study outcomes;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the need for continuation of the study, safety of the participants or the ethics of the study;
- Provide input on modification of the study protocol or possible early termination of the study because of attainment of study objectives, safety concerns, or inadequate performance (such as enrollment and retention problems).

9 Data management

An internet-based registration system designed by the DCC will be used for all of the pilot and feasibility studies of the Hemodialysis Novel Therapies Consortium in order to promote uniformity across studies. The central registration system will include a randomization module for each study that will confirm eligibility. Central participant registration will also allow the DCC to generate recruitment reports across concurrent studies.

An Oracle Clinical data management system (DMS) designed by the DCC will be used for the collection, storage and management of data. Site personnel will enter data directly using Oracle Clinical Remote Data Capture. Electronic case report forms (eCRFs) will incorporate range and logical edit checks, both within and across forms. Data entry will be followed daily with manual and programmed checks and edits for errors and omissions.

9.1 Data Quality

The DCC will collaborate with the Clinical Center investigators to establish parameters for primary and secondary outcomes, safety, and descriptive values. The data management team will use a data validation plan, rule set specifications, and programming logic to implement data validation rules. The DCC staff will interact with Clinical Center study staff to verify queried data and track all queries to resolution.

9.1.1 Quality Control Activities

The Quality Control Committee and the DCC will develop a quality assurance and control plan that ensures that study data are as precise and reliable as possible.

Manual of Procedures (MOP) – The MOP will describe the sequence of study conduct and provide detailed instruction for the performance of screening, baseline, enrollment, treatment allocation and follow-up procedures. The MOP will provide instruction in case report form (CRF) completion, use of the electronic DMS, and collection, documentation and transfer of specimens and tests to central laboratories.

Training and certification procedures – The DCC will conduct a training session before the study starts to train and certify personnel in the performance of study procedures. Personnel who join the study after

its initiation will be trained and certified in study procedures before being allowed to complete tasks associated with their role.

Site visits – Site visits will be conducted as outlined in the Study Monitoring Plan. Findings from site visits will be used to resolve problems and develop corrective action plans.

External data sources – The DCC will monitor quality control of data received from central laboratories.

Internal quality control procedures – A data validation plan, rule set specifications, and programming logic to implement data validation rules will be implemented.

9.1.2 Routine reports

The DCC will develop a set of standard enrollment, tracking, quality review, and safety monitoring reports. Adverse event reports, DSMB reports and reports for statistical analysis will be developed and produced on an appropriate schedule.

9.2 Data Security

The DMS will be designed to prevent unauthorized access to study data and to prevent data loss due to equipment failure or catastrophic events. The procedures to do so encompass user account management, user privilege assignment, data loss prevention (database backup), and DMS change management. User access will be controlled by assignment of confidential usernames and passwords.

Study data collected at the Clinical Centers will be entered into Oracle Clinical. This DMS uses a secure connection between the client browser at the Clinical Center and the web server at the DCC. Data transmitted over this connection is authenticated by the use of digital certificates and is encrypted as it travels the Internet to the DCC.

Where applicable, electronic files containing data from hand held devices and central laboratories will be transferred to the DCC using secure File Transfer Protocol (FTP) technology. The DCC team will maintain a secure FTP server. The files transmitted using this method will be encrypted during the exchange.

9.2.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke authorization for use of his or her PHI

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected before the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should

be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

9.2.2 Data Linkage

Participants will be asked to consent to provide their Social Security Number (SSN) to facilitate access to long term clinical outcomes after study participation has ended, in national databases at the Social Security Administration, the Center for Medicare and Medicaid Services 9CMS) and the United States Renal Data Systems (USRDS). Providing the SSN and access to national databases is optional, and is not required for participation in the study.

9.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a research study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: dialysis unit records, hospital records, clinical and office charts, laboratory reports, memoranda, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3.1 Case Report Forms

The study CRF is the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. "N/D" will be used to indicate on the CRF that a procedure was not done or a question was not asked rather than leaving a space blank. "N/A" will be used to indicate that an item is not applicable to the individual case. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated. Erasing or white-out will not be used for errors. For clarification of illegible or uncertain entries, the clarification will be printed above the item, and the clarification will be initialed and dated.

9.3.2 Maintaining Anonymity of Submitted Medical Records

Clinical site personnel will de-identify all medical records before sending them to the DCC by removing any PHI. Upon receipt, DCC personnel will review the records to ensure that no PHI is visible.

9.3.3 Data and Biosample Sharing

Research results will be made available to the scientific community and public in a timely manner. The primary method by which data will be shared with the scientific community will be through peer-reviewed publications and presentation at scientific and professional society meetings. In addition, data and results will be submitted to the NIH in the annual progress reports required under the terms and conditions of the funding award. This study will also be registered with clinicaltrials.gov before initiation.

Data from the study will be submitted to the NIDDK Data Repository in accordance with the NIDDK Data Sharing policy. The policy requires that data sets be transferred no later than 2 years after study completion or 1 year after publication of the primary results, whichever comes first. Through the repository, the study data will be made available to external investigators.

A portion of the serum and plasma collected at Baseline and Weeks 12, 24, and 28, as well as extracted DNA, will be submitted to the NIDDK Biosample Repository for future investigations. The NIH Data and Biosample Repositories will meet all NIH standards, and will provide data and/or specimens to researchers in accordance with IRB, HIPAA, and NIH procedures that protect the confidentiality of participants.

9.3.4 Records Retention

The site investigators will retain study documents, including participant files and Regulatory Binders, for at least 5 years after the close of the study, or longer depending on site institutional requirements.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

A monitoring plan that may include formal visits to the Clinical Centers by members of the Consortium (DCC, Clinical Center investigators and study coordinators, and NIDDK representatives) will be developed by the Consortium Executive Committee. Clinical Center investigators will allocate adequate time for such monitoring activities. The Principal Investigator will also ensure that the monitor and other compliance or quality assurance reviewers are given access to study-related documents and study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and have adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The DCC and Clinical Center investigators will permit study-related monitoring, audits, and inspections by the IRB, the NIH, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The DCC and Clinical Center investigators will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institution compliance and quality assurance offices.

11 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice, all applicable government regulations, and all local institutional research policies and procedures. .

This protocol and any amendments will be submitted to properly constituted IRBs, in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the

conduct of the study will be made in writing to the Clinical Center investigator and a copy of this decision will be provided to the DCC before commencement of the study at the site.

All study participants will be provided a consent form describing the study and providing sufficient information to make an informed decision about participating in the study. The consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a participant, using the IRB-approved consent form, must be obtained before that participant undergoes any study procedure. The consent form must be signed by the participant or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through grants from the National Institute of Diabetes and Digestive and Kidney Diseases of the U.S. National Institutes of Health. Anakinra and placebo and financial support for centralized ascertainment of patient-reported outcomes is provided by Sobi (Stockholm, Sweden).

12.2 Conflict of Interest

All investigators will follow the conflict of interest policies of the NIDDK and the National Institutes of Health, as well as their home institution. Any investigator who has a potential conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor before participation in this study.

12.3 Participant Stipends or Payments

Participants will be compensated for participating in the study. Compensation approaches will be determined by the Clinical Centers and approved by the local IRB.

13 Publication Plan

Neither the complete, nor any part of, the results of the study carried out under this protocol, nor any of the information provided by the Hemodialysis Novel Therapies Consortium for the purposes of performing the study, will be published or passed on to any third party without the consent of the Consortium Executive Committee and Steering Committee. Any investigator involved with this study is obligated to provide the DCC with results of all study-related testing and all data derived from the study.

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15 Attachments

15.1 Study Procedures

	SCREENING			BASELINE / RANDOM-IZATION	STUDY DRUG TREATMENT							Post-Treatment Follow-Up					
Procedure	**Pre screening**	**1st Screening Visit Day -30 to Day -14**	**2nd Screening Visit Day -10 to Day -1**	**Baseline Visit Day 0**	**Weeks 1-3**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**
Preliminary eligibility assessment	X																
Informed consent		X															
Confirm eligibility		X	X	X													
Demographics & medical history		X															
Concomitant medications		X		X	X	X	X	X	X	X	X	X					
CRP		X	X	X		X	X	X	X	X	X	X					
CBC with differential		X	X			X	X	X	X	X	X	X					
Serum pregnancy (WOCBP)[1]			X			X	X	X	X	X	X	X					
Testing for TB, Hep B/C, HIV			X														
Adverse events				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood collection for batched assays				X				X			X	X					
Physical Exam, Vital Signs Assessment				X													
FACIT-Fatigue				X				X			X	X					
BDI-II				X				X			X	X					
Dialysis Symptom Index				X				X			X	X					
Illness Effects Questionnaire				X				X			X	X					
KDQOL-SF12				X				X			X	X					
Hand Grip				X				X			X	X					
Study Drug Administration					3X / week at hemodialysis												
Drug Tolerability					X	X	X	X	X	X	X	X					

[1]Woman of childbearing potential includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal.

15.2 DSMB Charter

Data and Safety Monitoring Board (DSMB) Charter
Hemodialysis Novel Therapies Consortium

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) to monitor patient safety and evaluate the efficacy of the interventions. The Hemodialysis Novel Therapies Consortium – ACTION Trial is funded by the NIDDK.

DSMB RESPONSIBILITIES

The initial responsibility of the DSMB will be to review the study protocols, consent documents and plans for data safety monitoring, and approve the initiation of these clinical trials. After this approval, and at periodic intervals during the course of the trials, the DSMB responsibilities are to:

- review and approve major changes in the research protocol, informed consent documents and plans for data safety and monitoring, including all proposed revisions;
- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that may affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- protect the safety of the study participants;
- report on the safety and progress of the trial;
- make recommendations to the NIDDK, the Steering Committee and, if required, to the Food and Drug Administration (FDA) and the Institutional Review Boards (IRBs) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- if appropriate, conduct interim analyses of efficacy in accordance with stopping rules which are clearly defined in advance of data analysis and have the approval of the DSMB;
- ensure the confidentiality of the trial data and the results of monitoring;
- assist the NIDDK by commenting on any problems related to study conduct, enrollment, sample size, and/or data collection.

MEMBERSHIP

The DSMB will consist of at least eight members. Five participating members will constitute a quorum. The members have been appointed by the NIDDK. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the studies. Collaborators or associates of the investigators in this trial are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required.

Dr. Paul Palevsky of University of Pittsburgh School of Medicine has been selected by the NIDDK to serve as the DSMB Chairperson for the remainder of the study. He is responsible for overseeing the meetings and developing the agenda in consultation with the NIDDK Program Directors, Dr. Paul Kimmel and Dr. John Kusek. Dr. Kusek will serve as the DSMB Executive Secretary. The Chairperson is the contact person for the DSMB. Other NIDDK official (s) or NIDDK appointee (s) may serve as an ex-officio member (s) of

the DSMB. The DCC, University of Pennsylvania, shall provide the logistical management for the DSMB, in coordination with NIDDK (Dr. Yining Xie, as point of contact). Whenever possible, Dr. Robert Star, Director of the Division of Kidney, Urology and Hematology of NIDDK will also attend meetings.

BOARD PROCESS

The DSMB will meet a minimum of once a year at the call of the Chair, with advance approval of the NIDDK Program Director. An NIDDK representative will be present at every meeting.

Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the principal investigator(s) of the DCC and members of his/her staff, and by Clinical Center investigators, as needed. Meetings may be convened as conference calls/webinars as well as in person. An emergency meeting of the DSMB may be called at any time by the Chairperson or by the NIDDK Program Director should questions of patient safety arise. The DSMB Chairperson should contact the NIDDK Program Director prior to convening the meeting.

MEETING FORMAT

An appropriate format for DSMB meetings consists of open, closed and executive sessions. This format may be modified as needed. A brief closed and/or an executive session will usually be held before the open session.

Open Session:

The members of the DSMB, the NIDDK staff, the steering committee, including the study biostatistician will attend the open session. Issues discussed will include the conduct and progress of the study, including patient recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the study. Protocol amendments may also be presented in this session.

Closed Session:

The closed session will be attended by voting DSMB members, representatives from the NIDDK, or its appointees, and the study biostatistician. **The discussion at the closed session is completely confidential.**

Analyses of blinded outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups. However, the DSMB may request unmasking of the data for either safety or efficacy concerns.

Executive Session:

The executive session will be attended by voting DSMB members, and the NIDDK Staff, or its appointees.

The DSMB will discuss information presented to it during the closed and open sessions and decide whether to recommend continuation or termination, protocol modification or other changes to the

conduct of the study in the Executive Session. The DSMB can become unblinded if trends develop either for benefit or harm to the participants.

Should the DSMB decide to issue a termination recommendation, a full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended. Reasons for early termination may include:

- Serious adverse effects in the entire intervention group or in a dominating subgroup;
- Greater than expected beneficial effects;
- A statistically significant difference by the end of the study is improbable;
- Logistical or data quality problems so severe that correction is not feasible.

Final Open Session (optional):

The final session may be attended by voting DSMB members, steering committee members, the study biostatistician or other study members, and the NIDDK staff.

The Chairperson of the DSMB or the NIDDK Staff shall report on the recommendations of the DSMB regarding study continuation and concerns regarding the conduct of the study. Requests regarding data presentation for subsequent meetings will be made. Scheduling of the next DSMB meeting may be discussed.

REPORTS

Interim Reports: Interim reports will be prepared by the Data Coordinating Center, located at the University of Pennsylvania. The reports will be distributed to the DSMB and the NIDDK Program Director at least 7 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports generally consist of two parts:

Part 1 (**Open Session Report**) provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. This report is generally shared with all investigators involved with the clinical trial. The reports contained in this section may include:

- Comparison of Target Enrollment to Actual Enrollment by Month
- Comparison of Target Enrollment to Actual Enrollment by Site
- Overall Subject Status by Site, including: Subjects Screened, Enrolled, Active, Completed and Terminated
- Demographic and Key Baseline Characteristics by Group
- Treatment Duration for Subjects who Discontinue Therapy
- Adverse Events/Serious Adverse Events by Site and Subject

Part 2 (**Closed Session Report**) may contain data on study outcomes, including safety data, including serious adverse events or termination. Data will be presented by masked treatment groups; however, the DSMB may request that the treatment groups be unmasked to ensure that there are no untoward treatment effects. This report should not be viewed by any members of the clinical trial except the designated study statistician.

Reports from the DSMB: A formal report containing the recommendations for continuation or modifications of the study, prepared by the Executive Secretary with concurrence of the DSMB, will be sent to the Chair of the Steering Committee and the DCC PI. This report will also contain any recommendations of the NIDDK in reference to the DSMB recommendations. It is the responsibility of the DCC PI to distribute this report to all other PIs and to assure that copies are submitted to all the IRBs associated with the study.

Each report should include a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The NIDDK is responsible for notifying the Chair of the Steering Committee of a decision to terminate the study. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data, discussion of the unblinded data, or any other confidential data.

Mailings to the DSMB: On a scheduled basis, (as agreed upon by the DSMB) blinded safety data should be communicated to all DSMB members and the NIDDK Program Director. Any concerns noted by the DSMB should be brought to the attention of the NIDDK Program Director.

Access to Interim Data: Access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to interim data to the DSMB members relieves the investigator of the burden of deciding whether it is ethical to continue to randomize patients and helps protect the study from bias in patient entry and/or evaluation.

CONFIDENTIALITY

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.