COVER PAGE

Official Study Title: NIRVANA: NIcotinamide Riboside in SARS-CoV-2 pAtients for reNAl protection

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NIRVANA: NIcotinamide Riboside in SARS-CoV-2 pAtients for reNAl protection

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

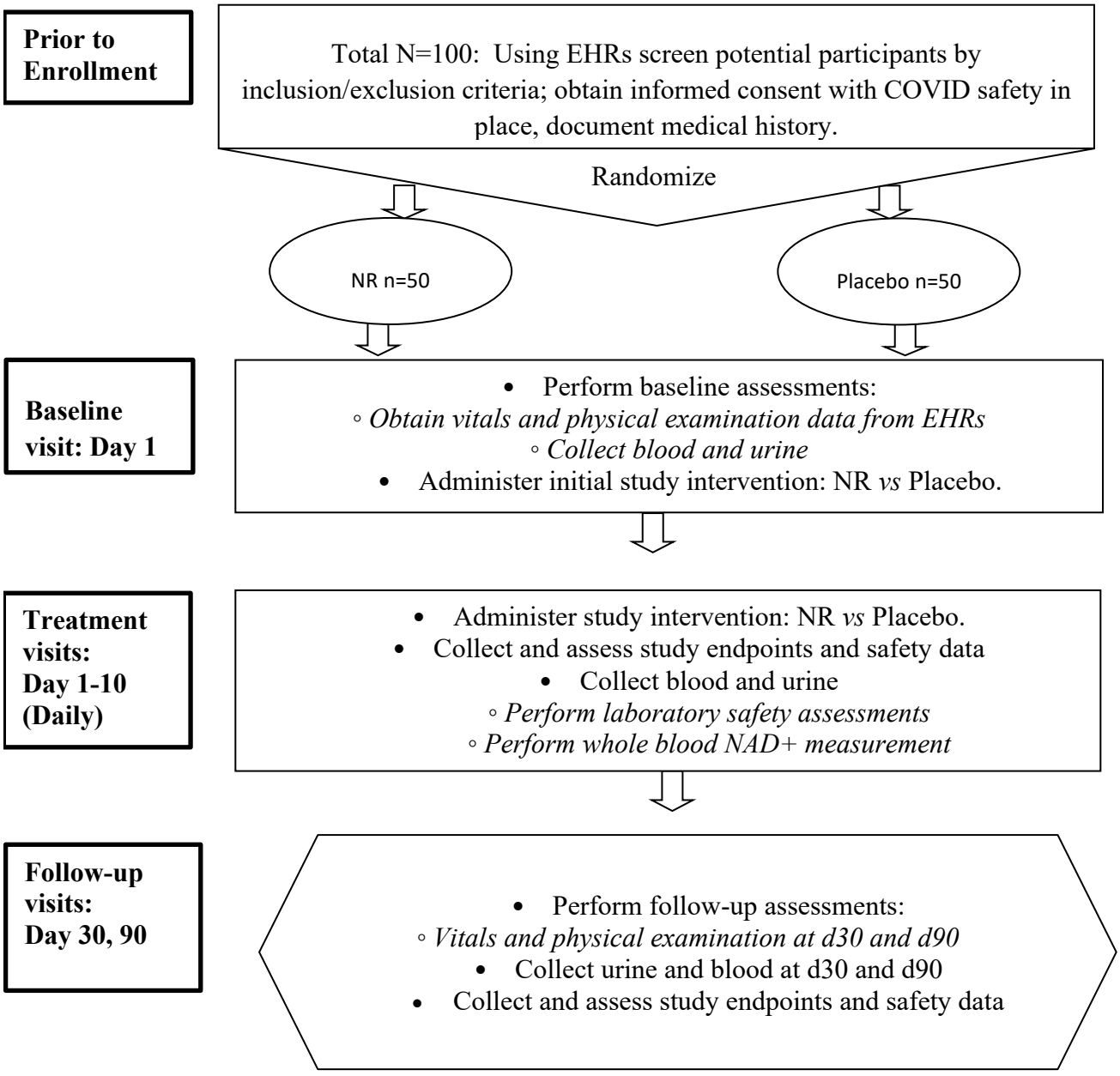
1.1 SYNOPSIS

Title	NIcotinamide Riboside in SARS-CoV-2 pAtients for reNAl protection (NIRVANA)
Study Description	*A pilot, double-blind, placebo-controlled, multicenter, interventional clinical trial with oral nicotinamide riboside (NR) 500 mg (versus placebo) twice daily for a total of 10 days in hospitalized participants with COVID-19.*
Objectives	***Primary***
	• *To determine the effect of nicotinamide riboside (NR) on whole blood NAD+ levels in hospitalized patients with COVID-19 infection and AKI during the 10-day intervention period;* • *To evaluate the safety of NR in patients with COVID-19 infection and AKI during the 10-day intervention period;*
	Secondary
	• *To determine the effect of NR on changes in area under curve (AUC) serum creatinine from baseline during the 10-day intervention;* • *To determine the effects of NR on serum creatinine AUC, dialysis, and death with an ordinal categorical outcome having four categories (labeled 1, 2, 3, 4), defined as, in order from least to most severe disease, 1. Serum creatinine AUC < median, 2. Serum creatinine AUC ≥ median, 3. Dialysis, 4. Death during the 90d period post randomization;* • *To determine the effect of NR on MAKE (Major Adverse Kidney Events; composite criteria defined as development or progression of chronic kidney disease, the initiation of long-term dialysis, or death from any cause) at 30d and 90d post randomization;* • *To determine the effect of NR on degree of kidney impairment defined with estimated glomerular filtration rate (eGFR) and proteinuria at 30d and 90d post randomization;*
	Exploratory
	• *To determine the relationship of whole blood NAD+ levels with AUC creatinine and surrogate markers of AKI such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL);*
Endpoints	***Primary***
	• *Rates of change in whole blood NAD+ level from baseline to day 10 in NR compared to Placebo.* • *Safety of NR in hospitalized patients with COVID-19 and AKI (defined as the occurrence of at least one serious adverse event of grade 3 or higher or the occurrence of thrombocytopenia (>25% decline in blood platelet count from baseline value).*

	Secondary
	• *Rates of change in AUC serum creatinine benchmarked to baseline from baseline to day 10 in NR compared to Placebo;* • *An ordinal categorical outcome with four categories (labeled 1, 2, 3, 4), defined as, in order from least to most severe disease, 1. Serum creatinine AUC < median, 2. Serum creatinine AUC ≥ median, 3. Dialysis, 4. Death;* • *Time to first occurrence of MAKE (doubling of serum creatinine, the initiation of long-term dialysis, or death from any cause) at 30 d and 90 d post randomization;* • *Kidney function defined by eGFR and proteinuria at 30d and 90d post randomization.*
	Exploratory
	• *Correlations between whole blood NAD+, AUC serum creatinine, and AKI surrogate markers of AKI such as KIM-1 and NGAL;*
Study Population:	*Participants will be >18 years old and admitted to hospital with a laboratory diagnosis of COVID-19 infection and AKI*
Phase:	*Phase 2*
Description of Sites/Facilities Enrolling Participants:	*The study is a multicenter study with University of Texas Health San Antonio (UTHSA) as the coordinating site. The three recruiting sites are: University Hospital affiliated with UTHSA, Icahn School of Medicine at Mount Sinai, New York, NY and Harborview Medical Center/University of Washington, Seattle, WA*
Description of Study Intervention:	*The intervention for this clinical trial is Niagen®, a nicotinamide riboside, an over the counter nutritional supplement*
Study Duration	*Estimated 2 years*
Participant Duration:	*The estimated time required for this study will be up to 90 days after consenting to study protocol. A total of up to 10 visits will occur during the initial 10 days with two follow-up visits – 30 days and 90 days from enrollment date.*

1.2 SCHEMA

Flow diagram of the NIRVANA Study



COVID, Corona virus disease; EHR, Electronic health records; NR, Nicotinamide Riboside

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1. Schedules of activities

Study Period ⇒	Screening	Treatment Period										Follow-up	
Visit Encounter ⇒ / **Procedure**	Visit 0/ Day 0	Visit 1/ Day 1 (Baseline)*	Visit 2/ Day 2	Visit 3/ Day 3	Visit 4/ Day 4	Visit 5/ Day 5	Visit 6/ Day 6	Visit 7/ Day 7	Visit 8/ Day 8	Visit 9/ Day 9	Visit 10/ Day 10	Visit 11/ Day 30 ± 3	Visit 12/ Day 90 ±3
Eligibility criteria	X												
Informed consent	X												
Demography	X												
Medical history	X												
Concomitant medications[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
STUDY INTERVENTION													
Randomization[2]		X											
Study drug administration[3]		X	X	X	X	X	X	X	X	X	X		
STUDY PROCEDURES													
APACHE-II	X	X	X	X	X	X	X	X	X	X	X		
Endpoint assessment		X	X	X	X	X	X	X	X	X	X	X	X
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X
Respiratory parameters[4]	X	X	X	X	X	X	X	X	X	X	X		
Mortality, ICU transfer, length of stay	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine output[5]		X	X	X	X	X	X	X	X	X	X		
CLINICAL LABORATORY													
Blood analysis[6]		X	X	X	X	X	X	X	X	X	X	X	X
SAFETY LABORATORY													
Blood analysis[7]		X	X	X	X	X	X	X	X	X	X	X	X
RESEARCH LABORATORY and REPOSITORY													
Blood and urine[8]		X	X	X	X	X	X	X	X	X	X	X	X

APACHE-II, Acute physiology and chronic health evaluation II; AE, adverse events; ICU, Intensive care unit;
** Baseline (Day 1) assessments should be performed prior to study drug administration;*
[1] Includes all inhospital and home medications (standard of care treatment, prescription, over-the-counter, supplements);
[2]Dosing of the first study drug will be administered as soon as possible (within 6 hours of obtaining consent and negative pregnancy test for women with childbearing potential);
[3] Participants who will be discharged or leave hospital before Day 10 intervention will be provided with study pills for the remaining days.
[4] Respiratory rate, FiO_2, O_2 saturation, ventilator parameters, if applicable and participant is hospitalized;
[5] Urine output data based on medical records or from first morning urine collections if discharged from hospital;
[6]Any laboratory tests performed as part of routine clinical care within the specified visit day may be used for safety laboratory testing by extracting values from the EHR;

[7] Creatine phosphokinase and liver function tests will be performed on Day 5 (see Table 4)
[8] Whole blood NAD+ and serum creatinine will be collected daily before study medication dosing; Blood will be collected at 3-hour and 6-hour post-randomization for future pharmacokinetics; Blood and urine for biomarkers will be collected at Baseline and daily during the intervention period, at day 30 ± 3 and day 90 ± 3;
[‖] If the participant is still hospitalized then inpatient safety laboratory test results will be collected from EHR

2 INTRODUCTION

2.1 STUDY RATIONALE

Impaired mitochondrial function has been recently recognized as a major mechanism for acute kidney injury (AKI) in septic shock and ischemia-reperfusion injury [1-5]. A major feature that limits mitochondrial function is the reduction of electron donors to the mitochondria in the form of nicotinamide adenine dinucleotide (NAD+). Reduced levels of NAD+ have been implicated in both animal models and humans with AKI, and stimulation of pathways that lead to enhancement of NAD+ appears to be beneficial [3, 4, 6]. Recent studies using oral nicotinamide (NAM) and nicotinamide riboside (NR) as NAD+ donors have found these agents to be safe, well-tolerated, and upregulate NAD+ pathways in a dose-dependent manner [7, 8]. NR provided *after* organ injury was found to be protective in pre-clinical studies [9, 10]. It has been demonstrated that NR is more orally bioavailable than NAM, safe in obese participants, and beneficial in many pre-clinical models of organ dysfunction [7, 8, 11-14]. NAM use during the perioperative period in participants undergoing cardiothoracic surgery showed reduced incidence of AKI in a pilot study [5]. NR use (in combination with pterostilbene, PT; NRPT) was found to increase NAD+ levels in patients with AKI as compared to the placebo group [15].

The kidneys are highly active metabolically, contain a high density of mitochondria, and consume the highest amount of oxygen after the heart. Mitochondrial energy (adenosine triphosphate or ATP) production requires the universal cofactor nicotinamide adenine dinucleotide (NAD). This essential metabolite serves as a key cofactor in a plethora of mitochondrial metabolic processes that facilitate energy production as well as several other important cellular functions [16]. Consistent with these key roles of NAD+, various stressors have been associated with decreased NAD+ levels [15], contributing to disease pathogenesis.

Rationale for Study Design:

We chose a treatment protocol with NR as a treatment for patients who will be admitted with COVID-19 related illness and develop AKI after admission. Treatment duration will be for 10 days and the primary study endpoint will be the change in whole blood NAD+ from baseline (to 10d, 2d, AUC) in NR group vs placebo group. We will evaluate whole blood NAD+ levels as a marker of efficacy and biological effect of NR based on two recent publications [8, 15]. We evaluated using a marker of efficacy for NR with the whole blood NAD+ based on two recent publications [8, 15]. In a study of healthy overweight subjects 40-60 years of age, Conze et al.

[8] found a 21 µg/ml mean NAD+ difference between patients randomized to 1000 mg NIAGEN® versus those randomized to placebo at day 7 (NIAGEN 42 µg/ml, Placebo 21 µg/ml) with a standard deviation of 10 µg/ml and approximately equal baseline means (NIAGEN 21 µg/ml, Placebo 24 µg/ml). Simic et al. [15] assessed a combination of NR with pterostilbene (NRPT) vs placebo in hospitalized patients of age ≥ 18 years with AKI and found an 18% increase in whole blood NAD+ within 48h post treatment in the NRPT group, and a 50% reduction from baseline in the placebo group with AKI. With reference to Conze et al. [8] al., this study will achieve >99.9% power for testing H_o:$R_{NR} = R_{Placebo}$ versus Ho: $R_{NR} \neq R_{Placebo}$ with alpha=0.05, autocorrelation (ρ)=0.5, and n=40 per arm where R_{NR} and $R_{Placebo}$ are the rates of change from baseline to day 10 in the NR and Placebo arms, if the effects observed in this study are the same as those observed by Conze et al. with regard to NAD+. In this setting the effect size is 2.1 [=(42-21)/10] and the minimally detectable effect size is 0.63.

Safety of NR will also be assessed as a primary endpoint in this study. Although NR is generally recognized as safe or GRAS [17] and has been demonstrated to be well-tolerated with mild, if any side effects, reported using variables doses from 100 mg/day up to 2000 mg/day [8, 11, 12] it will be informative to assure that serious adverse events (SAEs) are not increased with NR in patients with COVID-19 infection and AKI.

We also plan to assess the AUC of serum creatinine benchmarked to baseline and other clinical outcomes as secondary endpoints to determine if there are trends indicating that NR may be a promising treatment for hospitalized COVID-19 infected patients who develop AKI. We will also correlate whole blood NAD+ levels with AUC creatinine with well described surrogate markers of AKI (KIM-1, NGAL) as an exploratory outcome measure. If we demonstrate that NR increases whole blood NAD+ in COVID-19 positive patients with AKI and is safe, this result would be a compelling finding to support further clinical trials with NR in this population. Further support for future studies would be obtained from our secondary endpoints and will of great value in establishing power calculations for future definitive studies [9, 10].

Upon completion of the NRIVANA study, we plan to pursue a Phase IIb or Phase III study based on the following scenarios:

1. Demonstrate significant increase in whole blood NAD+ level in the NR group compared to placebo ($p<0.05$), no significant increase in harm with NR treatment and a positive trend or improvement in any one of the secondary outcomes ($p<0.2$) would warrant a future Phase III study.
2. Demonstrate significant increase in whole blood NAD+ level in the NR group compared to placebo ($p<0.05$) and no significant increase in harm with NR treatment would warrant a Phase IIb study.
3. Demonstrate significant improvement in any one of the secondary outcomes with NR compared to placebo ($p<0.2$) and no significant increase in harm with NR treatment would warrant a Phase IIb study.

In a future Phase III clinical trial, we envision the primary endpoint would be the MAKE (Major Adverse Kidney Events) – the proportion of subjects who develop any of the components of MAKE at d90 post randomization. In the NIRVANA study MAKE is one of the secondary endpoints.

2.2 BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the novel coronavirus 2019 disease (COVID-19), is responsible for the global pandemic which is taking a tremendous toll in the form of human morbidity and mortality. SARS-CoV-2 infection is unpredictable in its course as it may be asymptomatic in some patients but rapidly develop life-threatening complications in others leading to multisystem organ failure [18-21]. Kidney involvement is prominent in admitted patients with COVID-19 pneumonia with 75% exhibiting proteinuria, hematuria, or AKI [22]. In a comprehensive analysis of 5,449 patients admitted with COVID-19, AKI developed in 1,993 patients for an incidence rate of 37% [23]. The incidence of AKI is even higher (68%) in COVID-19 patients admitted to the intensive care unit (ICU) as reported from New York City [24]. Moreover, up to 86% of deaths in COVID-19 patients were associated with AKI [22]. The overall mortality in hospitalized COVID-19 infected patients was originally found to be 25.6% however more recent studies find the mortality rate to be now at about 7.6% [25]. The basis for AKI with COVID-19 is not known. The N3C database, as of 18 November 2020, indicated that of 1213 hospitalized COVID-19 patients with AKI satisfying our entry criteria and not satisfying our exclusion criteria, a total of 120 (9.9%) died. The actual dates of death are not known.

The pathophysiology of AKI is multifactorial, and, in many cases, the precise mechanism of AKI is unclear [26, 27]. Currently there is scarcity of data with regard to the underlying pathogenesis of AKI in SARS-CoV-2 patients. However, the “cytokine storm” appears to be the primary contributing factor to AKI and disease severity in patients with COVID-19 [28, 29]. Based on clinical observations, AKI occurs in critically ill patients with COVID-19 that are under severe metabolic stress originating from maladaptive systemic inflammatory immune response, hypoxemia, ischemia, microthrombi, sepsis, and toxins (e.g., rhabdomyolysis) [28]. The kidneys may also be the site for direct invasion of SARS-CoV-2 due to the high expression of ACE2 in renal tubular epithelial [30, 31]. Therefore, it is possible that inflammatory events and/or direct SARS-CoV-2 infection of renal cells lead to a metabolic derangement affecting the NAD+ metabolome and consequent mitochondrial dysfunction leading to AKI. At the present time there is no targeted treatment for AKI. Given the role of mitochondrial function and NAD+ in other models of AKI and multi-organ failure associated with infection and inflammation, we postulate that a similar process of reduced NAD+ and reduced mitochondrial function may underlie AKI with COVID-19 infection.

NR and NAD restoration in animal studies of organ injury

Mice receiving intraperitoneal administration of NR at 185 mg/kg for 6 days had about 100-fold increase in nicotinic acid adenine dinucleotide in the heart [32]. Another study also demonstrated that mice with NR administration of 400 mg compound/kg body weight per day caused increase of NAD+ levels in muscle and liver [33]. Interventional studies also showed beneficial effects of NR on specific organ injury. NR significantly reduced non-fasting and fasting blood glucose, weight gain and hepatic steatosis and protected neuropathy in diabetic mice supplemented with 3 g of NR per kg of their diet [32]. A study in rats of intestinal ischemia-reperfusion found that administration of NR (50 mg/kg) at end of ischemia period and early reperfusion led to endothelial protection and intestinal wall protection from reperfusion injury [9]. NR supplementation to murine models of dilated cardiomyopathy or heart failure restores myocardial NAD levels and preserves cardiac function via induction of the nicotinamide riboside kinase 2 (NMRK2) pathway for NAD+ synthesis [10]. Others also demonstrated that NR can prevent alcohol or non-alcohol induced liver injuries via replenishing NAD+, reducing oxidative stress, activating SIRT1-PGC-1α-mitochondrial biosynthesis or sirtuin (SIRT)1- and SIRT3-dependent mitochondrial unfolded protein response [34-36].

Therefore, a therapeutic to safely restore mitochondrial function in patients with recent onset AKI may be of major benefit to reduce the severity of AKI in newly admitted patients with COVID-19. We specifically hypothesize that supplementation with NR will reduce the severity of AKI in newly admitted SARS-CoV-2 patients.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The study drug NR may not prevent or treat the disease, or the condition of the participant or disease may worsen, but there is currently no accepted standard of care to prevent or treat AKI. As with any research study, there is a potential for side effects to occur with the administration of the study drug. All participants will be closely monitored on a daily basis for adverse events (AEs) defined as changes in health condition and laboratory parameters from baseline (Day 1). Few side effects have been identified for the use of NR, but the side effects that have been reported such as nausea, back soreness and muscle soreness have been typically mild [8].

NR is a formal precursor of NAD+ and naturally present in certain foods including milk. After absorption, NR enters the cell, and is metabolized into nicotinamide mononucleotide (NMN) by a phosphorylation step catalyzed by the nicotinamide riboside kinases (NRKs). NMN is subsequently converted to NAD by nicotinamide nucleotide adenylyltransferases (NMNAT1-3). However, the quantities in foods are quite low, and probably do not exceed the low micromolar range [37]. In the USA, NR is considered as GRAS or Generally Recognized as Safe for use in food products which supports its rapid implementation as a drug-like therapy [17].

NR has been demonstrated to be well-tolerated with mild, if any side effects reported using variables doses from 100 mg/day up to 2000 mg/day [8, 11, 12]. The current study intervention is 1000 mg/day administered as 500 mg twice a day.

NR was recently evaluated in a single center, double blind, placebo-controlled, and crossover study in which 12 elderly participants received 500 mg NR twice a day for 21 days. In this study NR was well tolerated without any SAE including no changes in hematological and clinical biochemistry safety parameters – i.e., renal, liver, and thyroid functions [14]. The reported symptoms included nausea, flushing, leg cramps and increased bruising in the NR group and headache, skin rash, flushing, fainting and drowsiness in the placebo group [7].

A dose escalation study was performed in 8 healthy subjects in a non-randomized, open-label pharmacokinetics (PK) study with 250 mg NR orally administered on days 1 and 2, then uptitrated to peak dose of 1000 mg twice daily on days 7 and 8. No clinically significant changes were seen at NR dose up to 1000 mg orally twice daily in any of the five pre-specified safety endpoints, i.e., potassium, creatine phosphokinase (CPK), glucose, uric acid and alanine aminotransferase. Serum potassium decreased by an average of 0.4 mEq/L, which was statistically significant ($p = 0.015$) but the individual levels remain in normal range. There was a slight though statistically significant decrease for hematocrit (mean difference = –2%, $p = 0.005$), hemoglobin (-0.4 g/dL, $p = 0.04$), and platelet count (-20,000/μL, $p = 0.03$). There were no significant changes in blood pressure, body temperature, body weight, white blood cell count, lactate dehydrogenase or aspartate aminotransferase. In addition, there were no significant changes in serum levels of sodium, chloride, urea nitrogen, creatinine, or in white blood cell differential [38].

In an investigator-initiated randomized, placebo-controlled, double-blinded study of 40 healthy men with BMI> 30 kg/m^2 NR was administered at a dose of 1000mg twice daily for 12 weeks [39]. Adverse events (AEs) were reported in 4 subjects in the NR group which included pruritis, excessive sweating, bloating and transient changes in stool. There were two AEs in the placebo group which were acid reflux and loose stools. The severity was mild in all cases. Laboratory analysis for blood counts and chemistries at 6 weeks revealed no abnormalities in the NR group.

A recent report evaluated a combination of NR with an anti-oxidant pterostilbene (PT; NRPT) in 24 hospitalized patients with AKI with a single dose ranging from 250mg NR, 500mg NR, 750mg NR to 1000mg NR twice a day [15]. Compared to the baseline timepoint, NRPT dose 500 mg/100 mg twice a day increased whole blood NAD+ levels 47% at 48 h, ($p = 0.04$). Whole blood NAD+ levels in patients with AKI receiving placebo decreased by 50% at 48 h ($p = 0.05$). Compared to placebo, there was no significant difference in creatinine, estimated glomerular filtration rate (eGFR), electrolytes (sodium, potassium), liver enzymes (ALT, AST, ALP), hemoglobin, white blood count or platelet count in patients treated with NRPT at 48 h. NRPT

was safe at all doses in patients with AKI with only minor side effects (bloating and gas, upper abdominal discomfort) reported that resolved without intervention. There were no side effects in placebo group. There was no SAE in either group [15].

Safety of NRPT (up to 500mg NR + 100mg PT/day) has also been evaluated in a randomized, placebo-controlled, double-blind study in a population of 120 healthy adults between the ages of 60 and 80 years for 8 weeks [40]. There was a total of six AEs – nausea, fatigue, headache, dyspepsia, abdominal discomfort, and diarrhea with mild to moderate intensity.

In the largest study to date, 140 healthy male and female participants (40-60 years of age) underwent a randomized, placebo-controlled study with 4 groups: placebo (n=35), 100 mg group (n=35), 300mg/d (n=35) and 1000mg/d (n=35) and supplementation was provided for 56 d [8]. One subject in placebo group dropped out due to nausea, one subject was withdrawn from 300 mg group due to non-compliance, two subjects in the 100 mg and two in the 1000 mg group withdrew consent and one subject in the 1000 mg group was lost to follow-up. Compliance ranged from 97.1%-99% across all groups. There were no serious adverse events (SAEs) and the type, incidence and severity of the AEs were similar across all groups – 17 participants in placebo group, 16 in 100 mg/d group, 14 in 300mg/d group and 14 in 1000mg/d group. There were a total of 22 AEs in the 1000mg NR group with 3 being reported as possibly related to study drug: sore back, muscle soreness, and nausea with mild in intensity. Hematological and chemistry profiles were similar in all groups. The effects of NR on muscle metabolism has been studied [14, 33]; however, these studies did not measure serum cystatin C or CPK.

There are paucity of data regarding the safety profile of NR in patients with CKD. Two clinical trials of NR in patients with eGFR 20-60 mL/min/1.73m2 are ongoing [41, 42]. Forms of vitamin B3 nicotinic acid (pyridine-3-carboxylic acid or niacin) and its circulating amide derivative nicotinamide (pyridine-3-carboxamide, NAM) have been tested in advanced CKD patients undergoing hemo- and peritoneal dialysis patients [43]. One randomized, placebo-controlled clinical trial tested NAM (750 mg twice daily) alone and in combination with lanthanum carbonate among individuals with eGFR 20–45 ml/min per 1.73 m^2 for 12 months [44]. This study reported severe nausea, severe diarrhea, flushing, hives, bruising and bleeding in the NAM group (n=51) which were not significantly different than that reported in the placebo group with the exception of hives. It is important to note that this particular study did not find any evidence of thrombocytopenia (platelet count <100,000/mm^2), liver function abnormalities, and elevated CPK (>800 U/L) in the NAM group compared to the placebo group [44]. In patients with hemodialysis, the documented safety profile of NAM included primarily flushing, pruritus, hypotension, hepatotoxicity, and gastrointestinal upset. Most studies reported NAM associated transient thrombocytopenia without any bleeding events in hemodialysis patients which returned to normal range within weeks of discontinuation of intervention [43, 45, 46]. In contrast, studies conducted in peritoneal dialysis patients did not report such hematologic changes associated with

NAM [47]. It should be noted that NR does not induce prostaglandin-mediated flushing or vasodilatory responses [48]. One study tested NAM 100 mg twice daily for 6 months in pediatric population (age 7-17 yrs) with hyperphosphatemia undergoing maintenance hemodialysis [49]. NAM group reported diarrhea, nausea, vomiting, and flushing which were not significantly different from the control group and did not result in withdrawal from the study. Despite a significant decline in mean platelet count from the baseline in the NAM group, the platelet level remained within the normal range and none of the participants experienced any bleeding disorder.

N-methyl-2-pyridone-5-carboxamide or 2PY, a major metabolite of NAM, is considered a uremic toxic in patients with impaired renal function [50, 51]. While serum 2PY level may increase significantly with NAM supplementation [46], the intracellular concentration may not rise compared to baseline in hemodialysis patients [52]. In general, available data conclude that NAM is safe and tolerable in adults at doses of below 3 g/day [53]. Taken together the available safety data of niacin and NAM indicate that in patients with impaired renal function both agents are tolerable [54-56]. The prominent side effects of NAM at therapeutic doses (i.e., 1000 mg/day) are gastrointestinal symptoms (mainly diarrhea) that generally resolve on treatment withdrawal or discontinuation. Develeopement of hetatoxicity require massive dose of NAM – 9 g/day and prolong therapy for months may cause thromobocytopenia [55, 56].
Based on the available data, the known potential risks of NR can be divided into those that are likely and those that are rare.

Likely

These risks are expected to occur in 5-15 participants or less out of 100 participants.

- Gastrointestinal disorders: nausea, heart burn (e.g., indigestion, gas, upper abdominal discomfort, and bloating), diarrhea, transient changes in stool;
- Musculoskeletal disorders: back soreness, muscle soreness;
- Skin disorders: pruritus, flushing, hives;
- Other disorders: leg cramps, increased bruising, excessive sweating;
- Laboratory findings: liver function abnormalities; decrease in blood urea nitrogen;

Rare

The following risk may occur at an unknown rate:

- Hematologic profile – e.g., <10% reduction in hemoglobin and platelet counts
- Allergic reaction or hypersensitivity

There is no available data on potential interactions between NR and standard treatment for comorbidities (concurrent medications) or any investigational agents for the treatment of COVID-19. Administering NR concurrently with other agents may lead to antagonism or synergy or may have no effect.

2.3.2 KNOWN POTENTIAL BENEFITS

The benefits of nicotinamide riboside (NR) administration in COVID-19 participants to prevent or treat acute kidney injury are not currently known.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This trial protocol incorporates numerous design elements to minimize risk to participants to meet human participant protection requirement. The dose of NR in this trial is comparable to the dose used in other published and ongoing clinical trials to increase blood NAD+ levels and have shown minimal to mild side effects. The duration of treatment in this trial of 10 days is significantly shorter than that of many published clinical trials with NR to reduce risk but likely sufficient to observe benefit. To further mitigate risk, we will exclude participants with concomitant niacin, nicotinamide, or NR supplementation.

The safety profile of NR has been reported in several small-scale randomized and non-randomized clinical trials involving heathy volunteers. Most of these reported risks are mild in a grading scale (see section 2.3.1). Based on prior data in healthy populations, obese participants and in those with AKI, there have been no reported major adverse events. Minor adverse events include gastrointestinal side effects, muscle and back pains. It remains possible that NR in patients with COVID-19 could have unexpected effects or make COVID-19 complications worse. The potential benefit would be less kidney injury and preservation of kidney function to reduce the degree of CKD in patients with COVID-19 infection. Taking into account the preliminary data available on the possible benefit of NR to boost NAD+ levels for kidney protection along with the relative lack of therapeutic options for AKI incidence and severity it appears to reasonably balance potential risks with possible benefit that may outweigh such risks. By appropriate daily clinical evaluation, laboratory monitoring, soliciting of symptoms and incident reporting by participants during the study, the risk to participants will be minimized.

Participants will receive the usual standard of care during hospitalization and during the 10-day active intervention period. The standard of care includes a daily review of health status, participant's report of any new symptoms and complaints, targeted physical exam and routine laboratory tests. Adverse events data will be retrieved from the electronic health records (EHR) and entered into the case report form for evaluation and comparison using the baseline values. For any missing data in the EHR and to collect additional information, the study team will obtain data from the primary care team and the participant. If participants are discharged from the hospital during the course of the study, they will be contacted by video visit or phone daily during period of intervention (first 10 days after enrollment) by a member of the study team to assess for any new symptoms or any intercurrent medical events and changes in symptoms severity from the previous day. After the 10-day interventional period, participants will have a study visit at Day 30 and Day 90 and will be asked about intercurrent events.

All collected AEs will be initially reviewed and evaluated by the site investigators. All AEs will be electronically captured into the study database. The site investigators will also make initial assessment of severity and causality. Unexpected AEs and SAEs will be submitted to an independent Safety Adjudication Committee (SAC) for further evaluation. The SAC will be composed by a team of medical monitors, one from each study site and independent of the study investigators, who will review unexpected AE /SAE data on a weekly basis during the active phase of the study. The SAC chair will meet weekly during the course of the study and be chaired by one of the independent SAC members. If a SAC member identifies a pattern of unexpected AEs or SAEs that is out of proportion to the current understanding of the natural history of the disease, the DSMB will be asked to review unblinded safety data in an ad hoc meeting. The DSMB will be appointed by the NIDDK.

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Based on the preceding assessment of risks and potential benefits, the risks to participants are reasonable in relation to anticipated benefits.

3 OBJECTIVES AND ENDPOINTS

Table 2: Study objectives, endpoints, and justification for endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
• To determine the effect of nicotinamide riboside (NR) on whole blood NAD+ levels in hospitalized patients with COVID-19 infection and AKI during the 10-day intervention period; • To evaluate the safety of NR in patients with COVID-19 infection and AKI during the 10-day intervention period.	• The primary endpoint is the rate of change in whole blood NAD+ level over the 10 day period from baseline to day 10. • Safety of NR in hospitalized patients with COVID-19 and AKI (defined as the occurrence of at least one serious adverse event of grade 3 or higher or the occurrence of thrombocytopenia defned as >25% decline in blood platelet count from baseline.	• Recent clinical data indicate a reduction of blood NAD+ level in AKI patients and an increase in NAD+ in 48 hrs with NR treatment; • The safety of NR in COVID-19 patients is not known
Secondary		
• To determine the effect of NR on changes in AUC	• The rate of change in AUC serum creatinine benchmarked to baseline;	• The recovery of AKI, as assessed by AUC serum

serum creatinine from baseline during the 10-day intervention; • To determine the effect of NR on serum AUC, dialysis, and death with an ordinal categorical outcome with four categories (labeled 1, 2, 3, 4), defined as, in order from least to most severe disease, 1. Serum creatinine AUC < median, 2. Serum creatinine AUC ≥ median, 3. Dialysis, 4. Death; • To evaluate the effect of NR on on MAKE (composite criteria defined as development or progression of chronic kidney disease), the initiation of long-term dialysis, or death from any cause) at 30d and 90d post randomization. • To determine the effect of NR on kidney function defined by eGFR and proteinuria at 30d and 90d post randomization.	• An ordinal categorical outcome with four categories (labeled 1, 2, 3, 4), defined as, in order from least to most severe disease, 1. Serum creatinine AUC in the first tertile, 2. Serum creatinine AUC in the second tertile, 3. Serum creatinine AUC in the third tertile, 4. Death; • Time to first occurrence of MAKE defined as doubling of serum creatinine, the initiation of long-term dialysis, or death from any cause at 30 day and 90 day post randomization; • Kidney function defined by estimated glomerular filtration rate (eGFR) and proteinuria at 30d and 90d post randomization.	creatinine during the 10 days of intervention and benchmarked to baseline, has been linked to reduced progression of chronic kidney disease (CKD). • The ordinal categories address the hierarchy of increase in severity as has been used in recent COVID-19 studies as per the World Health Organization clinical progression scale [57, 58] • AKI may progress to CKD which is associated with need for dialysis and increased mortality.
Exploratory		
• To determine the relationship of whole blood NAD+ levels with AUC creatinine and surrogate markers of AKI such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL);	• Correlations between whole blood NAD+, AUC serum creatinine, and surrogate markers of AKI such KIM1 and NGAL;	• AUC of serum creatinine is a direct assessment of the duration and severity of AKI; KIM-1 and NGAL are promising surrogate urinary biomarkers of AKI however, their clinical utility in COVID-19 patients with AKI is not known;

4 STUDY DESIGN

4.1 OVERALL DESIGN

The overall study design is depicted in Figure 1.

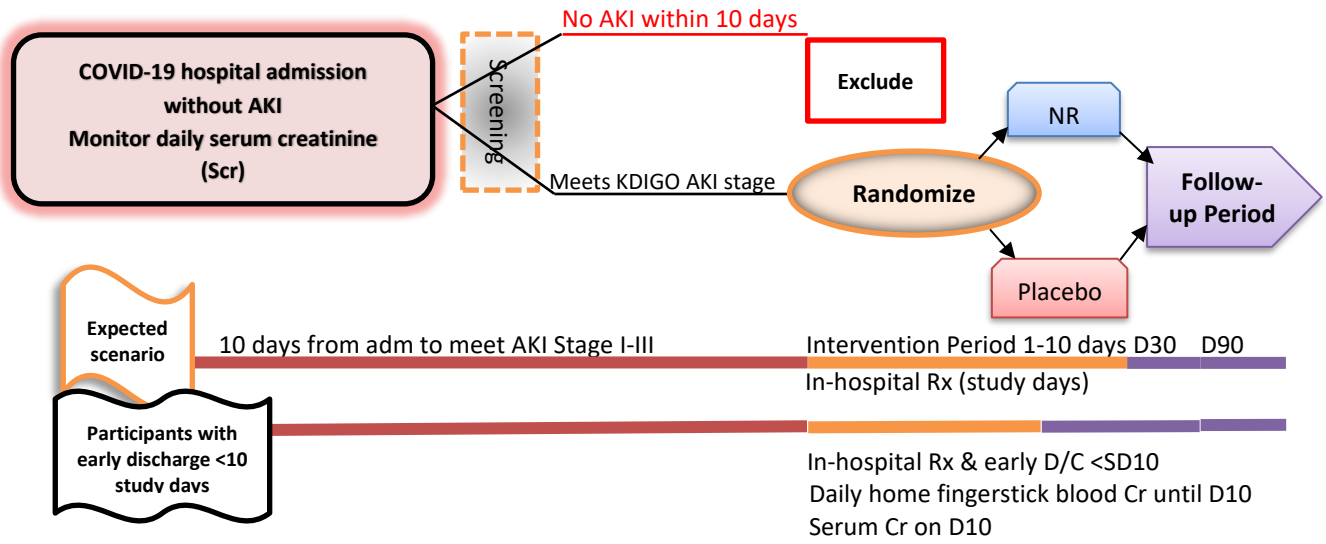


Figure 1. Study flow – screening and enrollment

- Phase 2 Study
- This is a prospective, pilot, double-blind, placebo-controlled, multicenter, clinical interventional trial
- Intervention: 2 arms – study drug (Nicotinamide riboside, NR) and placebo for 10 days
- Two follow up visits: at day 30 and day 90

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The NIRVANA Protocol describes a trial design to provide pilot data on the potential efficacy of nicotinamide riboside (NR) for the treatment of incident AKI or AKI severity in patients with COVID-19 infection admitted to the hospital while receiving available or usual standard of care.

AKI in patients with SARS-CoV-2 is being increasingly recognized as a major risk factor of morbidity and mortality. The incidence of patients with AKI ranged between 22% to 46% in independent analyses of inpatients with SARS-CoV-2 in NYC [24]. Recently, data from the Northwell Health System, NYC reported that 90% of COVID-19 patients on mechanical ventilation developed AKI [23]. The Mount Sinai Health System [24], also from NYC, documented a 3 times higher incidence of Stage 3 AKI vs Stages 1 or 2. In addition to these

extremely high morbidity indices for AKI, data from a single center in Wuhan, China reported a mortality hazard ratio of 4.7 in Stage 3 AKI patients [59]. Similar findings were found by Mount Sinai with a 52% mortality rate in patients with AKI, compared to mortality of only 9% in those without AKI admitted to the ICU. Surprisingly, 44% of SARS- COVID-19 patients with AKI did not fully recover kidney function by the time of discharge from the hospital [24]. Recent data suggest that mortality is lower in hospitalized patients with COVID-19 [25]. Therefore, strategies to identify and treat patients with impending AKI will be of major value to reduce mortality, hospital length of stay, hospital costs and potential progression to CKD.

To date, no standard treatment is available for SARS-CoV-2 infection. Since "cytokine storm" is considered a primary contributing factor to AKI and disease severity in patients with COVID-19 [28, 29], convective-based clearance may be a useful modality for removal of large-sized cytokines [60, 61]. However, this invasive approach may not be feasible as initial treatment for all COVID-19 patients at the time of hospital admission. Patients with severe COVID-19 infection often present with high levels of cytokines in the plasma, such as IL-6 [62, 63]. Clinical trials using anti-IL6 receptor (Sarilumab and Tocilizumab) are underway in hospitalized patients with COVID-19 [64]. Human recombinant soluble ACE2 (hrsACE2) has been touted as a competitive interceptor of SARS-CoV-2 by preventing binding of the viral particle to host tissues [65]. Although tolerable, the efficacy of hrsACE2 to prevent AKI is unknown [66, 67]. Treatment to inhibit viral replication with Remdesivir may reduce hospital stay but does not confer any benefit in reducing AKI incidence in COVID-19 patients compared to placebo [68]. Another approach is to focus on the cellular target of the virus. Cyclosporine, an immunosuppressor, has the potential to suppress the CD147-cyclophilin axis targeting ACE2. However, due to the potential high-risk of cyclosporine to cause AKI, it's use in AKI would be difficult to manage [69].

It is likely that the overall burden of AKI in COVID-19 is underestimated due to the fact that serum creatinine values at admission might not reflect true pre-admission baseline kidney function and pre-admission serum creatinine values might not be readily available. A key challenge for breakthrough treatments will be to establish paradigms for implementing precision medicine to prevent and mitigate progression of AKI in newly admitted patients with COVID-19. There are no known treatments for AKI including AKI due to COVID-19. The current proposal will address several major unmet needs by assessing a novel therapeutic approach for AKI with NR in patients admitted with COVID-19.

4.3 JUSTIFICATION FOR DOSE

NR (500 mg orally twice a day) or placebo will be administered for a period of 10 days. NR or matching placebo will be given via nasogastric tube in those participants who are intubated or felt to be at aspiration risk. [70] NR is more orally bioavailable than nicotinamide or niacin [38]. Limited data are available to shed light on the PK of NR in patients with comorbidities such as

obesity, diabetes, CKD and hypertension. One study [38] with healthy volunteers that administered NR in escalating dose regimen for 9 days reported that following the Day 9 dose, blood NR concentration peaked (Cmax) at t = 3 hours. The study did not evaluate PK after initial dose [38]. The NR dosing interval in the proposed study derives from the average steady-state blood concentration based on the area under the blood concentration-time curve over the 12-hour dosing interval [38]. In a 90-day toxicology study, the lowest observed adverse effect level (LOAEL) for NR was 1000 mg/kg/day [8].

Nicotinamide riboside is a dietary supplement, which is commercially available and designated as a "Generally Recognized as Safe" by the Food and Drug Administration (FDA) at oral doses of up to 1000mg (four 250 mg capsules) daily for adults [17]. The dietary supplement NR has been demonstrated to be well-tolerated with mild, if any side effects reported. There are several clinical trials currently underway employing variable dosages, including 1000 mg/day proposed in the current protocol, for numerous different conditions, both biomedical and behavioral [71]. The dose of 500 mg bid for 10 days was chosen as 1000 mg/d was found to give peak NAD+ levels in blood at 7 and14 days after starting oral administration of NR [8] with no further increase up to 56 days of treatment. The frequency of adverse effects in symptoms, vital signs or routine lab tests (chemistries and complete blood counts) in the 1000 mg/d of NR (group) was not different from the placebo group. Plasma and urine levels of the NAD+ metabolites were found to increase significantly in participants given the dose of 1000 mg/d of NR [8].

4.4 END OF STUDY DEFINITION

The study intervention period is for 10 days with follow-up visits at Day 30 and Day 90.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion and Exclusion Criteria must be confirmed by a clinician listed on the delegation log. If there is any uncertainty, the site principal investigator will make the decision on whether a potential participant is eligible for study enrollment.

In order to be eligible to participate in this study, an individual must meet all of the following inclusion criteria:

1. Provision of signed and dated informed consent form from a participant or legally authorized representative (LAR);
2. Male or female, >18 years old;
3. Admitted to hospital with a laboratory diagnosis of COVID-19 infection and COVID-19 related illness and evidence of persistent AKI as defined by the Kidney Disease:

Improving Global Outcomes (KDIGO) guidelines during the first 10 days following admission (Table 3);

4. Willing to adhere to the study intervention regimen;

Rationale: Persistent AKI Stage 1 will be defined as absence of recovery from the AKI stage within 24 hrs after receiving standard of care management by the primary provider team. The NIRVANA study team will monitor serum creatinine daily and participants with sustained AKI will proceed to randomization.

Table 3: Staging of AKI by the Kidney Disease: Improving Global Outcomes [72]

AKI Stage	Serum Creatinine	Urine output
1	1.5 – 1.9 x baseline	<0.5 mL/kg/h for 6-12 h
2	2.0 – 2.9 x baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline OR increase in serum creatinine ≥4.0 x baseline OR initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Hypersensitivity to nicotinamide riboside (NR);
2. Pregnant or lactating women confirmed with positive laboratory pregnancy tests as per local requirements;
3. eGFR <15 mL/min/1.73 m^2 as per the Chronic Kidney Disease Epidemiology Collaboration equation at admission lab;
4. Maintenance renal replacement therapy or initiation of renal replacement therapy before randomization
5. Currently on NR or nicotinamide or vitamin B3 (niacin) supplementation (multivitamins are allowed);
6. Concomitant cirrhosis of liver or acute liver failure;
7. Any medical history or condition that might, in the opinion of the attending physician, put the participant at significant risk if he/she were to participate in the trial;
8. Individuals with kidney transplant;
9. Individuals with blood platelet count <100,000/microL;

Rationale: The exclusion criteria are primarily designed for patient safety. In addition, these exclusion criteria address some uncertainties in the COVID-19 severity and effects of concomitant medications on disease progression. For example, the incidence of AKI in kidney transplant recipients with COVID-19 is not well studied [73]. Moreover, kidney transplant recipients are on maintenance immunosuppressive therapy with deleterious effects on infection

outcomes. An optimal management of immunosuppressive agents in this patient group with COVID-19 is not clear [74].

5.3 LIFESTYLE CONSIDERATIONS

Not-applicable.

5.4 SCREEN FAILURES

Pre-Screening
The site investigator or delegate will pre-screen hospitalized patients with laboratory confirmed COVID-19 (a positive laboratory test for SARS-CoV-2) for eligibility. After a COVID-19 patient is admitted to the hospital with a positive laboratory diagnosis of COVID-19, the study team will be notified by the COVID Admitting Team. In addition, the study team will identify eligible participants from the hospital COVID-19 database which is periodically updated every 6 to 8 hours.

Screening – Assessment of Eligibility and Exclusion Tracking
Eligibility screening will be performed by the study team, under IRB-approved HIPAA waiver, using the EHR. Certain screening visit laboratory assessments will be performed to determine eligibility after obtaining consent – blood draw for serum creatinine (if no routine value available within 24 hours prior to consenting) and pregnancy test for women with childbearing potential.

For participants who appear to meet inclusion criteria during screening, an electronic case report form will be completed to determine eligibility and track exclusions. All potential participants for which EHR screening is performed will be entered in a de-identified manner on the site screening log. At the time of entry into the screening database the participants will be assigned a screening number. The screening log will be maintained in the study REDCap database and will capture inclusion and exclusion criteria leading to a determination of “eligible” or “ineligible”. Additionally, the screening log will cover the period between screening and enrollment. As such, the screening log will also document the reason(s) “eligible” potential participants were not enrolled. The screening log will not contain identifiable health information.

The complete eligibility determination process may be suspended prior to complete screening procedures at any time if an exclusion criterion is identified by the study team. Only the reason for ineligibility will be collected on screen failures. For women with child-bearing potential, screening failure will be determined by pregnancy test performed after obtaining consent. Participants who are found to be ineligible will be told the reason for ineligibility and de-identified variables will be retained including month and year when participant was evaluated for study, age, sex, ethnicity, and reason(s) why the participant was excluded. Participants who fail screening will receive standard management for COVID-19 and comorbidities. Participants are

eligible to enter this study only once during the accrual duration. Screen failed participants will not be allowed to re-screen.

A participant already enrolled in an observational study or an open-label randomized clinical trial (RCT) would be eligible to participate in the NIRVANA study, provided eligibility criteria are met. With respect to double-blind RCT, the steering committee will determine trial by trial if a participant is eligible to enroll in the NIRVANA study.

If a participant appears to meet all eligibility criteria, the site investigator or delegate will approach the treating clinician to ask permission to approach the participant or LAR to confirm eligibility, discuss potential study recruitment, and proceed with informed consent.

Process of Obtaining Informed Consent (also see section 10.1.1.2)
Informed consent will be obtained from the participant or LARy. In most instances, bringing a paper consent form and pen to the bedside of a participant with known COVID-19 and then taking these out of the room would violate infection control principles and policies. Given the infectious risk from COVID-19 and potential shortages of personal protective equipment (PPE), there is a moral and practical imperative to minimize face-to-face contact between participants and non-clinical personnel. The current pandemic also presents unique challenges to obtaining consent from participant's LAR. To minimize infectious risk, many institutions are not allowing visitors to enter the hospital. Furthermore, the LAR is likely to have been exposed to the participant and may therefore be under self-quarantine at the time of the informed consent discussion. Therefore, in addition to the traditional approach of an in-person consent discussion and signed paper informed consent, we will allow use of "no-touch" consent procedures.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited from three participating sites: the University of Texas Health San Antonio (UTHSA), Icahn School of Medicine at Mount Sinai, New York, NY, and University of Washington (UW), Seattle, WA. The single IRB (sIRB) at the Washington University in St. Louis (FWA00002284) will serve as the Central IRB for all three participating sites. We will recruit and consent eligible participants and will advance them into the Treatment Period. A total of 100 participants will be randomized.

Each participating site and the coordinating site (UTHSA) will contribute to recruitment of study participants. Recruitment methods will focus primarily on the selection of eligible participants via identifying patients admitted to the respective hospitals with a diagnosis of COVID-19. Lead investigators at each site are physician scientists who will have direct access to eligible participants. For efficient recruitment, each site will employ the following approaches. After a COVID-19 patient is admitted to the hospital with a new positive laboratory diagnosis of COVID-19, the study team members will be notified by the COVID-19 Admitting Team. All

three participating sites also maintain a COVID-19 database which is updated every 6-8 hours and a designated study member will review the COVID-19 database twice a day. Each study team will have access to the respective hospital COVID-19 admission logs and EHR enabling them to review several eligibility criteria. The study investigators or clinical coordinators will approach the potentially eligible participants or LAR (when appropriate) and inform them of the study protocol. All participants will provide written consent for participation in the study. Sites have the ability to use one of the FDA approved options for obtaining written signature during a pandemic, based on their institutional requirements.

During consenting process, each participant will receive clear and detailed information about the NIRVANA study with an emphasis on risks, benefits, and alternative to enrollment. Participants will be given opportunities and time to learn about ongoing clinical trials for COVID-19 and their eligibility to enroll in another competing study. Voluntary participation will be discussed and participants will be allowed to withdraw from the current study at any time point after providing consent.

At present, all COVID-19 clinical trials in all three participating institutions are reviewed by a COVID-19 clinical trials committee or a COVID-19 task force. As stated, the committee or task force reviews all new studies prior to approval. In addition, the group evaluates current resources and standard of care when determining whether a study can proceed once approved.
The anticipated duration of the study recruitment period is approximately 15 months. The proposed study intervention is 10 days. At least 80% adherence with study intervention is expected because of short (10-day) intervention with minimal burden for study participants. NR is a safe nutritional supplement and poses only a few side effects which are mild in nature. It is likely, however, that 15% of enrolled participants may withdraw from the current study and enroll to another COVID-19 trial. We expect an additional attrition rate of 5% during the follow-up period due to extended isolation, travel restrictions, or relocation. Statistical methods will be based on the Intent-to-Treat Principle that every randomized subject will be assumed treated as randomized and all randomized patients will be included in the analysis regardless of noncompliance, protocol violations or withdrawals.

The data coordinating center (DCC) at UTHSA will email weekly recruitment reports showing study-wide weekly and cumulative enrollment in baseline and randomization. The reports will also include each site's current baseline goal, achievement of baseline goal, randomization goal, and achievement of randomization goal. Clinical site investigators will meet weekly with their study teams to discuss progress on weekly goals, identify barriers and problems, and revise recruitment plans as necessary. The investigators at three participating sites will meet by conference call at regular scheduled intervals to review each site's recruitment progress, share problems and successes, and revise recruitment plans as necessary.

The enrollment will be tracked and paused after 50 participants until the DSMB reviews primary outcome data from all 50 participants; a decision to continue enrollment will be made by the NIDDK after reviewing DSMB recommendations while the investigators remain blinded.

Participant retention is paramount to the success of this study. The following approaches will be included to minimize loss of data and to maximize the retention especially for the follow-up visits: participants will be reminded about the upcoming visits at least a week before; asking a participant for the name and contact number of a family member or friend who can be contacted to reach the participant; and use of email contact (with care to maintain confidential medical information over nonsecure email). As COVID-19 infection results in prolonged isolation periods, the study team will be trained in compassionate and emotionally positive interactions with participants via virtual visits. If a participant is unable to attend clinic visit for any logistical issues, they will be offered a phone or video call to collect vital status followed by a home visit. The home visit will be limited to blood and urine collections with all safety precautions in place. Each site has an existing post-COVID care program composed of clinicians, social workers, and researchers. The study site will coordinate with the post-COVID care program to enhance retention of our participants for the duration of this study. For any missing visit/contact or missing data, the reason for the missing visit/contact and/or data will be recorded in the REDCap case report form (eCRF).

Replacement of Participants:
Randomized participants who are randomized but do not receive study intervention (NR or placebo) may be replaced to maintain the stipulated cohort sizes. This would include participants who are randomized and then withdrew consent before receipt of the intervention. Participants who are discontinued from further dosing or follow-up procedures or withdraw their informed consent to all follow-up study procedures may be replaced, if deemed necessary by site investigator, to ensure that data are collected from a sufficient number of participants. The SAC will be notified within 48 hours if a participant permanently discontinues study drug or withdraws consent to all follow-up visit procedures. A determination whether to replace the subject will be made jointly between the site investigator and SAC.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Baseline Visit (Day 1)
After obtaining consent, baseline visit procedures will be performed as listed in Table 1 (Schedules of Activities in Section 1.3). Participants will be randomized after abstracting the following data from the EHR: sociodemographic, contact information, medical/surgical history,

comorbidities, and routine medications on admission, standard of care at hospital, home medications, all concomitant medicines including dietary or nutritional supplements and over-the-counter medications, vitals and physical examinations, routine laboratory test results.

Randomization will be accomplished through the use of an online randomization service. Participants will be randomly allocated to 1:1 ratio to receive either nicotinamide riboside (NR) or placebo. Only the study statisticians (Drs Michalek and Zelnick) and the local hospital Research Pharmacists will have access to the randomized assignment for the purpose of tracking randomization and study drug dispensing, respectively. Study investigators and study participants will be blinded to the intervention assignments. Neither the statisticians nor the pharmacist will have direct contact with the study participants.

Eligible study participants enter intervention phase after consenting to the study protocol:

- Nicotinamide riboside (NR, Niagen®) or placebo will be administered orally (or via nasogastric tube) 500 mg twice a day for 10 days during hospitalization or prescribed for at home administration if discharged before 10 days from the hospital.
- Placebo capsule manufactured by ChromaDex to match NR or Niagen®

TREATMENT PERIOD

All measures related to study treatment visits are harmonized to standard of care to minimize care interruption and disruption to hospital staff workflow. Most of the treatment procedures are standard of care or routine procedures for COVID-19 participants in an acute care setting. These data will be obtained from the EHR. If any treatment procedure is not available through the EHR, the study team will obtain these data from the primary care team or directly from the participant. Where multiple results are present in the EHR, they will all be recorded in the study database so that all relevant values are captured. A summary of the trial's schedule of event is included in Table 1 (Section 1.3).

Treatment Visits 1 to 10 (Day 1 to Day 10) for participants with hospital duration of at least 10 days

Participants will be assessed daily while hospitalized during the intervention period. The following clinical and laboratory data will be collected daily from the EHR during the Visits 1 to 10 while hospitalized:

1. Review of current medications and treatment
2. Adverse events
3. Vital Signs, including temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure
4. Study drug administration and accountability
5. Evaluation of APACHE-II (Acute physiology and chronic health evaluation II)
6. Assessment of fluid intake, if applicable

7. Assessment of urine output, if applicable
8. Respiratory parameters
9. Ascertainment of endpoint assessment (serum creatinine and urine volume), mortality, intensive care unit (ICU) transfer rate, and length of hospital stay
10. First morning void urine collection (optional and if indicated by primary care team)
11. Blood collection

The list of daily laboratory tests is provided in Table 4.

Treatment Visits 1 to 10 (Day 1 to Day 10) for participants with hospital duration of <10 days

During each daily virtual phone visit, following information will be collected from each participant and/or family caregivers:

1. Review of current medications and treatment
2. Any new health issues or changes from previous day
3. Vital Signs, including temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (if available)
4. Respiratory parameters (if available)
5. Study drug administration and accountability (virtual review of compliance log)
6. Endpoint assessment (fingerstick creatinine using StatSensor Xpress®)
7. Ascertainment of mortality or hospitalization

Each day participants will collect first morning void urine which will be picked up daily until Day 9 by the courier service (FedEx same day delivery service) for delivery to the hospital laboratory. Urine specimens will be aliquoted and stored at the hospital laboratory by the hospital staff and will be picked up by the study team for storage in the COVID designated biorepository.

To monitor clinical measures necessary for primary outcome, a phlebotomist and a study team member will visit participant's home for the day 10 collection of blood with safety precautions in place including necessary PPE. At this home visit, study staff will collect the POC device and urine specimen from the participant. Both blood and urine specimens will be delivered to the hospital laboratory by research staff. The biosamples will be aliquoted and stored at the hospital laboratory by the hospital staff. The research aliquots will then be picked up by the study team for storage in the COVID designated biorepository.

FOLLOW-UP PERIOD:

There are two follow-up visits.

Follow-up Visits 11 and 12 (Day 30 ± 3 and Day 90 ±3)

The Day 30 ± 3 and Day 90 ± 3 follow-up visits will be performed at the outpatient clinic. However, restrictions due to local infection control measures may limit some participants from leaving their residences and returning to the clinic for the follow-up visit. In that circumstance follow-up by phone visit will be conducted in conjunction with review of medical records to complete the applicable procedures listed below. A phlebotomist will visit the participant at home to collect blood and urine if participant cannot or is unwilling to come to the clinic. For participants who are allowed and willing to come to clinic, the following assessments will be performed at the clinic:

1. Review of current medications and treatment
2. Vital Signs, including temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure
3. Physical examination
4. Endpoint assessment
5. Adverse events – collection of health status based on participants reported and review of EHR
6. Ascertainment of mortality or hospitalization
7. First morning void or random urine collection
8. Blood collection

6.1.2 DOSING AND ADMINISTRATION

Participants, randomized to the study drug nicotinamide riboside (NR) group, will receive a total daily dose of 1000 mg (four 250 mg capsules) NR administered orally or via nasogastric tube as 500 mg (2 capsules) every 12 hours for up to 10 days during hospitalization.

Participants, randomized to the placebo group, will receive matching placebo, two capsules orally every 12 hours for up to 10 days during hospitalization.

Participants with hospital stay of <10 days will be provided with study drug in a pill box for the remaining days to maximize compliance at the time of discharge. Verbal and oral instructions will be provided for oral intake of study drug every 12h and daily virtual visits will record timing of administrations.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

NR and matching placebo will be obtained from ChromaDex, Irvine, CA. NR is manufactured in a Good Manufacturing Practice (GMP)-compliant facility according to ISO/IEC 18025:2005 standards.

For all study drugs (NR and placebo), a system of numbering in accordance with all requirements of Good Clinical Practice (GCP) will be used, ensuring that each dose of study drug can be traced back to the respective batch of the ingredients. Lists linking all numbering levels will be maintained by the PI. A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the study file.

Following randomization of a participant, a computer-generated system will generate randomization number, medication numbers, and treatment code. During the hospital stay the hospital nursing staff will administer drug to a participant as prescribed: 2 capsules of each 250 mg orally every 12 hours and document the administration in compliance log. The local hospital research pharmacist will prepare study drug for nasogastric tube administration as per guidelines from ChromaDex.

Participants with hospital stay of <10 days will be provided with study drug in a pill box at the time of discharge to maximize compliance for the remaining days. These participants will receive clear verbal and written instructions on administering of and compliance with study drug.

All expired and unused products will be returned to supplier ChromaDex for destruction.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

NR is supplied as capsule white in color and each capsule contains active ingredient nicotinamide riboside chloride 250 mg. Placebo capsules will be identical in appearance (size, shape, color). The study drug will be labeled as required by law: Caution: New Drug. Limited by Federal Law to Investigational Use.

Preparation of NR or matching placebo for administration via nasogastric tubing will be prepared daily, as needed, in an aqueous suspension in 100 ml of water and will be made by each local hospital research pharmacist.

6.2.3 PRODUCT STORAGE AND STABILITY

All study drugs will be stored at the respective site hospital Research Pharmacy and will follow GCP and GMP requirements. Study drugs will be inaccessible to unauthorized personnel. Both NR and placebo are stable at room temperature. Storage conditions (minimum and maximum temperatures) and a complete record of batch numbers and expiry dates will be maintained in the study file.

Participants discharged before completing 10-day in-hospital intervention will store study drug at home in a cool dark place at temperature below 25◦C preferably in a refrigerator.

6.2.4 PREPARATION

If participants require nasogastric tube administration, NR will be available in a powder form and the NR and placebo will be prepared by pharmacist so that both solutions are not visually distinguishable.

Both NR and placebo will be available in capsule form for oral administration. NR or matching placebo will be administered via nasogastric tube to those participants who are intubated or felt to be at aspiration risk. Hospital research pharmacist will prepare the nasogastric preparation for both NR and matching placebo. The pharmacist will weigh out and prepare the bulk NR or matching placebo powder in purified water immediately before administration. Powder NR yields slight yellowish-brown color when dissolved in water. To mask this, pharmacist will dissolve brown sugar in water. For example, to match 1 gram of Niagen in 50 mLs of purified water, placebo will be prepared by dissolving ~75 mgs of brown sugar in 50 mLs of purified water for administration via NG tube.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Eligible participants who provide voluntary consent will advance to randomization. In order to minimize bias, the set inclusion and exclusion criteria offer broader participation from a wider range of participants who may be eligible in three geographically diverse study centers. The set of inclusion and exclusion criteria do not compromise the scientific integrity.

The study drug (NR or placebo) packaging and labeling will be designed to maintain the blinding of the investigator's team and the participants. The study drug allocation will remain blinded to the study participants and study investigators according to standard operating procedures. The randomization and blinding procedures will be described in a corresponding manual of operation (MOP).

If participants require nasogastric tube administration, NR will be available in a powder form and the NR and placebo will be prepared by pharmacist so that both solutions are not visually distinguishable. Using a dark opaque sterile draping the participant will not visually perceive the NG administration of study drug. The hospital nurse will administer the nasogastric feeding and use an opaque sterile draping so participant and study personnel will not visually perceive the drug administration of study drug.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. However, the treatment blind may be broken to provide unblinded information to the study site only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the participant. In the event of an emergency or any finding that requires unblinding, the investigator may break the blind for an

individual participant. This will allow the investigator, or other responsible person, to identify the study drug if there is an emergency, without jeopardizing the double-blind integrity of the remainder of the study. The code can be broken by the investigator, or other responsible person, when knowledge of the participant's treatment is required for the clinical management of the participant. If it becomes necessary to know the individual treatment during the study and thus to break the code for that participant, the date and reason for unblinding are to be recorded on the relevant source document and in the REDCap eCRF.

6.4 STUDY INTERVENTION COMPLIANCE

Each dose of study product will be administered by hospital nursing staff to randomized participants while they are in the hospital. Study drug administration will be documented in the site medication administration record or research record according to local procedures. A compliance log will be maintained in the eCRF containing participant ID, bottle number and batch number, route, and date and time of administration. Problems with participant medication adherence during hospitalization is not anticipated as the medications will be managed by hospital nursing staff. Upon discharge, if this occurs before 10 days of hospitalization, participants will receive study drug for the remaining days to complete a total duration of 10 days. These participants will receive verbal and written instructions on administering study drug. Participants will be asked to keep a written log as to when they self-administered study drug with dates and times recorded. If a care provider (i.e., family member) is present in the participant's home, daily pill counts will also be performed during the virtual phone or video visit.

6.5 CONCOMITANT THERAPY

All standardized treatment and management for any comorbidity and concomitant condition are permitted. Concomitant therapy with niacin, nicotinamide, NR and their derivatives are prohibited during the duration of the study.

6.5.1 RESCUE MEDICINE

To our knowledge there is no specific rescue medicine for NR as there is no known toxicity associated with this compound. If a rescue medicine is being considered for a participant for underlying COVID-19 or other intercurrent illness, this may be a reason that warrants stopping study drug. Any such decision will be made by the primary care team and the participant and the study team will be informed.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from study intervention does not mean discontinuation from the study (i.e., withdrawal of consent), and remaining study procedures will be completed as indicated by the study protocol. Randomized participants who wish to discontinue study medications will be encouraged by the site PI and study coordinator to continue with the visits, laboratory tests, and data collection so data will be available for intent to treat analysis of the trial. The site PI will encourage passive data collection such as hospitalization documentation and EHR for participants who no longer want to attend visits.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request, for any reason, and without any consequence. Participants should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the investigators to make efforts to continue to obtain data. A participant has a right to withdraw from the current study and enroll in a different research study at any time point. However, participants will remain in the current study and all data will be collected as per the Schedule of Activities (section 1.3), Table 1 unless participants withdraw consent.

The study investigators have the right to discontinue the study drug at any time, which may be due but not limited to the following reasons:

- For an individual participant, a suspected drug-related event of hypersensitivity Grade 2 or higher;
- The investigator believes that for safety (e.g., SAE) or tolerability reasons it is essential for the participant to stop treatment;
- The investigator formally unblinds the participant's treatment allocation for safety reasons;
- The participant requires renal replacement therapy or dialysis of any type (Note: The requirement for dialysis is the only endpoint for which treatment with double-blind study drug should be discontinued;
- The participant takes prohibited NR supplements (multivitamins are allowed);
- Newly reported results of parallel clinical studies and/or animal studies indicating toxicity, teratogenicity, carcinogenicity or reproduction toxicity of NR at similar doses administered in this study;

Participants who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments unless consent is withdrawn from further study participation, or the participant is lost to follow-up.

In the event of a study drug discontinuation due to safety and tolerability, participants will continue to receive available and/or standard management for COVID-19 and comorbidities as

clinically indicated. Participants who discontinue study drug will continue subsequent study visit procedures (including biosample collections) to assess safety and worsening or progression of any health issues that might be attributable or plausibly related to study drug. As the study is an intent to treat analysis, all participant data will be obtained and processed in the same manner regardless of study drug discontinuation for any reason.

The reason for participant discontinuation or withdrawal from the study will be recorded on the REDCap eCRF. Withdrawal of consent prior to receipt of study drug will constitute a screen-failure and will be recorded. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Data recorded up to the point of withdrawal will be included in the trial analysis, unless consent to use data has also been withdrawn. Withdrawal of consent after randomization and administration of one or more doses of study drug will lead to discontinuation of study interventions but study site will request access to EHR for data related to the trial.

Criteria for Stopping Study Drug

Administration of the blinded study drug may be stopped temporarily or permanently for (1) adverse events, (2) clinical deterioration, or (3) evidence of an alternative cause to the participant's symptoms. Study intervention will also be discontinued permanently when a participant:

a) receives dialysis treatment for the management of AKI;
b) develops thrombocytopenia defined as <75,000/microL in blood platelet count;
c) is found to have abnormal liver function test (AST, ALT, total bilirubin, or alkaline phosphatase) >4 times the upper limit of normal without other identifiable cause;
d) is found to have abnormal serum CPK levels >4 times the upper limit of normal without other identifiable cause.

If a participant experiences an AE that the patient (or LAR), the treating clinicians, or investigators feel merits temporarily or permanently stopping the study drug, the study drug will be stopped. The explanation for stopping the study drug will be recorded in the REDCap eCRF, and the AE will be recorded and reported according to the AE reporting guidelines. Participants will stop study drug, but data collection will continue as usual.

7.3 LOST TO FOLLOW-UP

The following actions will be taken if a participant is not able to be contacted or fails to return to the clinic for the required follow-up study visits:

- The study team will attempt to contact the participant and/or relative(s) in file and to reschedule the missed visit as soon as participant is available after the protocol-specific time window or perform a remote phone visit at the least.
- Before a participant is deemed lost to follow-up, a study team member will make every effort to regain contact with the participant and/or relative(s) in file (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods).

Should the participant continue to be unreachable, EHR will be reviewed to document participant's vital status, and he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Given the infectious risk from COVID-19 and potential shortages of PPE, we will minimize face-to-face contact between participants and non-clinical staff. Additionally, minimizing research activities and conducting the trial in a pragmatic manner will increase the ability to complete the trial in the face of strained clinical and research resources during the COVID-19 pandemic. We will emphasize data that can be collected from the EHR, laboratory values as part of routine clinical care, and assessments that can be completed over the telephone as needed.

Medical History
A complete medical history will be obtained from the EHR at the Screening Visit (Day 0) and any changes (i.e., adverse events) from the Baseline visit (Day 1) will be documented at every visit thereafter. The information will be recorded on the REDCap eCRF.

Physical Examination
A complete physical examination will not be performed if there is a documented physical examination by a physician or nurse practitioner provider in the EHR within 24 hours prior to consenting. The findings of the examination will be recorded on the eCRF and serve as baseline findings.

Vital Signs
Temperature, heart rate, oxygen saturation, respiratory rate including respiratory parameters, and blood pressure will be obtained at the screening visit and during every visit from the EHR. The results will be recorded on the REDCap eCRF.

Review of Concomitant Medications

All concomitant medications and treatments will be captured at the Baseline and all subsequent visits in the REDCap eCRF. These data collection will include routine medications on admission, inhospital standard of care treatment, concomitant medications for th management of comorbidities, any prophylactic medications, dietary or nutritional supplements, and over-the-counter medications. In addition, EHR will be reviewed on daily basis to update REDCap eCRF to capture changes in standard of care and clinical management for COVID-19 in a dynamic landscape. Study team will inquire and record any home medications 7 days prior to enrollment. At the Screening visit, concomitant medication list will be solicited from the participant or LAR.

For the baseline visit, treatment intervention, and the follow-up visits, the following assessments will be completed:

Baseline variable collections:

- Presence or absence of inclusion and exclusion criteria
- Date and time of admission
- Demographics (age, sex, race, and ethnicity)
- Vitals and respiratory parameters
- Physical examination
- Comorbidities
- Acute signs and symptoms
- Parameters to assess severity-of-disease using the Acute Physiologic and Chronic Health Evaluation (APACHE) II classification, as applicable
- Current use of home and inhospital medications including over-the-counter
- Receipt of open label study medication
- Receipt of invasive procedures
- Blood and urine collections and analyses (see Table 4)
- Other procedures as per the Schedule of Events (see Section 1.3 Table 1)

Study intervention period (daily):

- Date and time of randomization
- Drug administration and accountability
- Vitals and respiratory parameters
- Physical examination
- Comorbidities
- Acute signs and symptoms
- Review of current medications
- Receipt of invasive procedures
- Hospital data including adverse events, endpoints, and outcomes

- Collect hospital data to complete APACHE-II
- Blood and urine collections and analyses (see Table 4)
- Other procedures as per the Schedule of Events (see Section 1.3 Table 1)

Assessments following Hospital Discharge: Early discharge (before completing 10-day intervention) and Follow-up visits

Early discharge: Using daily phone call or videoconferencing, following data will be collected

- Drug accountability
- Vitals and respiratory parameters
- Comorbidities
- Acute symptoms
- Review current medications
- Query about adverse events, endpoints, and outcomes
- Review EHR for additional data, if applicable
- Fingerstick blood creatinine using the POC device will be performed by the participant/care provider until Day 10 (see Table 4)
- Daily urine collections for biorepository (see Table 4)
- Blood collection will be done on Day 10 for research laboratory analysis and biorepository (see Table 4)
- Other procedures as per the Schedule of Events (see Section 1.3 Table 1)

Assessments for participants with early hospital discharge

It is reasonable to expect that a percentage of participants may be discharged home prior to completing 10-day in hospital intervention. In the event that participants will be discharged prior to the 10-day study intervention days of study drug administration, the study drug will be provided to participants in a pill box with written and verbal instructions to take twice daily for the remaining days to complete a 10-day course. To monitor compliance, at the time of discharge each participant will receive study drug administration and accountability log with instructions.

In addition, to monitor pattern of fingerstick creatinine, each participant will be provided with a StatSensor Xpress®, a home fingerstick point of care (POC) device for fingerstick creatinine measurement. The device is similar to a glucose meter that utilizes a test strip and a small drop of blood from finger stick. Participant and accompanying family member will receive a demonstration on how to use this device at the time of discharge along with lancets, alcohol swabs, test strips, and safe disposal biohazard waste containers. Using all safety measures, the study team will use the POC device using participant's fingerstick blood. The POC device generated fingerstick creatinine value will be documented and compared with the discharge day routine serum creatinine value. Participants will use POC fingerstick creatinine device daily for

the duration of the 10-day intervention period. Participants will receive daily virtual visit from the study staff to collect health status, provide study drug reminder and compliance, and collect POC device result. There will be a home visit at Day 10 to collect urine and blood in compliance with all local and applicable COVID-19 safety measures.

Follow up visits: At each follow-up visit (Day 30 and Day 90), the following assessments may occur at clinic or at home or by phone or videoconferencing and procedures will vary:

- Review of current medications
- Comorbidities
- Record vital signs and physical examination
- Collect data on adverse events, endpoints, and outcomes
- Collect blood and urine for research laboratory analyses and biorepository (see Table 4)
- Other procedures as per the Schedule of Events (see Section 1.3 Table 1)

Biospecimens Collections and Measurements

Primary and secondary endpoints from routine daily laboratory tests and clinical care:

Daily serum creatinine: Blood will be collected daily for the measurement of serum creatinine and documented for the study starting Day 1 and up to 10 days of hospitalization for participants who remain hospitalized or via StatSensor Xpress® for creatinine and outpatient serum creatinine measurement for participants who will be discharged prior to the 10-day intervention period. There will be a serum creatinine measured on the 10^{th} day for discharged participants, in addition to the StatSensor Xpress® fingerstick creatinine measurement. AUC will be computed cumulatively across days for each patient.

Daily urine output: Daily urine output will be reported as part of routine clinical care and documented for the study starting Day 1 and up to 10 days of hospitalization. Daily urine outputs will not be obtained for participants who will be discharged prior to 10-day intervention period.

Onset of dialysis: Timing of onset of dialysis will be reported as part of routine clinical care and documented for the study starting Day 1 and up to 10 days of hospitalization.

Research Laboratory Biospecimens Collections for future Biomarkers Analysis:
Blood and urine will be collected at Visit 1 and then every visit thereafter for secondary or sub-study analyses. Baseline (Day 1) blood and urine collections will be performed before participants receive first study drug dosing and after obtaining consent. There will be additional blood and urine collections on Day 1 at hour 3 and hour 6 after first drug administration for pharmacokinetics and analyses of biomarkers. Day 1 to Day 10 blood and urine collections will coincide with routine collection by the hospital staff. Hospital laboratory will aliquot and store

the specimens and they will be picked up by the study team for storage in a COVID-19 designated biorepository. Each day, participants will collect first morning void urine into a provided container which will be kept refrigerated and picked up daily (until Day 9) by the courier service for delivery to the hospital laboratory. At Day 10, the study team will visit the participant at home to collect blood and first morning void urine and will deliver to the hospital laboratory. Both blood and urine biospecimens will be aliquoted and stored at the hospital laboratory by the hospital staff and will be picked up by the study team for storage in the COVID-19 designated biorepository at UTHSA. The list of research laboratory tests is provided in Table 4.

Blood and urine collections on Day 30 ± 3 and Day 90 ± 3 will take place when participants return to clinic or when the study team visits participants at home for follow-up visits. Collection, handling, and processing of all biospecimens will be performed in Biosafety Laboratory (BSL) 2 environment as per current US Centers for Disease Control and Prevention (CDC) guidance. Blood and urine biospecimens for analysis of biomarkers will be shipped to UTHSA and stored in a COVID-19 designated biorepository.

All blood and urine biospecimens will be tracked in the REDCap study database. Biosamples will be reconciled with the study schedule of events to assure that all expected biosamples are accounted for. Study biosamples in the UTHSA COVID-19 designated biorepository will retain association with the clinical data.

All assessments will be detailed in the MOP.

8.2 SAFETY AND OTHER ASSESSMENTS

Assuring participant safety is an essential component of this protocol. NR is considered GRAS (Generally Recognized as Safe) as filed for designation to FDA. Use of NR for the prevention and or treatment of AKI in COVID-19 positive participants, however, raises unique safety considerations. This protocol addresses these considerations through:

- Exclusion criteria designed to prevent potential overdose effects by excluding participants with concomitant intakes of niacin, nicotinamide, and NR;
- Daily assessment of participants health status;
- Systematic collection of safety outcomes;
- Structured reporting of adverse events;
- Appointment of independent safety adjudication committee (SAC)

Study procedures and evaluations to be done as part of the study to monitor safety and support the understanding of the study intervention’s safety. For all visits starting from baseline until the last follow-up visits, the following assessments will be completed:

- Physical examination: A physical examination at the baseline visit or a record of routine physical examination performed within 24 hours prior to consenting, and at Day 30, and Day 90 follow-up visits.
- During the 10-day intervention period, participant's health status will be obtained on a daily basis from the participant and from EHR. Health status of participants will be collected by the study team at Day 30, and Day 90 follow-up visits. Participants will be specifically asked for any new symptoms on a daily basis.
- The safety clinical laboratory parameters will be performed at each visit while hospitalized. Any laboratory tests performed as part of routine clinical care (Clinical Laboratory Tests) within the specified visit window will be used for safety laboratory testing (see Table 4).

Research laboratory tests:
Blood for the first whole blood NAD+ level will be drawn within 6 hours prior to the first study drug dosing (i.e., baseline NAD+ level, Day 1). Whole blood NAD+ level will be measured daily for a total of 10 days while hospitalized starting at the baseline.

Safety laboratory from routine daily laboratory tests:
Safety laboratory will be performed at Visit 1 and then every visit thereafter for hospitalized participants. Clinical laboratory tests performed as part of routine clinical care in the 24 hours prior to first study drug dose will be accepted for the baseline (Day 1) safety laboratory tests. Any clinical laboratory tests (see Table 4) performed as part of routine clinical care within the specified visit can be used for safety laboratory testing within the period of hospitalization up to 10 days prior to starting the study drug.

Rationale for specific safety laboratory tests:
Several case studies reported that COVID-19 patients may present with mild symptoms such as muscle weakness with elevated CPK and laboratory confirmation of rhabdomyolysis [75-77]. Although, the incidence of rhabdomyolysis in COVID-19 is not known, several case reports indicate an association between rhabdomyolysis and AKI in COVID-19 patients [78-80]. One study reported elevated levels of CPK in about 14% of patients [21], suggesting involvement of muscle injury.

NR has been evaluated on the development of aging-induced non-alcoholic fatty liver disease in mice [81]. It was found that AST (aspartate transaminase) level was significantly reduced by NR supplementation while the alanine transaminase (ALT) level decreased without significance compared to baseline [81]. One human study demonstrated that NR significantly reduced AST level at day 56 from baseline [8]. It is likely that COVID-19 patients will be receiving different medications for comorbidities and as per the FDA guidance [82], liver function tests will be performed as listed in the Table 4.

Table 4: Blood and urine tests for research laboratory, safety, and repository

Research laboratory tests	Safety laboratory tests	Repository
Daily during Study Day 1 to Study Day 10		
Blood (daily): 1. Whole blood NAD+ 2. Serum creatinine (performed if routine test is missed or not available) **Urine (daily):** 1. Urinalysis 2. Urine creatinine 3. UACR and UPCR 4. Urine glucose 5. Lactate 6. Urine phosphate 7. Urine NAD+ metabolome	**Blood:** 1. CPK on day 5 2. Liver function tests on day 5 3. Daily CBC and platelets (performed if routine test is missed or not available)	**Blood:** • Future biomarkers • Genetic analysis **Urine:** • Future biomarkers **Note**: additional collections at hour 3 and hour 6 post-randomization study drug for PK analysis
Day 30 and Day 90		
Blood: 1. Serum creatinine 2. Whole blood NAD+ 3. Serum electrolytes (Na, Cl, K) 4. Bicarbonate 5. Calcium and phosphate 6. Blood glucose 7. CBC with platelets **Urine:** 1. Urinalysis 2. Urine creatinine 3. UACR and UPCR 4. Urine glucose 5. Lactate 6. Urine phosphate 7. Urine NAD+ metabolome		**Blood:** • Future biomarkers • Genetic analysis **Urine:** • Future biomarkers

Due to limited direct interactions with the participants, safety assessments will be performed by collection of EHR data, participant interviews, vital sign measurements, physical examination, and laboratory tests, including complete blood count and comprehensive metabolic panel, and diagnostic tests or procedures. Participants' reported symptoms or complaints recorded in the medical record will be reviewed and recorded in the appropriate eCRF. In addition, information will be solicited from the participants and designated staff physicians to supplement accurate and complete safety assessment.

Each participating investigator will have primary responsibility for the safety of the individual participants under his or her care. The investigators will determine daily if any adverse events occur during the period from enrollment through study intervention and will determine if such adverse events are reportable. Thereafter, adverse events will not be required to be reported unless the investigator feels the adverse event was related to the study drug or study procedures.

The site investigator will (i) provide a verbatim term (a diagnosis where possible) for detected and reportable AE, (ii) each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome, (iii) classify and assign a grade to each detected and reportable adverse event using the CTCAE v. 5.0 classification system, and (iv) rate the likelihood that the event was related to the study drug.

A team of medical monitors (Safety Adjudication Committee, SAC), composed of three clinicians with expertise in infectious disease or acute care management, one from each study site, independent of the study investigators will review the medical charts for unexpected AE /SAE data weekly during the study intervention period. The senior SAC member will serve as SAC Chair. The SAC will confirm the verbatim term (a diagnosis where possible) for detected and reportable adverse event with knowledge of the study site physician's rating and then classify and assign a grade to each detected and reportable adverse event using the CTCAE v. 5.0 classification system. Disagreements between the study site investigator and the SAC member will be adjudicated weekly on a call facilitated by the SAC Chair.

All AEs will be recorded on the AE eCRF. Verbatim terms for AEs will be coded to the current version of the MedDRA coding dictionary at the DCC. Verbatim terms will be coded at the Lower Level Term (LLT) where possible and to the Preferred Term (PT) otherwise. Accurate mapping to CTCAE will be confirmed during the coding review process. AEs and SAEs will be aggregated and reported for the DSMB at the PT level. If the SAC identifies an unexpected SAE, sIRB and FDA expedited reporting procedures will be followed and the DSMB will be notified.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, (which may cause worsening of a pre-existing medical condition), whether or not it is considered intervention-related [FDA (21 CFR 312.32 (a))].

Any medical condition that is present at the time participant provided consent to the protocol will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases after consenting, it will be recorded as an AE.

Given the nature of severity and unpredictable clinical course and outcomes of the underlying illness, participants will have many symptoms and abnormalities in health or vital status and laboratory findings. All Grade 3 and 4 AEs will be captured as AEs in this trial. These grades are according to the CTCAE (Common Terminology Criteria for Adverse Events, Version 5.0, November 27, 2017. U.S. Department of Health and Human Services, National Institutes of Health).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is defined as "An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- A life-threatening AE;
- New hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Death,
- Any other event requiring medical or surgical treatment to prevent one of the outcomes above

All SAEs, as with any AE, will be assessed for severity and relationship to study intervention. All SAEs will be recorded on the appropriate SAE eCRF. All SAEs will be followed through resolution or stabilization by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site PI or Sub-Investigator).

In this protocol, other safety events will be defined as follows:

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with risks outlined in the study protocol), serious, and meets the definition of a suspected adverse reaction. A Serious Unexpected Serious Adverse Reactions (SUSAR) is any SAE where a causal relationship with the study product NR is at least reasonably possible but has not been documented in currently available published reports or data. In making this assessment, there should be consideration of the probability of an alternative

cause (for example, COVID-19 itself or some other pre-existing conditions or comorbidities preceding randomization), the timing of the event with respect to study treatment and the response to withdrawal of the study treatment.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

In the protocol, the following guidelines will be used to describe severity of adverse events:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe (Grade 3): Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
- Severe (Grade 4): Events that are potentially life threatening.
- Death (Grade 5)

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Study investigators will grade the strength of the relationship of an adverse event to study drug or study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the participant's clinical state or other therapies; and c) Evaluation of the participants' clinical state indicates to the investigator that the experience is definitely related to study procedures.
- Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.
- Probably Not Related: The event occurred while the participant was on the study but can reasonably be explained by the known characteristics of the participant's clinical state or other therapies.
- Definitely Not Related: The event is definitely produced by the participant's clinical state or by other modes of therapy administered to the participant.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

8.3.3.3 EXPECTEDNESS

The study investigators will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention and hospital course.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The study investigators will assess and record all events with start dates occurring any time after informed consent is obtained until Day 90 – the last visit. The study investigator will review EHR daily to collect and assess all AEs (including SAEs) from the time participants provided consent to the study until Day 10 and again during Day 30 and Day 90 follow-up visits regardless of its relationship to study drug. At each visit, the investigator will inquire about the occurrence of any new and the prognosis of already documented AE/SAEs since the last visit. All AEs will be captured in detail and followed to satisfactory resolution or stabilization, until the investigator deems the event chronic or not clinically significant and until the participant is considered to be stable. The participants will receive standard of care for the events. Site investigators will consult with treating physician to monitor the event progression. Study investigators will also assess if there is a reasonable possibility that the study drug or procedure caused the event. Investigators will also consider if the event is explained by the participant's underlying medical conditions, anticipated clinical course, previous medical conditions, and concomitant medications.

Routine and safety laboratory values from the respective hospital laboratories will be reported by each site investigator to the SAC as soon as the results are available to the study database. Participants will receive standard of care for the event and followed to satisfactory resolution or stabilization, The DCC will review laboratory results for completeness. Any abnormal laboratory test results (clinical chemistry, hematology, or urinalysis) or other safety assessment (e.g., CPK), including those that worsen from the baseline, felt to be clinically significant in the medical and scientific judgement of the investigator, will be recorded as AEs. The SAC will review AEs weekly and SAEs on a daily basis and any events that the clinical centers categorize as requiring treatment discontinuation for safety reasons.

The following laboratory results will be flagged as expected study AEs in this trial:

- Thrombocytopenia: Platelet count >25% reduction from the baseline;
- Liver function test abnormalities: AST, ALT, total bilirubin, alkaline phosphatase > 4 times the upper limit of normal;
- Creatinine phosphokinase (CPK): > 4 times upper limit of normal;

The following symptoms will be flagged as expected study AEs in this trial:

- Bruising
- Bleeding
- Severe diarrhea
- Severe nausea
- Flushing
- Hives
- Heartburn.

8.3.5 ADVERSE EVENT REPORTING

Information on all AEs will be recorded on the appropriate eCRF. All related and relevant signs, symptoms, and results of diagnostic procedures performed because of an AE will be grouped together and recorded as a single diagnosis. AEs and SAEs related to COVID-19 outcomes or expected AEs with NR or study procedures will not be reported to sIRB and not adjudicated by SAC. Any baseline medical condition and laboratory results that are present at the time that the participant consented to the study but do not deteriorate will not be reported as an AE. However, if the medical condition deteriorates and any laboratory results become abnormal at any time during the study, these will be reported as AEs. Unexpected AEs and their relatedness to study drug or procedure will be reported.

Aggregate analyses of adverse events observed from the NIRAVA trial will detail new information regarding the investigational product NR (i.e. new side effects or increasing frequency of side effects) will be reported to SAC on weekly basis. Significant non-clinical findings will also be reported to SAC if they are suggestive of increased risk for study patricians.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigators will report all unexpected serious adverse events and their relatedness to study drug or procedure to the DCC within 24 hours of awareness or initial assessment. The DCC will then notify the sIRB and NIDDK. These reporting will follow the criteria outlined in 21 CFR 312.32(c). The SAC will be blinded to the randomization code and will determine if the event is unexpected and define the relationship to NR based on section 8.3.3.2. An adverse event is considered “unexpected” if it is not listed in the study protocol (21 CFR 312.32(a)). If a determination is made that a serious adverse event which is not exempt and has a reasonable possibility of having been caused by a study procedure or the study drug, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a SUSAR.

The DCC will report all unexpected deaths, serious and treatment related adverse events, and SUSARs to the DSMB and NIDDK within 7 working days after receipt of the report from a

clinical site. A written report will be sent to the DSMB, FDA, local IRB, and the sIRB within 15 calendar days. The DSMB will also review all reported adverse events and clinical outcomes during scheduled DSMB meetings. The DCC will distribute the written summary of the DSMB's periodic review of reported adverse events to the local IRB and sIRB in accordance with NIH guidelines (*http://grants.nih.gov/grants/guide/notice-files/not99-107.html*).

In addition, (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction will be reported to all investigators, sIRB, local IRB, the FDA, and the DSMB no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)].

Clinical Outcomes that will be Exempt from Serious Adverse Event Reporting

Pre-specified laboratory safety endpoints will be designated to evaluate possible laboratory abnormalities that might be seen with NR based on previous studies with NR (i.e., <10% reduction in hemoglobin and >25% reduction in platelet counts from baseline).

Study-specific outcomes of COVID-19 infection and critical illness will be systematically collected for all participants in both study group and are exempt from adverse event reporting unless the investigator considers the event to be Definitely or Possibly Related (or of an Uncertain Relationship – section 8.3.3.2) to the study drug or study procedures. Examples of study-specific clinical outcomes include:

- Death not related to the study procedures
- Cardiovascular events
  - Receipt of vasopressors
  - Atrial or ventricular arrhythmia
  - Cardiac arrest
  - Respiratory events
  - Hypoxemia requiring supplemental oxygen
  - Acute respiratory distress syndrome
  - Receipt of mechanical ventilation
  - Receipt of extra-corporeal membrane oxygenation
- Gastrointestinal events
  - Elevation of aspartate aminotransferase or alanine aminotransferase
  - Acute pancreatitis
  - Severe diarrhea
- Hematological events
  - Anemia

- Thrombocytopenia

Note: A study-specific clinical outcome may also qualify as a reportable adverse event.

8.3.7 EVENT ADJUDICATION PROCESS

Unexpected AEs and SAEs occurring from the time the informed consent signed through the Day 90 visit will be documented, recorded, and reported. Upon entry into REDCap eCRF, a notification will be generated to the independent site SAC member that unexpected AEs are ready for review. SAC members will be expected to review unexpected AEs within one week of notification. (Unexpected SAEs will have different language in the text and will require same day review by the SAC member.) SAC review will be separate from the expedited SAE reporting process and incomplete SAC assessment will in no way delay expedited SAE reporting.

Adjudicators will be blinded to the study treatment actually given to each patient and will use subject matter knowledge to render opinions regarding, for example, relatedness to treatment. The database will be configured so that certain baseline data will be viewable, including age, race, gender, BMI, diabetic status (diabetic, not diabetic), and current smoking status (smoker, not a smoker).

The REDCap adjudication module will compare the site investigator's AE grade and relatedness with that of the independent site SAC Physician. Where they agree, no further action will be needed and the AE will be submitted to statistician for reports to DSMB. Where the independent site SAC Physician disagrees with site investigator's AE grade and relatedness, the site investigator will be notified to review the report. Where the site investigator and independent SAC member agree, AEs that are not also other reportable events will be considered complete. AEs meeting the definition of other reportable events such as SAEs will trigger those processes with automated system notifications. Where the site investigator and independent SAC member disagree, the AE will be labeled as needing adjudications. Weekly adjudication meetings will be held if there are unexpected AEs needing adjudication. The study investigator will work collaboratively with the SAC on adjudication calls to make a final determination if an adverse event or reaction has a reasonable possibility of having been caused by the study drug or procedure as outlined in 21 CFR 312.32(a)(1). The protocol for handling of unexpected AEs and SAEs which are not uniformly adjudicated will be established. Any change to an adjudicated AE by a site investigator or SAC member will trigger review by the safety desk for impact on the adjudication. Where changes impact the adjudication decision, the event will be triggered for re-adjudication by the safety desk. The Adjudication process will be tracked and managed by DCC staff filling the Safety Desk role. AEs will be summarized for the DSMB as described in the DSMB plan.

8.3.8 REPORTING EVENTS TO PARTICIPANTS

Information regarding this clinical trial will be available on ClinicalTrials.gov. The study investigators will notify SAC, sIRB, DSMB, and FDA if new safety information regarding the nutritional supplement becomes available from ChromaDex and any published literature during the implementation of the study within three calendar days of obtaining the information. Study investigators will follow DSMB recommendation regarding how quickly the information is to be disseminated to participants.

8.3.9 EVENTS OF SPECIAL INTEREST

Not-applicable.

8.3.10 REPORTING OF PREGNANCY

Not-applicable.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An Unanticipated Problem (UP) is any event, incident, experience, or outcome that meets the following criteria:

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

8.4.2 UNANTICIPATED PROBLEM REPORTING

All unanticipated problems will be collected and defined as per the Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) – HHS regulations at 46.103(b)(5).

To satisfy the requirement for prompt reporting, UP will be reported
using the following timeline:

- UPs that are SAEs will be reported to the sIRB, local IRB, and the SAC within 24 hours of the investigator becoming aware of the event per the SAE reporting process described above.
- Any other UP will be reported to the sIRB, local IRB, and the SAC within 3 days of the investigator becoming aware of the problem.

As per the FDA guidelines [21 CFR 312.32(c)(2)], any unexpected fatal or life-threatening suspected adverse reactions to study active agent will be reported to the sIRB, local IRB, FDA, and DSMB no later than 7 calendar days after initial receipt of the information.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not-applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary analysis will perform a two-sided $\alpha = 0.05$ test of the null hypothesis of no difference in mean whole blood NAD+ level changes from the baseline and day 10 between the two arms, versus the alternative that participants randomized to the intervention arm have a different mean change than those randomized to placebo..

9.2 SAMPLE SIZE DETERMINATION

We evaluated using a marker of efficacy for NR with the whole blood NAD+ based on two recent publications [8, 15]. In a study of healthy overweight subjects 40-60 years of age, Conze et al. [8] found a 21 µg/ml mean NAD+ difference between patients randomized to 1000 mg NIAGEN versus those randomized to placebo at day 7 (NIAGEN 42 µg/ml, Placebo 21 µg/ml) with a standard deviation of 10 µg/ml and approximately equal baseline means (NIAGEN 21 µg/ml, Placebo 24 µg/ml). Simic et al. [15] assessed a combination of NR with pterostilbene (NRPT) vs placebo in hospitalized patients of age ≥ 18 years with AKI and found an 18% increase in whole blood NAD+ within 48h post treatment in the NRPT group, and a 50% reduction from baseline in the placebo group with AKI. With reference to Conze et al. [8] al., this study will achieve >99.9% power for testing H_o:$R_{NR} = R_{Placebo}$ versus H_o: $R_{NR} \neq R_{Placebo}$ with alpha=0.05, autocorrelation (ρ)=0.5, and n=40 per arm where R_{NR} and $R_{Placebo}$ are the rates of change from baseline to day 10 in the NR and Placebo arms, if the effects observed in this study are the same as those observed by Conze et al. with regard to NAD+. In this setting the effect size is 2.1 [=(42-21)/10] and the minimally detectable effect size is 0.63.

9.3 POPULATIONS FOR ANALYSES

We will summarize the number of participants that are screened, enrolled, and randomized, including reasons for exclusion at each step. In accordance with the intention-to-treat principle, the primary analytic population will consist of all randomized participants, who will be evaluated according to their randomly assigned treatment arm and regardless of whether they adhere to study protocol or complete the study. We will further analyze the safety population of all randomized participants who receive any amount of study drug, analyzed according to the study drug received rather than the assigned intervention..

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

In general, continuously distributed data will be summarized with the sample size, mean, standard deviation, median, minimum, and maximum. Categorical and binary data will be summarized with frequencies and percentages. Raw data storage, documentation, and security will be effectively served with the REDCap platform. Participants will be randomized to treatments in randomly permuted blocks of size 2 and 4 stratified by clinical site.

The number of participants screened, the number of screen failures by reason, and the number eligible for randomization, the number randomized, and, by treatment (Placebo, NR), the number withdrawing from the study for any reason, lost to follow-up by reason, unable to receive at least one dose and replaced, and the number completing the study per protocol will be tabulated and summarized with a CONSORT Diagram. We will also describe adherence to treatment over the course of the study, overall and by treatment arm.

Randomized controlled trials often suffer from two major complications, i.e., noncompliance and missing outcomes. One potential solution to this problem is a statistical concept called intention-to-treat (ITT) analysis, to be used in this trial. ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. ITT analysis maintains prognostic balance generated from the original random treatment allocation. In ITT analysis, estimate of treatment effect is generally conservative [83].

Missing data can threaten the inferences made about study questions. The study team will make every effort to minimize the impact of missing data, including attempting to obtain final information on participants even if adherence to study procedures is poor or they do not follow the randomized treatment. In cases where missing data is unavoidable, we will use multiple imputation using chained equations to impute outcomes and relevant covariates to mitigate the potential impact of missing data, combining across imputations with Rubin’s rules to account for

the variability in the imputation procedure [84]. Any data point that appears erroneous or inexplicable based on clinical judgement will be investigated by study staff. If data points are considered to be outliers then sensitivity analyses will be carried out with and without the suspected outlier. Under the missing at random (MAR) assumption the estimates provided by our planned repeated measures statistical models using maximum likelihood estimation will be asymptotically unbiased [85].

All data will be summarized by treatment and clinical site in all randomized participants. Statistical estimates of treatment effects (with 95% confidence intervals, where appropriate), and p-values will be tabulated. All statistical tests will be two-sided with a significance level of 5%. R and/or SAS will be used throughout. Due to the overall exploratory nature of this study corrections for multiple comparisons will not be applied.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

PRIMARY END POINT: Blood NAD+ level

The null hypothesis to be tested is H_o:R_{NR}=$R_{Placebo}$, where R_{NR} and $R_{Placebo}$ are the rates of change from baseline to day 10 in the NR and Placebo arms. We expect that the rate of change in NAD+ from baseline to day10 with NR treatment will be increased relative to Placebo. Whole blood NAD+ will be measured daily in each patient during the first 10 days upon randomization. NAD+ level changes from the baseline will be graphically summarized with overlaid line and whisker plots of the mean trajectory for each arm with the whiskers being of length equal to one standard error of the mean. The significance of treatmement group differences with regard to the rate of change of NAD+ will be assessed using the methods of Schluchter et al [86] to address informative censoring, due for example to dialysis and death, with a random subject effect to account for the correlation among repeated measures within an individual. The model will include treatment and day. The day by treatment interaction will be of interest and will be addressed with the coefficient of the day by treatment interaction term to be added to the unadjusted model. Adjusted analyses will be carried out with age, race, clinical site, baseline serum creatinine, treatment and day included in the model. The unadjusted and adjusted models will be summarized with the coefficients, standard errors, 95% confidence intervals and p-values. A day by treatment interaction term, treatment by day, and treatment by clinical site interactions will be considered and reported and described if found significant ($p<0.10$). We will examine potential treatment interactions among subgroups of interest such as age, and sex. Consistent with the power calculation (Section 9.2), these models will be used to provide treatment group contrasts on the mean rate of change (estimated by the coefficient of day in the model, also known as the slope parameter), summarized with the model-based mean rates of changs, mean differences in rates of change and 95% confidence intervals and p-values. Spaghetti plots and plots of the mean NAD+ trajectories by treatment group, and mean rates of change, will be reported.

Potential participants who may have severe AKI or advanced CKD will be considered with a binary independent variable in the models addressing this condition with corresponding displays of the line and whisker plots by treatment group and summary tables of coefficients, standard errors and p-values. Interactions between this binary variable and treatment will be of interest and will be described.

Capture and tabulation of concomitant medications, dialysis, co-enrollment in another COVID-19 clinical trial, any new standard of care, pre-existing CKD, and treatments by study arm (NR, Placebo) may be used to define other potential adjustments with binary or categorical variables to be defined post hoc in exploratory analyses. Such models may motivate extended interpretations of any treatment effects found.

PRIMARY END POINT: Safety

All reportable AEs will be listed by Preferred Term by subject, treatment, clinical site, grade, relation to treatment, severity, and seriousness. All unanticipated events will be listed by treatment and clinical site with a detailed description of each event, incident, experience or outcome. An unblinded statistician will summarize safety data periodically for the DSMB.

AEs will be tabulated by treatment and clinical site, displaying, for each event, the number and percentage of participants experiencing at least one Grade 3 or 4 occurrence and he null hypothesis to be tested is H_o: $p_{NR}=p_{Placebo}$ where p_{NR} and $p_{Placebo}$ are the probabilities of experiencing at leat one Grade 3 or Grade 3 event in the NR and Placebo groups. H_o will be tested with Fisher's Exact test, overall and by clinical site. Additionally, treatment groups will be contrasted on the occurrence at least once of each event with Fisher's exact test. All statistical testing will be two-sided with a significance level of 5%.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

SECONDARY END POINT: AUC Serum creatinine over 10 days adjusted for baseline serum creatinine

We expect that rate of change in AUC serum creatine will be decreased in the NR group relative to the Placebo group. The null hypothesis to be tested is H_o:$R_{NR}=R_{Placebo}$, where R_{NR} and $R_{Placebo}$ are the rates of change in serum creatinine from baseline to day 10 in the NR and Placebo arms. Serum creatinine will be measured daily in each patient during the first 10 days upon randomization. Serum creatinine AUC will be graphically summarized with spaghetti plots and overlaid line and whisker plots of the mean trajectory for each arm with the whiskers being of length equal to one standard error of the mean. To address non-ignorable missingness due to dialysis, death, or withdrawal of consent, all of which may be considered as informative

censoring, the statistical method will be the same as that specified for NAD+. Potential participants who may have severe AKI or advanced CKD will considered with a binary independent variable in the models addressing this condition with corresponding displays of the line and whisker plots by treatment group and summary tables of coefficients, standard errors and p-values. Interactions between this binary variable and treatment will be of interest and will be described.

SECONDARY END POINT: Serum creatinine AUC and ordinal categorical outcome with four categories including dialysis and death

Serum creatinine AUC will be computed using the trapezoidal rule within each patient starting from randomization to day 10, and will be assigned to Category 1 if AUC < median AUC, to Category 2 if AUC ≥ median AUC in those who do not experience dialysis and who do not die during the first 10 days of hospitalization. Patients who experience dialysis at any time during the 10 day period will be assigned to the Category 3 and those who die during the first 10 days of hospitalization will be assigned to Category 4. The null hypothesis is H_o: $OR_1=OR_2=OR_3=1$, where OR_1, OR_2, and OR_3 are the odds ratios for Categories 1, 2, 3, and 4. If the proportional odds model holds the null hypothsis is H_o:OR=1 where OR is the single odds ratio summarizing the treatment effect. With NR treatment we expect that the odds of Category 1 will be increased, the odds of Category 2, 3, and 4 will be decreased.

The primary analysis will be based on a cumulative logit model for ordinal data of the primary outcome with terms for treatment, age, gender, clinical site, and baseline serum creatinine. The proportional odds assumption will be tested with a score statistic and empirical logit plots. If the proportional odds assumption is violated then the analysis will be conducted under a partial proportional odds assumption. Under a partial proportional odds assumption, three odds ratios will be estimated; if evidence suggests that the proportional odds assumption holds, a single odds ratio will summarize the treatment effect. In either case, the odds ratio estimate(s), 95% confidence interval(s), and p-value(s) will be reported. Further study will be indicated if the p-value for any treatment effect suggesting benefit in the NR arm is less than or equal to 0.05.

SECONDARY END POINT: Major Adverse Kidney Events (MAKE)

The null hypothesis is H_o:HR=1 where HR is the ratio of the hazard of MAKE with NR treatment to the hazard of MAKE with Placebo treatment. We expect that HR will be less than 1. MAKE is defined as Yes if a doubling of serum creatinine (from baseline), the initiation of long-term dialysis, or death from any cause is observed, and No otherwise. Treatment arms will be compared with regard to the time to the first occurrence of MAKE over the entire duration of the study from baseline to 90 days post-randomization with proportional hazard models of time to MAKE in terms of treatment without and with adjustment for age, race, clinical site, baseline

serum creatine. The coefficients, standard errors and 95% confidence intervals and corresponding hazard ratios will be reported without and with adjustment for covariates. The proportional hazards assumption will be assessed with Schoenfeld residuals and log survival plots. The unadjusted model will be graphically summarized with overlaid Kaplan Meier curves and the p-value for the corresponding log rank test. Covariate interactions with treatment will be of interest and will be explored.

SECONDARY END POINT: Kidney impairment as indicated by eGFR and proteinuria at 30 and 90 days

The null hypothesis to be tested is H_o: $R_{NR}=R_{Placebo}$, where R_{NR} and $R_{Placebo}$ are the mean rates of change of eGFR in patients randomized to NR or to Placebo respectively from baseline to day 30 and day 90. We expect the eGFR rate of change to be increased with NR relative to Placebo. The same hypothesis will be tested for proteinuria, using log-transformed urinary albumin-to-creatinine ratio, where we expect the mean proteinuria rate of change to be decreased with NR relative to Placebo.

We will quantify kidney dysfunction at 30 days and 90 days post-randomization, measured by eGFR calculated by the CKD-EPI (the Chronic Kidney Disease Epidemiology Collaboration) equation [87] and the urine protein/creatinine ratio (PCR). To address non-ignorable missingness due to dialysis, death, or withdrawal of consent, all of which may be considered as informative censoring, the statistical method will be the same as that specified for NAD+.

eGFR will be evaluated untransformed, while urine PCR will be log-transformed to evaluate percent change because urine PCR is highly skewed and relative changes in urine PCR are proportional to risk of adverse renal and cardiovascular outcomes. We will include time, treatment, and interactions of treatment with time as independent variables in a mixed effects linear model. We will focus on the coefficient for the interaction of treatment with time as the primary measure of treatment effect. We will consider a p-value <0.05 for this interaction term to indicate a significant treatment effect. These analyses will be further adjusted for baseline characteristics that are prognostic of the outcome, including age, sex, clinical site, and stage of AKI at randomization. Adjustment will be accomplished by adding covariates and interactions of covariates with time.

9.4.4 SAFETY ANALYSES

Please see section 9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Treatments groups will be summarized overall and by clinical site at baseline with regard to demographic characteristics (age, race, ethnicity, and gender), and clinical, laboratory and questionnaire measurements of efficacy (Section 8.1).

9.4.6 PLANNED INTERIM ANALYSES

An O'Brien-Fleming procedure will be used to conduct an interim analysis for safety when 50% of the patients complete the study. A statistical basis for stopping the study at the first look will be achieved if the test statistic for the primary safety endpoint (the occurrence of at least one serious adverse event of grade 3 or higher or the occurrence of thrombocytopenia less than 50,000 per microliter) indicates harm in the NR arm at $p \leq 0.003$. If the test statistic does not reach $p \leq 0.003$ at the first look then the trial will proceed to the final analysis. The statisticians (Drs. Joel Michalek and Leila Zelnick) will inform the principal investigator if the interim analysis crosses the boundary in the direction of harm is observed ($p \leq 0.003$). A treatment effect will be declared harmful at the final analysis if the test statistic indicates harm and $p \leq 0.047$. The safety data will be summarized at interim analysis. The statisticians will inform the DSMB if there are any safety concerns at the interim analysis. Any decision on stopping the study based on safety will be made in coordination with NIDDK and the DSMB.

9.4.7 SUB-GROUP ANALYSES

Not applicable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

9.4.9 EXPLORATORY ANALYSES

EXPLORATORY END POINTS:
Correlations between whole blood NAD+, AUC serum creatinine, and surrogate markers of AKI (such as KIM-1 and NGAL) will be quantified with Pearson or Spearman correlation coefficients, 95% confidence intervals and p-values and visualize with scatter plots and overlaid least square lines. Relationships between these variables by treatment group will tabulated and summarized graphically with scatter plots and overlaid line specific to each treatment. Principal component analyses may be used. Data may be log transformed prior to analysis and graphics.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

This study will be conducted in conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research (US National Commission for the Protection of Human Participants of Biomedical and Behavioral Research; April 18, 1979), and the federal policy for the Protection of Human Participants codified in 45 CFR Part 46, 21 CFR Part 50 (Protection of Human Participants), and the ICH E6 (R2).

Each institution engaged in this research will hold an OHRP-approved FWA. sIRB will review and approve this protocol, associated informed consent documents, recruitment material, and handouts or surveys intended for the participants, prior to the recruitment, screening, and enrollment of participants. The sIRB review shall be in accordance with 45 CFR 46 and 21 CFR 50, 21 CFR 56 (IRBs), and other federal, state, and local regulations and policies, as applicable. Local site IRBs may have additional national and local regulations.

Any amendments to the protocol or consent materials will be approved by the DSMB and followed by sIRB before they are implemented. sIRB review and approval will occur at least annually throughout the duration of the study. The investigator will notify the sIRB of any deviations from the protocol and SAEs, as applicable to the sIRB policy.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Consent forms describing in detail about the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Investigators or designated research staff will obtain a participant's informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed. All consent forms will receive prior approvals from sIRB followed by institutional/hospital IRBs with the incorporations of any local guidelines or requirements.

Typically, participants or their LAR receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. Participants (or

LAR) must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the participant or the LAR for their records.

Many of the participants approached for participation in this research protocol will have impaired decision-making capacity due to critical illness and will not be able to provide informed consent. Accordingly, informed consent will be sought from the participant's LAR. Regarding consent from the LAR, the existing federal research regulations ('the Common Rule') states at 45 CFR 46.116 that "no investigator may involve a human being as a subject in research…unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative"; and defines at 45 CFR 46 102 (c) a LAR as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures(s) involved in the research." The Office of Human Research Protections (OHRP) defined examples of "applicable law" as being state statutes, regulations, case law, or formal opinion of a State Attorney General that addresses the issue of surrogate consent to medical procedures. Such "applicable law" could then be considered as empowering the LAR to provide consent for participant participation in the research. Interpretation of "applicable law" may be state specific and will be addressed by the sIRB and local IRB.

Participants for whom consent was initially obtained from a LAR, but who subsequently regain decision-making capacity while in the hospital will be approached for consent for continuing participation, including continuance of data acquisition. The consent form signed by the LAR should reflect that such consent should be obtained.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved. Due to the unique challenges of COVID-19 infection and risk to others in close proximity several alternatives have been considered for the informed consent procedure. In most instances, bringing a paper consent form and pen to the bedside of a participant with known COVID-19 and then taking these out of the room would violate infection control principles and policies. Given the infectious risk from COVID-19 and potential shortages of PPE, there is a moral and practical imperative to minimize face-to-face contact between participants and non-clinical personnel. The current epidemic also presents unique challenges to obtaining consent from participant's LAR. The LAR is likely to have been exposed to the participant and may therefore be under self-quarantine at the time of the informed consent discussion. Therefore, in addition to the traditional approach of an in-person consent discussion and signed paper informed consent, we will allow use of "no-touch" consent procedures.

The first preference will be to use the FDA COVID MyStudies App platform to obtain informed consent via iPads or smartphones securely from participants or LAR in accordance with 21 CFR 50.27(a). Once the participant or representative has signed the form, he or she will receive an electronic copy. The study team will then access the signed consent in a secure manner and print it or transfer the file electronically.

If this approach is not possible (e.g., not compatible with the existing phone or computer device), the next approach will be providing an unsigned consent form to the patient by a hospital staff or study team member with appropriate PPE who has entered the room. The study team will arrange a telephone call with the participant to review the informed consent document and to obtain verbal confirmation by the participant that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the informed consent document that is in their possession. The consent form will document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party will witness the entire consent process and sign the consent document. If a participant is unable to provide consent on their own behalf, then the study team will obtain consent from a LAR and verbal consent with a witness will be obtained with appropriate documentation as described above. Finally, the participant, the hospital staff or study team takes a photograph of the signed informed consent document. The study team enters the photograph into the trial records and documents the consent process in the source document. If it is not possible to obtain a digital image of the signed page, the study team will document that the participant signed and dated the ICF, document that an imaging device was not available; and have a witness to the consent process. The entire consent process will be documented in the study records..

Attestation of informed consent

If none of the options outlined above (traditional signature and storage of a paper consent form, electronic photographs of a signed consent page, or e-consent) are available, study personnel may attest to completion of the informed consent process using the procedures outlined below. Importantly, the process of informed consent using this attestation option should not change compared with the traditional method of obtaining informed consent for trial participation except for the method of documenting the consent process in the research record. Rather than storing a paper document with the participant's signature, a member of the research team and an impartial witness will attest to completion of the informed consent process and that the participant signed the informed consent document. This option of attestation of informed consent will not be available when obtaining consent through an LAR.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

If the study is prematurely terminated or suspended, the site investigator will promptly inform study participants, the sIRB, and the FDA and provide the reason(s) for the termination or

suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sIRB, the FDA and the NIDDK.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning participants in the study, or the data will be released to any unauthorized third party without prior written approval. All research activities will be conducted in as private a setting as possible. Participant confidentiality will be maintained when study results are published or discussed in conferences.

The representatives of the sIRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or regulatory requirements. All collected data including electronic and hard copy source records and hard copies will be securely stored. Hard copy records will be stored in a locked cabinet in the principal investigator's Research Office accessible to study coordinator and investigator or other designated research staff. The electronic records will be saved and stored in an institutional computing server accessible by designated study staff such as study coordinator and investigator using unique username and password.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a participant through a code key maintained at the clinical site.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be stored and analyzed at the coordinating site principal investigator's laboratory. After the study is completed, the de-identified, archived data will be stored on the UTHSA server for the Nephrology Division in a folder specifically for this project, for use by study investigators and researchers included in this study. Biosamples will be made available to non-study investigators via NIH policy guidelines.

Secondary Human Subject Research is defined as the re-use of identifiable data and/or identifiable biospecimens that were collected from the primary study – the NIRVANA study. Each specimen will be labeled only with a barcode and a unique tracking number to protect participant confidentiality. Secondary research with coded specimens and data may occur; however, participant confidentiality will be maintained.

A participant's decision can be changed at any time by notifying the study doctors in writing. If the participant subsequently changes his/her decision, the samples will be destroyed if the specimens have already not been used for research or released for a specific research project.

All data collected in this study will follow NIH Data Sharing Polices. Data from this study may be used for secondary research. All of the individual participant data collected during the study will be made available after de-identification. The investigator may request removal of data on individual study participants from NIH data repositories in the event that a research participant withdraws or changes his or her consent. However, some data that have already been distributed for approved research use cannot be revoked or retrieved.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator/Sponsor	
Kumar Sharma, MD	
University of Texas Health San Antonio-Department of Nephrology	
7703 Floyd Curl Drive, San Antonio, Texas 78229	
210-567-4700	sharmak3@uthscsa.edu

The Steering Committee will consist of the PI's of each of the study sites.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the DSMB. The SAC will adjudicate all reportable AEs (including SAEs) using supporting documents. The unexpected AEs and SAEs will be reported to the SAC who will determine if the DSMB will need to evaluate for unblinding. To avoid bias, SAC member will be masked to the study arm of a participant. Adjudicators will receive training on the adjudication process.
Once data are submitted for a participant, the database will notify SAC member that data are available and require AE review. SAC member will either confirm or refute the initial assessment reported by site investigators blinded to the treatment assignment. If discrepancies occur between the assessments, the disagreements will be adjudicated on a weekly adjudication call with the site investigator and the site SAC member. If disagreement persists, the site investigators and the SAC members will formally meet to discuss the event and come to a consensus decision. All SAEs will trigger immediate notification to the site investigator, site SAC member, DCC staff, and the statistician.

There will not be any formal clinical site monitoring for conduct of the site activities. However, institutional IRB and Human Subject Protection Committee or institutional compliance may perform auditing according to local procedures to ensure that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) formed and appointed by the NIDDK/NIH. Details of the NIDDK policies regarding DSMBs can be found at the following URL *https://www.niddk.nih.gov/research-funding/human-subjects-research/policies-clinical-researchers/data-safety-monitoring-plans*. Members of the DSMB will remain independent from the study conduct and free of conflict of interest. The DSMB will provide its input to the steering committee and NIDDK, and any relevant safety findings will be reported to NIDDK, the FDA and to the sIRB.

10.1.7 CLINICAL MONITORING

There is no clinical site monitoring for this study. However, each site investigator and sub-investigators will conduct weekly meetings to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). In these weekly meetings, site investigator will review the regulatory files, accountability records, eCRFs, ICFs, medical and laboratory reports, training records, and protocol and GCP compliance.

The local IRB may monitor and audit or otherwise supervise the study activities. Institutionally provided regulatory auditing by the respective site's human protection office as well as applicable oversight committees may occur after enrollment of the first participant and at least once a year until the study is completed. In addition, respective site's Research and Compliance office or equivalent (e.g., Human Research Protection Program) may conduct random or for cause audits of the study and report any findings to the respective IRB. These roles and responsibilities of the local IRB will be explicit in the authorization agreement with sIRB.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the REDCap data entry system and data checks for missing, out of range and logically inconsistent data values that will be run on the database. The Principal Investigator will be responsible for overseeing data management.

All sites will maintain written Standard Operating Procedures (SOPs) covering study activities. The site principal investigator will verify that the clinical trial conduct, data generation, and biological specimen collection, documentation and recording, storing, and reporting are in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP).

All study personnel at three recruiting sites will be trained on study protocol including (i) participant screening methods and techniques, (ii) eligibility determination, (iii) consenting process, (iv) completion of each study visit procedures, (v) data collection, entry, and reporting, (vi) biospecimen collection and processing, and storage via Webinar and PowerPoint slides using Zoom or other audiovisual methods for consistency and harmonization. The DCC, in collaboration with two other sites, will prepare the MOP to ensure consistency in protocol implementation from study activation/inception until closure and data collection across participants and study sites. The MOP will be developed by the DCC as soon as protocol is finalized. All sites will strictly adhere to the MOP to maintain scientific credibility and provide reassurance that participant safety and scientific integrity are closely monitored. The MOP for the NIRVANA protocol will contain details of the study's conduct and operations including (i) study's organization, (ii) operational data definitions, (iii) recruitment, (iv) screening, (v) enrollment, (vi) randomization, (vii) follow-up procedures, (viii) data collection methods, data

flow, eCRFs, and (ix) guidelines for site-level quality control procedures. The MOP will be amended in a timely manner to reflect any amendment to the protocol.

The DCC will determine site activation (shipment of study supplies) based on successful completion of training, a signed site agreement, and a successful study activation web-meeting. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of auditing and inspection by local and regulatory authorities.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. Each local site principal investigator will maintain complete and accurate source documentation. All source documents will be completed in an ALCOA (Attributable, Legible, Contemporaneous, Original and Accurate) legible manner to ensure accurate interpretation of data.

Sites will follow Good Documentation Practices for all study documentation. Each site will maintain a local (site) Trial Master File. This is sometimes referred to as site "regulatory documents". The DCC will maintain a TMF for DCC trial documentation originating at the DCC. Each site will create and maintain source documents as defined in ICH E6 R2 for each participant.

The DCC will draft a formal Data Management Plan that specifies all operations performed on data from study data acquisition through database lock when no further changes to data are allowed. The majority of the Data Management Plan will be accomplished through a web-based Electronic Data Capture (EDC) system for the study developed using REDCap. Sites will be trained on use of the study database including screening log completion, data entry, independent Source Document Verification for point estimation of the medical record abstraction error rate, responding to identified data discrepancies, biosample tracking, CTCAE classification and grading, and the SAC event review and adjudication processes. Study-specific procedural documentation for these processes will be provided in the MOP.

REDCap Study Database: The REDCap database for the NIRVANA study will be developed and maintained by the DCC. Access to the REDCap data system will be granted to individuals upon completion of training. Accessing the REDCap study database will require a user account with permissions on the study. A user-maintained password will be entered to log into the system. All study data will be entered by sites into the REDCap study database. To the extent of the REDCap system capabilities, upon entry data quality checks for missing, out of range and logically inconsistent values will be run. These checks should be resolved by sites during data entry. Because REDCap has limitations with respect to rule-based identification and tracking of data discrepancies, comprehensive discrepancy identification and tracking will be performed through the Informatics Data Exchange and Acquisition System (IDEAS). Complex checks not

possible in REDCap will be accomplished through the IDEAS system. Where noted below, workflows will be automated based on data collected in the REDCap database. Study data will be accessible to sites from the REDCap system.

Screening Log: All potential participants for which EHR screening is performed will be entered in a de-identified manner on the site screening on REDCap. At the time of entry into the screening database the participants will be assigned a screening number. The screening log will capture inclusion and exclusion criteria leading to the site determination of "ineligible". Additionally, the screening log will cover the period between screening and enrollment. As such, the screening log will also document the reason/s "eligible" potential participants were not enrolled. The screening log will not contain dates or other information considered identifiable health information. The screening log will contain de-identified data elements that may be used to compare enrolled and non-enrolled participants to assess generalizability.

Clinical Data: Clinical data from the EHR (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the REDCap study database.

Adverse Events and Serious Adverse Events: Reportable AEs will be entered into the REDCap study database. Reportable AEs will be entered, classified, and graded according to the most current versions of the CTCAE by the site investigator and independent site SAC Physician. Adverse events indicated as Serious Adverse Events will result in real-time alerts through the REDCap system to support expedited reporting. Entry of reportable Adverse Events will trigger notification to the independent SAC physician to initiate the independent review and adjudication process as described in section 8.3.7. AEs will be coded at the DCC using the MedDRA controlled terminology.

Biosample Inventory and Tracking: The REDCap study database will include screens at each visit for sites to report samples obtained and shipped to the UTHSA COVID-19 Repository. Sample tracking will trigger notification to the repository. Samples received will be reconciled with REDCap biosample tracking on the day of receipt. Data status reports will flag expected and missing sample tracking data.

Data Status Reports: Enrollment data will be entered into REDCap on the day of enrollment. Enrollment entry enables tracking and management of participant data and samples and will trigger notification to the site and DCC study team. Data entry will be entered every day during the 10-day treatment period and within one week of follow-up visits. Late data will be listed on an exception report by site and by participant. Similarly, data discrepancies will be resolved within a week of firing. Late data discrepancy resolutions will be listed on an exception report by site and by patient. Data will be reviewed by the DCC within 24 hours of complete entry.

The site investigator will be responsible for review of data collection tools and processes, and review of data and reports.

10.1.8.2 STUDY RECORDS RETENTION

Study related records, including the regulatory file, study product accountability records, consent forms, participant's source documents and electronic records should be maintained for a period no shorter than 2 years following the completion of the study and may be retained longer per institutional policies. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in nonexempt human subject research. Local institutional and applicable NIH policies will be adhered to and records will be retained according to whichever policy dictates a longer period in order to remain compliant with retention policies.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Major Deviation: Major protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participants' rights, safety, or well-being. Examples may include:

- Enrolling participants who did not meet eligibility criteria
- Performing study procedures before obtaining informed consent
- Failure to obtain and/or document informed consent
- Failing to follow protocol procedures that specifically relate to the primary safety or efficacy endpoints of the study

Minor Deviation: Minor protocol deviations are a subset of protocol deviations that do not have a major impact on either the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Examples may include:

- Follow up visits occurring outside the protocol required time frame because of the participant was not available or other restrictions;
- Blood samples being obtained at times close to but not precisely at the time points specified in the protocol.

All protocol deviations will be entered on the Protocol Deviation Log in REDCap and submitted to the sIRB as well as respective site's IRB per their policies. All major deviations will be promptly submitted to sIRB and local IRB. Site will also submit all protocol deviations to DSMB as per DSMB guidelines. The site investigator is responsible for knowing and adhering to the sIRB and DSMB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Following completion of the study, collected data will be analyzed, interpreted, and disseminated in the form of abstracts or posters to relevant scientific society meetings and published in relevant peer-reviewed journals. In addition, results will be posted at clinicaltrials.gov. Data sharing will conform to NIH policies.

Data from this study may be requested from other researchers with no end date after the completion of the primary endpoint by contacting the coordinating site principal investigator. Data will be available immediately following publication of study findings, with no end date, with data sharing at the discretion of the Sponsor NIH. Publication may occur prior to completion of a final clinical study report for the entire trial.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry (ChromaDex), is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Committee
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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