Clinical Study Protocol

Protocol Title:	**A Pilot Trial of Thymalfasin (Ta1) to Prevent COVID-19 Infection in Elderly Renal Dialysis Patients**
Investigational Drug:	ZADAXIN® (thymalfasin/Ta1) Lyophilisate for Solution for Injection
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Date: 17 April 2020

1 INVESTIGATOR AGREEMENT SIGNATURE PAGE

Protocol Title: A Pilot Trial of Thymalfasin (Ta1) to Prevent COVID-19 Infection in Elderly Renal Dialysis Patients

Original Protocol Issue Date: 17 April 2020

I have read the attached protocol and appendices dated 5 April 2020 and agree to abide by all provisions set forth therein. I will provide copies of the protocol and other pertinent information to all individuals responsible to me who will assist with the study.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 Code of Federal Regulations Parts 11, 50, 54, 56, and 312.

Before study initiation, during the study if there are changes that affect my financial disclosure status, and after the study is completed, I agree to ensure that Financial Disclosure Statements will be completed by:

- Myself and dependent children
- My Subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

17 April 2020

_____ _____

Signature of Principal Investigator Date (DD MONTH YYYY)

_____

William B. Ershler, MD

2 PROTOCOL SYNOPSIS

Product:	ZADAXIN® (thymalfasin/Ta1) lyophilisate for solution for injection
Title of Study:	A Pilot Trial of Thymalfasin (Ta1) to Prevent COVID-19 Infection in Elderly Renal Dialysis Patients
Phase of Development:	Pilot Study
Background and Rationale:	Ta1 is a naturally occurring peptide with immunomodulatory activities. ZADAXIN® Ta1 is a synthetic version currently approved for use in 37 countries; in particular it is approved in China hepatitis B and to enhance vaccine response. Ta1 has also been studied in multiple clinical trials in the United States. Ta1 has been used clinically in pilot studies for treatment of SARS and other lung infections including acute respiratory disease (ARD) and chronic obstructive pulmonary disorder (COPD), as well as infections after bone marrow transplant. The beneficial clinical effects of Ta1 result from activation of toll-like receptor (TLR) 9 in dendritic and other immune system cells, resulting in augmentation of T helper (Th1) function, natural killer (NK) cell activity, and increased antibody responses to T-cell dependent antigens. Importantly, Ta1 also leads to an increase in IL-10 producing regulatory T cells, which create feedback inhibition of cytokine production, hence dampening immune response and preventing a pro-inflammatory cytokine storm. Based on post-marketing treatment experience of more than 600,000 patients, Ta1 has been well tolerated. Ta1 has been administered to elderly subjects (up to 101 years old), children (as young as 13 months), and immunocompromised patients. The most common adverse events in previous clinical trials include injection-site pain (such as burning and itching) which was mild and lasted for less than 30 minutes, as well as fever, nausea, and flu-like symptoms which were mild to moderate in severity. Thus, while Ta1 is one of only a few immunomodulatory agents that have been approved for human use, it does not appear to induce most of the side effects and toxicities commonly associated with other biological response modifiers (BRMs) in this class, such as interferon and interleukin-2. The actual dose, frequency, and length of treatment with Ta1 have differed depending upon the indication, ranging from 1.6 mg twice a week for up to 12 months; 1.6 mg twice a day

	for several weeks; 6.4 mg daily, 4 days a week, for 2 weeks out of every month up to 6 months in duration; and 16 mg twice a week for four weeks, with few adverse events observed. The proposal to evaluate Ta1 at a dose of 1.6 mg is based on previous studies which have shown an increase in dose above 1.6 mg to show little, if any, improvement in response. Patients with end-stage renal disease (ESRD) on hemodialysis, in addition to their intrinsic kidney disease and frequent burden of comorbidities, also have increased risk of exposure to communicable diseases as they are treated several times each week at hemodialysis centers with several other patients and clinic staff in attendance. The majority of patients are over 60 years of age and many are receiving immunosuppressive medications. Accordingly, ESRD patients are particularly susceptible to COVID-19 infection. Ta1 has been shown to be safely administered to hemodialysis patients on a similar schedule to that proposed below, and was efficacious in enhancing influenza vaccine responses [1].
Objectives:	**Primary Objective** To demonstrate that Ta1 administered twice weekly for eight weeks to renal dialysis patients 60 years and older will reduce the incidence of COVID-19 infection compared with a similar population of patients who do not receive Ta1. **Secondary Objectives** 1. To demonstrate that renal dialysis patients treated with Ta1 who become infected with COVID-19 will have a milder course of infection in terms of hospitalization rate, requirement (length) for ICU stay, requirement for mechanical ventilation, and survival than renal dialysis patients not treated with Ta1. 2. To demonstrate a decrease in hospitalization rates in renal dialysis patients treated with Ta1 who are not infected with COVID-19 compared to those not treated with Ta1.
Study Design:	It is our hypothesis that a course of Ta1 administered to individuals at high risk for COVID-19 infection will reduce the rate of infection (primary objective) and severity of infection (secondary objective) with COVID-19, compared to untreated individuals in the same hemodialysis units with

	comparable risk. The secondary objectives also include an evaluation of the need for hospitalization in those patients who do not become infected with COVID-19. Ideally, a randomized clinical trial with placebo control would be a preferred approach to address this hypothesis. However, the urgency of the current situation necessitates a simpler research design and implementation. Accordingly, we consider this a pilot study from which meaningful clinical data may rapidly be apparent. After screening, renal dialysis patients 60 years and older who meet the inclusion criteria will receive Ta1 (1.6 mg) administered subcutaneously (SC) twice weekly for eight weeks. Individuals in the control arm will be followed on the identical protocol but will not receive twice weekly Ta1. After the treatment period, all subjects will be followed for efficacy outcomes for an additional 4 months.
Sample Size:	A total of up to 240 patients will be enrolled
Countries:	U.S.
Study Period:	Once FDA and IRB approval are obtained, the research team will promptly initiate the process of subject recruitment. Recruitment of all subjects will be completed in four months and the observation phase in one year.
Diagnosis and Main Criteria for Inclusion:	1. Age 60 or greater 2. Signed informed consent 3. End-stage renal disease (ESRD) who receive hemodialysis 2 or more times each week and are expected to continue on dialysis indefinitely.
Main Exclusion Criteria:	1. Patients on short-term hemodialysis, such as those with transient renal dysfunction associated with acute illness who are projected to have return in renal function 2. Patients for whom renal transplantation is anticipated within the next six months 3. Patients with an anticipated survival of less than 3 months 4. Patients with symptoms that might be attributable to COVID-19 infection (see Appendix 1 for symptom questionnaire) 5. Patients who test positive for SARS-CoV2

	6. Patients with active infectious disease requiring antibiotics 7. Patients with hospitalization within the previous 3 months for acute myocardial infarction or congestive heart failure 8. Patients with advanced malignancy receiving cytotoxic chemotherapy 9. Patients with a Karnofsky Performance Scale score of less than 60 10. Patients with prior history of solid organ (kidney, liver, heart, lung, pancreas) or bone marrow transplant 11. Patients with active autoimmune disease on immunosuppressive medication 12. Patients receiving Plaquenil 13. Participation in an investigational drug or device trial in previous 30 days 14. History of allergy or intolerance to Ta1 15. Any other medical or psychiatric condition that, in the opinion of the Investigator, would compromise patient safety or interfere with the objectives of the protocol or completion of the protocol treatment.
Drug Formulation:	Ta1 is contained, stored, and dispensed from individual tamper-proof glass vials with 1.6 mg Ta1 as a lyophilized cake containing 5% mannitol, buffered with phosphate to pH 6.4-7.3. Vials are reconstituted with 1 mL of supplied diluent (sterile Water for Injection), prior to subcutaneous administration.
Dose and Mode of Administration:	Active arm: 1.6 mg Ta1 in 1 mL SC injection twice weekly after dialysis
Duration of Treatment:	8 weeks
Reference Therapy, Dose and Mode of Administration:	Control arm: standard care
Duration of Treatment:	8 weeks
Randomization:	Patients will be randomized 1:1 Randomization will be stratified by site
Efficacy Endpoints:	**Primary Efficacy Endpoint**

	The primary efficacy endpoint is reduction in documented infection with COVID-19. **Secondary Efficacy Endpoints** The secondary efficacy endpoints are: 1. Need for hospitalization 2. Hospital length of stay 3. ICU admission 4. ICU length of stay 5. Mechanical ventilation 6. Duration of mechanical ventilation 7. Recovery time from COVID-19 8. Change in any existing comorbidities (e.g., worsening congestive heart failure) or occurrence of newly diagnosed disease 9. Incidence of non-COVID-19 infections (other respiratory, urinary tract, cellulitis, etc.) 10. Change in T lymphocyte subsets (CD4, CD8) 11. Mortality
Safety Endpoints:	Adverse events, vital signs, and laboratory parameters

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4 ABBREVIATIONS

Abbreviation	Full Term
ADL	activities of daily living
AE	adverse event
ARDS	acute respiratory disease
CBC	complete blood count
CFR	Code of Federal Regulations
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disorder
CRF	case report form
CRP	C-reactive protein
CTM	clinical trial material (i.e., ZADAXIN or placebo)
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IL	interleukin
IND	investigational new drug
IRB	Institutional Review Board
LDH	lactate dehydrogenase
mL	milliliter
mg	milligram
2019-nCoV	2019 novel coronavirus
NK	natural killer
NOEL	no observable effect level
SAE	serious adverse event
SARS	severe actute respiratory syndome
SC	subcutaneous(ly)
Ta1	ZADAXIN thymalfasin, thymosin alpha 1
Th1	Th1-type T cell
TLR	Toll-like receptor
WHO	World Health Organization

5 INTRODUCTION AND STUDY RATIONALE

5.1 Introduction

In December of 2019 a cluster of unexplained pneumonia cases were reported in Wuhan, China. Shortly thereafter, the causative agent of this mysterious pneumonia was identified as a novel coronavirus [2]. On January 12, 2020 the World Health Organization (WHO) temporarily named this new virus the 2019 novel coronavirus (2019-nCoV) and later named it severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In February 2020 the term COVID-19 was introduced as the name of the disease caused by SARS-CoV-2. The COVID-19 epidemic has now reached pandemic proportion and spread beyond China prominently throughout the world including Asia, Europe, United States and over 150 sovereign nations [3-5]. COVID-19 causes a respiratory illness characterized initially by sore throat, fever, cough and malaise but progressing in some patients to lower respiratory infection, respiratory failure and mortality [6]. COVID-19 is highly contagious and it has been projected that as many as 40% of the entire United States population may become infected [7, 8]. One thing that has become increasingly clear is that older individuals, and particularly those with comorbidities and/or immunosuppression are at particularly high risk for adverse outcomes including requiring hospitalization, intensive care management, ventilatory support and mortality [9].

With the current and rapidly expanding burden of infection in the United States there has been great emphasis on disease treatment as well as vaccine development. Indeed, already there are clinical trials of antivirals and/or antimalarials that are currently enrolling patients. Vaccines are also on the fast track for development but it has been projected that their availability will be at least 12-18 months from now.

As we await the availability of an effective vaccine, we propose the investigation of an immune enhancing synthetic peptide with established safety and efficacy in a variety of clinical situations in the context of viral disease. This study should demonstrate feasibility and possibly provide evidence of efficacy. Further, our findings may be particularly valuable once a COVID-19 vaccine is available. At that time there may be efforts to enhance vaccine efficacy among at risk populations, such as in patients of advanced age or with comorbidities. Thymalfsin (thymosin alpha 1 or Ta1), the subject for this research protocol, is also known to provide increased response to vaccines. In previously published Phase 2 clinical trials carried out in the United States in over 400 geriatric (66 to 99 years) and kidney dialysis patients, Ta1 was reported to safely and significantly increase antibody responses to the influenza vaccine and reduce symptoms of influenza following infection [1, 10, 11].

5.2 Background and Rationale

Ta1 is a naturally occurring peptide that has been evaluated for its immunomodulatory activities and related therapeutic potential in several conditions and diseases, including infectious disease and cancer. ZADAXIN® brand Ta1 is a synthetic version currently approved for use in 37 countries; in particular it is approved in China hepatitis B and to enhance vaccine response. Notably, Ta1 has been used clinically in pilot studies for treatment of severe acute respiratory syndome (SARS) [12] and other lung infections including acute respiratory distress syndrome

(ARDS) [13] and chronic obstructive pulmonary disorder (COPD) [14], as well as infections after bone marrow transplant [15]. Larger clinical trials have shown significant efficacy for treatment of severe sepsis [16, 17] and hepatitis B [18], along with certain cancers such as melanoma, hepatocellular, and lung cancer [19]. Ta1 has also demonstrated improvement in response to vaccines in the elderly and in patients immunocompromised by renal disease. The beneficial clinical effects of Ta1 result from activation of toll-like receptor (TLR) 9 in dendritic and other immune system cells, resulting in augmentation of T helper (Th1) function, natural killer (NK) cell activity, and increased antibody responses to T-cell dependent antigens. Importantly, Ta1 also leads to an increase in IL-10 producing regulatory T cells, which create feedback inhibition of cytokine production, hence dampening immune response and preventing a pro-inflammatory cytokine storm.

Based on post-marketing treatment experience of more than 600,000 patients, Ta1 has been well tolerated. Ta1 has been administered to elderly subjects (up to 101 years old), children (as young as 13 months), and immunocompromised patients. The most common adverse events in previous clinical trials include injection-site pain (such as burning and itching) which was mild and lasted for less than 30 minutes, as well as fever, nausea, and flu-like symptoms which were mild to moderate in severity. Thus, while Ta1 is one of only a few immunomodulatory agents that have been approved for human use, it does not appear to induce most of the side effects and toxicities commonly associated with other biological response modifiers (BRMs) in this class, such as interferon and interleukin-2.

The actual dose, frequency, and length of treatment with Ta1 have differed depending upon the indication, ranging from 1.6 mg twice a week for up to 12 months; 1.6 mg twice a day for several weeks; 6.4 mg daily, 4 days a week, for 2 weeks out of every month up to 6 months in duration; and 16 mg twice a week for four weeks, with few adverse events observed. The proposal to evaluate Ta1 at a dose of 1.6 mg is based on previous studies which have shown an increase in dose above 1.6 mg to show little, if any, improvement in response.

Patients with end-stage renal disease (ESRD) on hemodialysis, in addition to their intrinsic kidney disease and frequent burden of comorbidities [20], also have increased risk of exposure to communicable diseases as they are treated several times each week at hemodialysis centers with several other patients and clinic staff in attendance. The majority of patients are over 60 years of age and many are receiving immunosuppressive medications. Accordingly, ESRD patients are particularly susceptible to COVID-19 infection. Ta1 has been shown to be safely administered to hemodialysis patients on a similar schedule to the one proposed below, and was efficacious in enhancing (> 4fold) the antibody responses to the influenza vaccine in geriatric & renal dialysis patients [1].

6 OBJECTIVES

6.1 Primary Objective

Primary Objective

To demonstrate that Ta1 administered twice weekly after dialysis for eight weeks to renal dialysis patients 60 years and older will reduce the incidence of COVID-19 infection over a six-month period compared with a similar population of patients who do not receive Ta1.

6.2 Secondary Objectives

Secondary Objectives:

1. To demonstrate that renal dialysis patients 60 years and older treated with Ta1 who become infected with COVID-19 will have a milder course of infection in terms of hospitalization rate, requirement for and length of ICU stay, requirement for mechanical ventilation, and survival than renal dialysis patients not treated with Ta1.

2. To demonstrate a decrease in hospitalization rates in renal dialysis patients treated with Ta1 who are not infected with COVID-19 compared to those not treated with Ta1.

7 STUDY DESIGN

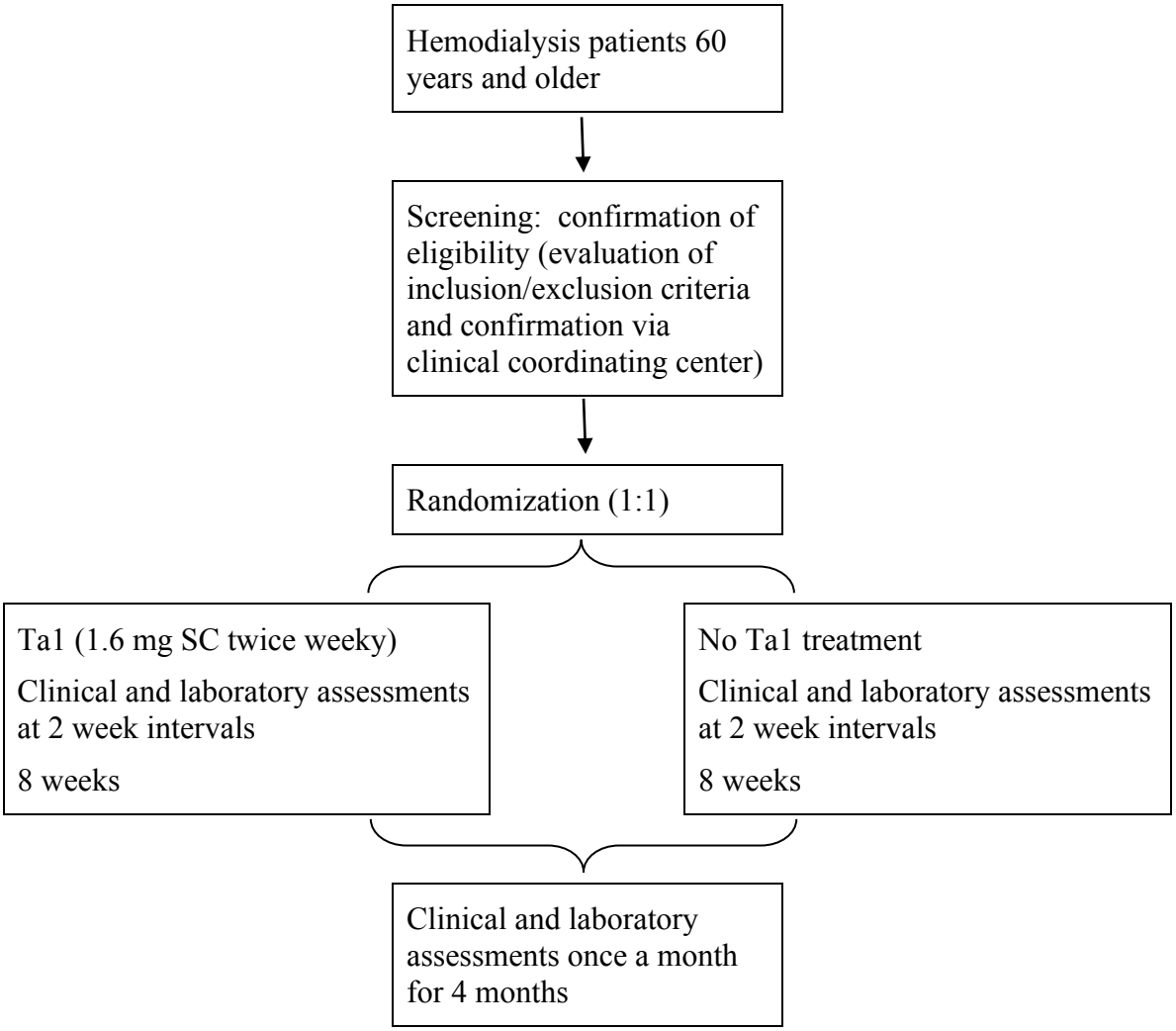
It is our hypothesis that a course of Ta1 administered to individuals at high risk for COVID-19 infection (hemodialysis patients 60 years and older) will reduce the rate of COVID-19 infection (primary objective) and severity of infection (secondary objective) with COVID-19, compared to untreated individuals in the same hemodialysis units with comparable risk. The secondary objectives also include an evaluation of the need for hospitalization in those patients who do not become infected with COVID-19.

Ideally, a randomized clinical trial with placebo control would be a preferred approach to address this hypothesis. However, the urgency of the current situation necessitates a simpler research design and implementation. Accordingly, we consider this a pilot study from which meaningful clinical data may rapidly be apparent.

After screening, renal dialysis patients 60 years and older who meet the inclusion criteria will receive Ta1 (1.6 mg) administered SC twice weekly for eight weeks. Individuals in the control arm will be followed on the identical protocol but will not receive twice weekly Ta1. After the treatment period, all subjects will be followed for efficacy outcomes for an additional 4 months. The total duration of the trial will be 1 year, including the estimated time required for screening.

A schema outlining the study design is presented in Figure 1.

Figure 1: Study Design Schema



8 ENDPOINTS

8.1 Primary Endpoint

The primary efficacy endpoint is reduction in documented infection with COVID-19. This is defined as clinical suspicion (presence of symptoms of respiratory infection; see Appendix 1 for questionnaire) and laboratory confirmation of COVID-19 infection.

8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

1. Need for hospitalization
    - This is defined by documentation in the case report form (CRF) of physician referral to hospital for admission
2. Hospital length of stay
    - The number of overnight stays in the hospital, entered into the CRF
3. ICU admission
    - Documentation in the CRF of physician recommendation for ICU transfer.
4. ICU length of stay
    - The number of overnight stays in the ICU
5. Mechanical ventilation
    - Documentation in the CRF of administration of mechanical respiratory assistance and length of time such assistance required
6. Duraton of mechanical ventilation
    - Documented in the CRF by physician
7. Recovery time from COVID-19
    - Defined as testing negative, plus the time for full recovery as determined by physician
    - Documented in the CRF by physician
8. Change in any existing comorbidities (e.g., worsening congestive heart failure) or newly diagnosed disease
    - Documented in the CRF by physician
9. Incidence of secondary non-COVID-19 infections (relapses, superinfections and new infections).
    - Documented in the CRF by physician
10. Change in T lymphocyte subsets (CD4, CD8)
    - Samples taken at enrollment, at 8 weeks and at 6 months, or at time of hospital admission if that is required
11. Mortality
    - COVID-19 related, or non-COVID-19 related; documented in the CRF by physician.

8.3 Safety Endpoints

The safety endpoints include adverse events (AEs), vital signs and laboratory parameters.

9 STUDY POPULATION

9.1 Sample Size

A total of up to 240 patients will be enrolled. Dr. Musio (Co-Investigator) is a member of Nephrology Associates of Northern Virginia. This group manages over 700 hemodialysis patients at several sites in or near Fairfax Va. Three of these sites will participate in this research project. Members of the Neprhology Associates of Northern Virginia have reviewed the proposed research and have endorsed participation.

9.2 Inclusion Criteria

1. Age 60 years or greater
2. Signed informed consent
3. Patients with ESRD, receiving hemodialysis 2 or more times each week and expected to continue on dialysis indefinitely.

9.3 Exclusion Criteria

1. Patients on short-term hemodialysis, such as those with transient renal dysfunction associated with acute illness who are projected to have return in renal function
2. Patients for whom renal transplantation is anticipated within the next six months
3. Patients with an anticipated survival of less than 3 months
4. Patients with symptoms that might be attributable to COVID-19 infection (see Appendix 1 for symptom questionnaire)
5. Patients who test positive for SARS-CoV2
6. Patients with active infectious disease requiring antibiotics
7. Patients with hospitalization within the previous 3 months for acute myocardial infarction or congestive heart failure
8. Patients with advanced malignancy receiving cytotoxic chemotherapy
9. Patients with a Karnofsky Performance Scale score of less than 60
10. Patientswith prior history of solid organ (kidney, liver, heart, lung, pancreas) or bone marrow transplant
11. Patients with active autoimmune disease on immunosuppressive medication
12. Patients receiving Plaquenil
13. Patients who have participated in an investigational drug or device trial in the previous 30 days
14. Patients with a history of allergy or intolerance to Ta1
15. Patients with any other medical or psychiatric condition that, in the opinion of the Investigator, would compromise patient safety or interfere with the objectives of the protocol or completion of the protocol treatment.

9.4 Removal of Subjects

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the study at any time for any reason. The Investigators (used throughout this protocol to refer to primary investigator or co-investigator) also have the right to withdraw subjects from the study. Subjects may be removed from the study for the following reasons:

- Adverse events (AEs)
- At the request of the Investigator
- Subject is unwilling or unable to comply with study protocol (noncompliance)
- Termination of the study.

If the reason for removal of a subject from the study is an AE, the specific event and any related test results will be recorded on the CRF. The subject will be followed until the AE resolves, becomes chronic, or the subject is lost to follow up. If a subject dies, the date of the last dose of clinical trial material (CTM) and all observations collected up to the time of study termination will be recorded on the CRF as will be the reason for death.

If a subject or the Investigator chooses to discontinue CTM, the Investigator will inquire whether the subject will agree to participate in remaining study evaluations.

If a subject is removed from the study at the request of the Investigator, the date of the last dose of CTM and all observations collected up to the time of termination will be recorded on the CRF along with the reason for termination, and scheduled safety evaluations and follow-up examinations will be conducted, if possible.

The date that a subject discontinues and the reason for discontinuation will be recorded in the CRF. Subjects who discontinue after randomization will not be replaced. If a subject withdraws consent from the study during treatment, follow-up visit study procedures should be conducted, as possible.

10 STUDY TREATMENT

10.1 Treatment Plan

For those in the treatment arm, Ta1 at a dose of 1.6 mg will be administered SC in 1 mL of diluent upon completion of dialysis treatment twice weekly (separated by at least 2 full days without Ta1 injection) after dialysis for a total of 8 weeks. Control patients will not receive injection injections.

Subjects who report respiratory illness symptoms (see Appendix 1 for symptom questionnaire) at the designated inventory times (Table 1) or in the interval between those designated times will be tested for COVID-19 virus. If the COVID-19 assay is positive, this will complete the treatment phase of the research protocol for that individual. However, the subject will remain on study with continuation of the designated assessments to assess severity of disease (e.g., need for hospitalization, ICU management, mechanical ventilation, mortality).

10.2 Identity of Clinical Trial Material

Ta1 clinical trial material (CTM) will be generously provided for this study by SciClone, Inc (China). Ta1 is contained, stored, and dispensed from individual tamper-proof glass vials with 1.6 mg Ta1 as a lyophilized cake containing 5% mannitol, buffered with phosphate to pH 6.4 - 7.3. Vials are reconstituted with 1 mL of supplied diluent (sterile Water for Injection), prior to subcutaneous (SC) administration.

10.3 Labeling and Packaging

ZADAXIN lyophilisate for solution for injection is a sterile, white to off-white lyophilized powder, containing Ta1 manufactured by solid-phase peptide synthesis.

The CTM intended for investigational use will be stored in a locked area with limited access, refrigerated between 2°C and 8°C.

10.4 Study Drug Accountability

The Investigator or designed site personnel are responsible for ensuring adequate accountability of all used and unused CTM. This includes acknowledgement of receipt of each shipment of CTM (quantity and condition), and documentation of dispensing, returns, and destruction of CTM. Dispensing records will document quantities of CTM received. Quantities dispensed will be documented, including date dispensed, subject identification number, and the initials of the person dispensing the CTM. Study drug accountability records must be readily available for inspection by regulatory authorities at any time.

The Investigator will not allow CTM to be given to any subject not enrolled into the treatment arm of the study or any unauthorized person.

10.5 Method of Assigning Subjects to Treatment

Subjects who meet all inclusion and exclusion criteria will be centrally randomized 1:1 to receive either no treatment or 1.6 mg Ta1 in 1 mL doses to be delivered twice weekly after dialysis (with treatment days separated by at least 2 full days without Ta1 injection), via SC injection for 8 weeks, in accordance with a computer-generated randomization schedule prepared by the Inova Biostatistical core.

Randomization will be stratified by dialysis site.

10.6 Selection of Doses

For those randomized to the treatment arm, Ta1 will be administered SC at doses of 1.6 mg twice weekly after dialysis for 8 weeks, similar to the dose and regimen used in many previous clinical trials and in commercial use in China.

This dose is supported by safety studies which show that Ta1 is well tolerated; in particular, no safety signals were seen in studies which enrolled subjects with: acute respiratory disease due to cytomegalovirus (CMV) or pneumonia, chronic obstructive pulmonary disease, severe lung infections, ESRD requiring hemodialysis, chronic infections (hepatitis B, hepatitis C, HIV/AIDS), cancer and those being treated with chemotherapy, or elderly subjects.

Pharmacokinetic studies show that there is no accumulation of Ta1 and the $T_{1/2}$ is 2 hours.

The proposal to evaluate a single dose rather than dose escalation is based on previous studies which have shown that doses above 1.6 mg showed show little, if any, improvement in response, and the mechanism of action of Ta1 (immune modulation rather than directly targeted therapy) suggests that the optimal dose should be equivalent no matter which indication is being investigated.

Support for the safety of the proposed dosing regimen is also seen in the nonclinical safety studies, which showed no adverse effects in rodents (mice and rats) at doses up to 20 mg/kg/day for acute dosing or 6 mg/kg/day for 6 months with repeat dosing; and no adverse effects were seen in marmosets dosed at 1 mg/kg/day for 6 months of repeat dosing. Conservatively, the marmoset no adverse effect level (NOEL) of 1 mg/kg/day represents a 50–fold safety margin over dosing of 1.6 mg.

10.7 Concomitant Therapy

Any concomitant therapy used from the time a subject signs an ICF through the 6-month end of study visit will be recorded on the CRF. In addition, for any serious adverse events (SAEs) that require medication for treatment, those medications will be recorded on the concomitant medications page. The medication name, dose, route of administration, start and stop dates and indication for use will be recorded.

There are no prohibited medications for this study protocol.

10.8 Standard of Care

The Investigator will follow routine standard of care for elderly renal dialysis patients.

The Investigator or any physician member of the Nephrology Associats of Northern Virginia may prescribe any concomitant medication or supportive therapy deemed necessary to provide adequate standard of care.

Subjects who have been determined to have received investigational products (exclusion criteria #6) either 30 days prior to their initiation of the study, or during the course of the study, will not be removed from the study; however, this fact will be recorded.

11 ASSESSMENTS

11.1 Efficacy Assessments

Clinical and laboratory evaluations of each participating subject will occur at two-week intervals. This will include initial medical history and physical examination (Investigator), a brief interview, symptom inventory and examination (vital sign, physical exam; see Appendix 1 for symptom questionnaire) twice weekly during the study period (research nurse), and serial laboratory evaluations obtained every 2 weeks during the treatment phase and then monthly for a total of 6 months.

All clinical and laboratory data will be entered on the subject's CRF with data entered at times indicated in Table 1 and secured in a cloud-based secure archive. The clinical data will include a symptom inventory, change in medical status (infection or non-infection), hospitalizations, intensive care unit admission, requirement for mechanical ventilation (respirator or extracorporeal membrane oxygenation [ECMO]), length of stay in the hospital and in the ICU, and survival. If subjects report respiratory symptoms (see Appendix 1 for symptom questionnaire), they will be tested for SARS-CoV2 and influenza. If these tests are negative, a full respiratory viral infection panel will be run.

In addition to screening for SARS-CoV2, routine complete blood count (CBC), and standard chemistry evaluations, additional markers of infection including procalcitonin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) will be followed. Further, T lymphocyte subsets CD4 and CD8 will be determined by flow cytometry at enrollment, at eight weeks and upon completion of the six-month project.

Aliquots of serum will be cryopreserved for all subjects to assess COVID-19 antibody throughout the course of this study once the methodologies have been worked out and the assays are commercially available. It is anticipated that these serum samples will all be run upon completion of the trial.

Subjects who report respiratory illness symptoms (see Appendix 1 for symptom questionnaire) at the designated inventory times (Table 1) or in the interval between those designated times will be tested for COVID-19 virus. If the COVID-19 assay is positive, this will complete the treatment phase of the research protocol for that individual. However, the subject will remain on study with continuation of the designated assessments to assess severity of disease (e.g., need for hospitalization, ICU management, mechanical ventilation, mortality).

In addition to infection with COVID-19, the following assessments will be collected and recorded at intervals in Table 1:

- Need for hospitalization
- Hospital length of stay
- ICU admission
- ICU length of stay
- Mechanical ventilation
- Mortality
- Incidence of secondary infections
- CD4, CD8, CD4/CD8.

Assessment for secondary infections will be documented in the CRF. Sites will be required to record all infections occurring from the time of enrollment until completion of the study 6 months after enrollment. Data will include the site of the infection, the evidence of infection, the organism cultured, and the antimicrobial susceptibility data.

The study will use the Inova Central Laboratory for conducting all laboratory investigations included in this study.

11.2 Safety Assessments

Safety will be assessed by collecting, recording AEs and reviewing all adverse events in a timely fashion. The investigators, study nurse and clinical trials specialist will meet weekly (Safety Meeting) for this purpose, or as needed if a serious adverse event is recognized that requires immediate attention.

Each enrolled subject will be briefly examined at two week intervals. Included in that exam will be vital signs, examination of the head, eyes, ears nose and throat and auscultation of the chest.

Routine clinical labs which include complete blood count with white blood cell differential and comprehensive metabolic panel (sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine calcium, total protein, albumin, total protein, aspartate amino transaminase, alanine amino transaminase) will be reviewed for each research subject at two week intervals. These data will be reviewed at the weekly Safety Meeting.

The Investigator will assess all abnormal clinical laboratory results for clinical significance in a timely fashion. A notation of clinically significant or not clinically significant, with initials and date, will be documented on the respective laboratory report next to any abnormal value. An abnormal laboratory value of clinical significance will be considered and documented as an AE if, in the opinion of the Investigator, it is clinically significant and not considered part of the underlying clinical condition.

Investigators will classify adverse events and laboratory findings as mild, moderate, or severe based on the perceived clinical significance of the event and laboratory finding in the patient. The Investigator will follow proper AE and SAE reporting procedures.

12 STUDY PROCEDURES

12.1 Schedule of Events

A schedule of study procedures is outlined in Table 1.

12.2 Screening

Once FDA and IRB approval are obtained, the research team will promptly initiate the process of subject recruitment. Recruitment of all subjects will be completed in four months and the observation phase in one year. Posters and leaflets will be prepared for distribution at the study sites. Interested individuals will be directed by site personnel to discuss the study with any of our research staff and informed consent will be obtained by the Investigator or research nurse.

The following screening observations and procedures will be completed prior to randomization:

- Obtain a signed Health Insurance Portability and Accountability Act (HIPAA) authorization
- Assess a subject against the inclusion/exclusion criteria
- Obtain a signed IRB-approved informed consent (ICF)
- Perform physical exam and obtain medical history
- Assess performance status (Karnofsky Performance Scale)
- Take a nasopharyngeal swab to test for SARS-CoV2
- Draw blood sample for:
    - Complete blood count (CBC) and standard chemistry surveys
    - Nonspecific markers of infection (procalcitonin, CRP, and LDH)
    - CD4, CD8 (flow cytometry)
    - Serum cryopreservation for future serologic assay once it is available.

12.3 Weekly Study Procedures (for 8 weeks)

The following observations and procedures will be conducted:

- Record abbreviated physical exam, height, weight, viral signs
- Record respiratory virus symptoms (see Appendix 1 for questionnaire)
- Record comorbidity signs and symptoms
- Record any concomitant medications
- Record AEs and SAEs
- Record secondary infections
- Administer dose of Ta1 (or no treatment) after dialysis (twice per week, with at least two full days between treatments).

12.4 Every Other Week Study Procedures (for 8 weeks)

The following observations and procedures will be conducted:

- Record any concomitant medications
- Record AEs and SAEs
- Record secondary infections
- Draw blood sample for serology
  - Routine complete blood count (CBC) and standard chemistry surveys
  - Serum cryopreservation for future serologic assay once it is available.

12.5 Additional Blood Draws at Week 4, Week 8

- Draw blood sample for serology
  - Nonspecific markers of infection (procalcitonin, CRP, LDH)
  - CD4, CD8 (flow cytometry).

12.6 Additional Procedures if respiratory infection symptoms are seen

- Take nasopharyngeal swabs for analysis
  - SARS-CoV2 and influenza assay
  - If SARS-CoV2 and influenza assay are negative: full respiratory virus panel.

12.7 Monthly Follow-up Visits (for 4 months)

The following observations and procedures will be conducted:

- Record vital signs, including temperature, systolic and diastolic blood pressures, heart rate, and respiration rate
- Record respiratory virus symptoms (see Appendix 1 for questionnaire)
- Record any concomitant medications
- Record AEs and SAEs
- Record secondary infections
- Draw blood sample for serology
  - Routine complete blood count (CBC) and standard chemistry surveys
  - CD4, CD8 (flow cytometry)
  - Serum cryopreservation for future serologic assay once it is available.

13 ADVERSE EVENT REPORTING

Throughout the study, AEs will be recorded onto the CRF regardless of whether or not the AEs are considered study treatment-related. All AEs with onset dates after the date the subject signed the ICF through the second week 8 visit will be recorded as an AE on the CRF. Conditions existing prior to signing the ICF will be recorded as part of the subject's medical history. All SAEs with onset dates after the subject signs the ICF through the second week 8 visit must be recorded following the guidelines in Sections 13.4 and 13.8. To avoid confusion, AEs will be recorded in standard medical terminology.

The Investigator is responsible for assessing the relationship of AEs to CTM (see Section 13.3).

13.1 Adverse Event Definition

An *adverse event* is any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to this investigational product. This includes an event that emerges during treatment having been absent pre-treatment or an event that worsens relative to the pretreatment state. Recurrent symptoms of a chronic preexisting condition are not considered AEs, unless they occur in a worse or unexpected pattern during CTM administration.

13.2 Assessing Severity of Adverse Events

The severity of AEs will be designated by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or fatal (Grade 5),

Adverse Event Severity

Grade	Definition
Mild – Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate – Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[1]
Severe – Grade 3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2]
Life-threatening – Grade 4	Life-threatening consequences; urgent intervention indicated
Death – Grade 5	Death related to AE

[1] *Instrumental ADL* refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] *Self-care ADL* refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

13.3 Assessing Relationship of Adverse Event to Study Treatment

All AEs will be categorized by the Investigator with respect to their possible relationship to study treatment. The relationship between study treatment and the AE may be considered related or not related. The criteria for each category are listed below:

- Related: When there is a reasonable possibility that the study treatment caused the reported AE
- Not related: When there is no reasonable possibility that the study treatment caused the reported AE.

13.4 Recording of Adverse Events

All AEs with onset dates after the subject signed the ICF through the 6-month visit will be recorded on the CRF. All AEs must be recorded on the appropriate CRF, regardless of their severity or relationship to the CTM. All AEs that meet the seriousness criteria (Section 13.6) will be recorded as an SAE.

All clinical events are to be recorded, including both observed (such as any reaction at injection sites) and volunteered problems, complaints, or symptoms. The need to capture this information does not depend upon the clinical event's association with the use of the CTM. Adverse events resulting from concurrent illnesses, reactions to concurrent medications, or clinically significant progression of disease states are also to be recorded.

13.5 Adverse Event Recording Period

AEs will be collected and recorded on the CRF from the time the ICF is signed by the subject through the 6-month follow-up visit.

13.6 Serious Adverse Event Definition

A *serious adverse event* (SAE) is defined as any AE occurring at any dose regardless of relationship to CTM that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Other significant medical events.

In addition, all AEs assessed by the investigator with severity of Grade 4 or Grade 5 should be reported as SAEs. An important medical event that may not result in death, be life-threatening or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Complications that occur during hospitalization are AEs. If a complication prolongs a hospitalization, it is an SAE.

As used in this study, the term *inpatient hospitalization* is defined as formal admission to a hospital for medical reasons or evaluation in the Emergency Department of a hospital even if not admitted.

When an SAE occurs in a subject receiving a product as a concomitant medication, the SAE must be processed and reported.

13.7 Serious Adverse Event Recording Period

The Investigator will collect and record SAEs from the time the subject signs the ICF through the 6-month follow-up visit.

13.8 Regulatory Reporting of Adverse Events

The Investigator will determine whether the SAE must be reported to the FDA within 7 or 15 days, and if so, will report the event to the FDA. The Investigator will report all SAEs to their IRB, as required. Adverse events will be reported to regulatory authorities in compliance with local and regional law and established guidance. The format of the reports will be dictated by local and regional requirements.

13.9 Data Safety Monitoring Board (DSMB)

Acknowledging the inherent vulnerability of our study population (older hemodialysis patients), a DSMB will be established with a mission to ensure that the interests of the patients entered in the trial are being well served (i.e., the risk-benefit ratio is appropriate) and that the scientific integrity of the trial is maintained from trial initiation to completion [21]. The DSMB will be comprised of three independent physicians with expertise in nephrology, geriatric medicine and infectious disease as well as one independent biostatistican. The committee will meet at trial initiation and quarterly for the one-year duration of the study.

The study will be stopped if the DSMB believes that the number or severity of treatment-related adverse events suggests that it is in the best interests of the patients to do so.

14 DATA MANAGEMENT

Data will be entered onto the CRFs. The Investigator should ensure the accuracy, completeness and timeliness of the data recorded on the CRFs.

15 STATISTICAL ANALYSIS

15.1 Sample size justification

It has been speculated that infection rates may be as high as 40% in the general population and for those over the age of 60 years, particularly those with underlying comorbidities, the rate may be higher. Further, patients who receive dialysis two or three times weekly at dialysis centers are more likely to be exposed to virus than the general elderly population. In as much as there are no existing data demonstrating the effects of Ta1 in prevention of COVID-19 infection, in this pilot project we have elected to sample 240 subjects, anticipating that 40 subjects will drop off study for any of a number of reasons. That will leave ~200 enrolled subjects with complete data availability. We justify the choice of sample size below.

Each sample size calculation depends on the type of endpoints, the variability of data, analysis methods used, and the minimal difference (or effect size) that we wish to be able to detect between the treatment (with Zadaxin) or control (without Zadaxin) groups. There are four types of endpoints for this study, dichotomous (e.g., infection of COVID19, the primary endpoint; ICU admission; or mortality), polytomous (e.g., health changes: no change, moderate, severe changes), counts (e.g., occurrence of non-COVID-19 infections), or continuous outcome variables (e.g., CD4, CD8, CD4/CD8, length of hospital stay, recovery time from COVID19). For a dichotomous outcome, a suitable model is a logistic regression with the treatment status (treated or not treated with Zadaxin) as the primary covariate, demographic information (age, gender, race), health/medical information (e.g., Karnofsky score, co-morbidity, and other biomarkers) and environmental information (treatment center, among others) as other relevant covariates. Assume the infection rate for the control group is about 0.40 and with a significance level of 0.05 (unless specified otherwise), if we use a simple logistic regression, a sample of size 200 will be able to detect a change at least at 0.185 in the infection rates between the treatment and control groups with a power of 80%. If we have a bigger sample size, say 234, we would be able to detect a change with a minimal difference of 0.17 with the same power or a minimum difference of 0.185 with a power of 86.5%. Using more comprehensive procedures (below) or if the actual difference is (much) larger than the minimal difference, we will have a (much) higher power than 80% to detect the actual difference. If we make a conservative adjustment for multiple comparisons incorporating other covariates after a pre-screening step, at an adjusted significance level 0.005, a sample of size 205 will provide 80% power for detecting a change of at least as large as 0.23. Using a multiple logistic regression model that takes into account the correlation among the various covariates, say if the correlation is 0.2, we can detect a minimal difference at 0.202 with a sample size of 200. If the correlation is 0.5, the minimum detectable difference would be 0.25. The highly correlated covariates that lead to multicollinearity will indicate the need for removal of redundant covariates in modeling the endpoint, and the removal will lead to more degrees of freedom in our study and the same power in detecting the even smaller difference. We will use all the sample we have and incorporate censored data or treat missing information with survival or a more comprehensive model than the logistic regression; thus, we expect to be able to detect a smaller minimal difference or have a much higher power to detect the actual difference in the infection rates than given above.

For a continuous endpoint, with a sample size of 201, using the simplest testing procedure (with a possible transformation of the endpoint variable), we will be able to detect an effect size at least at 0.35 between the treatment and control groups with a power of 80%. Since we will use a general linear model to delineate the effects or variations due to covariates/factors, we expect to be able to detect a smaller minimal effect size or a higher power to detect the actual difference that is bigger than the minimal effect size. In a very conservative sense, comparing a polytomous response between treatment and control can be viewed as a multiple testing problem of comparing proportions for each of the categories. For response variables with three categories, if the proportion of a certain category is approximately 0.3, a sample of size 202 will enable us to detect a minimal change of 0.19 with a power of 80%. We emphasize that this calculation is very conservative, and we expect have much better performance, both in terms of detection of smaller departure and having better power. For the ordinal polytomus outcome, we are interested in

identifying if the treatment improves the proportion of different categories of the outcome than that of control. Assume that the response has 3 categories with equal proportion in the overall population (averaged over control and treatment). With a sample size of 200 we can detect a minimal improvement of size 0.725 in the overall odds ratio with 80% power. The count variables can be modeled as continuous with appropriate transformation and the sample size justification will be similar to that of a continuous response.

15.2 Data analysis plan

The primary goal of the analysis is to study the effect of the treatment on the outcome variables, in consideration of other covariates, including the demographic information and medical history of the participants and dialysis centers, which can potentially interact with the treatment. First, we will do an exploratory analysis of all the covariates altogether and stratified in the treatment and control group. We will study the effect of each of these covariates separately and together on the outcome. In the comprehensive study of all factors, we will build several models, including both parametric and tree-based models. We will also consider relevant interaction between the independent variables in the model. For the parametric models, we will use logistic regression for the binary outcomes, general linear regression (after a possible transformation of some covariates) for the continuous outcomes, Poisson regression with an over-dispersion test or a general log-linear model, for count outcomes, and a multinomial regression for the categorical variables with more than two categories. We will assess the fitted models based on model diagnostics and goodness-of-fit/prediction measures, such as adjusted R^2, AIC, BIC, and cross-validation. A follow-up analysis will be done based on the results obtained from the various regression models. All the significant first-order and interaction effects will be further analyzed to understand the nature of the effect, and possibly considering further models stratified by relevant covariates.

Interim analyses will be done at least in the interval of 1, 3, and 6 months for the purpose of monitoring, presentations to the monitoring board, and any remedies (as needed) to ensure the quality of the study and safeguard the study population.

16 ETHICS

16.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, in particular ICH GCP E6, and with the laws and regulations of the United States. Because this study is conducted under a U.S. IND, the Investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined, for example, in 21 CFR §312.50 and 312.56.

16.2 Institutional Review Board

The protocol and ICF for this study must be reviewed and approved by an appropriate IRB before subjects are randomized into the study. It is the responsibility of the Investigator to assure that all aspects of the institutional review are conducted in accordance with the requirements of all regulatory authorities.

16.3 Subject Information and Informed Consent

In accordance with regulatory and local ethics committee requirements, before study procedures are performed, subjects will be informed about the study and required to sign the IRB-approved ICF along with authorization to collect protected health information under HIPAA. This form will be signed after adequate explanation of the aims, methods, objective and potential hazards of the study and prior to undertaking any study-related procedures. Informed consent will be obtained according to the applicable IRB requirements. No subject is to be screened or treated until an ICF has been obtained. The signed ICF will be retained with the study records. Each subject will also be given a copy of his or her signed ICF at the screening visit.

16.4 Financial Disclosure by Investigators

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR §54 is adhered to. A "covered" clinical trial is any study of a study drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or the FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety. This requires that Investigators (inclusive of family members) provide documentation of their financial interest or proprietary interests in the study drug being studied. This documentation must be provided prior to the participation of the Investigator.

16.5 Archiving and Data Retention

According to 21 CFR §312.57, an Investigator shall retain adequate records for the study including copies of each subject's CRFs, medical records, laboratory reports, ICFs, study drug accountability records, safety reports, information regarding subjects who were withdrawn and any other pertinent data. All records are to be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the study drug for the indication for which it is being investigated or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified. The records will be available for copying and inspection if requested by regulatory authorities.

If the responsible Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping records, custody must be transferred to a person who will accept the responsibility.

16.6 Confidentiality

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties.

The Investigator must keep a screening log showing names and addresses for all screened subjects and all subjects randomized into the trial.

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Table 1: Study Schedule

PROCEDURE	[1]SCREEN	STUDY ACTIVITIES											
		W1	W2	W3	W4	W5	W6	W7	W8	M3	M4	M5	M6
Informed Consent	●												
Inclusion/Exclusion Criteria Reviewed	●												
Medical History	●												
[2]Physical examination	●												●
Abbreviated PE, height, weight, vital signs		◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
[4]Respiratory virus symptom inventory (see Appendix 1)	●	●	●	●	●	●	●	●	●	●	●	●	●
SARS-CoV2 assay	●		●		●		●		●	●	●	●	●
[3]Clinical and research blood draws	●		●		●		●		●	●	●	●	●
Lymphocyte Subsets (CD4, CD8); markers of infection (procalcitonin, CRP, LDH)	●				●				●				
Secondary infections	●	●	●	●	●	●	●	●	●	●	●	●	●
[5]Comorbidity inventory	●	●	●	●	●	●	●	●	●	●	●	●	●
[6] SARS-CoV2 and influenza assays; if negative: respiratory virus panel		*-- conducted if signs of infection are seen --*											
Record AEs, SAEs		●	●	●	●	●	●	●	●	●	●	●	●
Record Concomitant Therapies/Procedures	●	●	●	●	●	●	●	●	●	●	●	●	●
[6]Ta1 administration		® ®	® ®	® ®	® ®	® ®	® ®	® ®	® ®	® ®				
Subject Compensation			●		●		●		●		●		●

[1]Screening and enrollment to be completed no more than 14 days prior to initiation of study.
[2]Full physical exam to be performed either at screening or on Day 1 and again at completion of study.
[3]Clinical and research labs – please refer to the Study Procedures section (Serum will be cryopreserved until completion of study and assays run once serologic assay is available for COVID-19)
[4]Respiratory virus symptom inventory to include the description of cough, fever, shortness of breath, malaise, sore throat occurring over the prior week. If any are present, the information will be brought to the attention of PI or CoI.
[5]Signs and symptoms correlating with pre-existing or newly developed comorbidities will be inventoried.
[6]Ta1 will be administered twice weekly on dialysis days immediately upon completion of dialysis, with at least two full days between treatments.

18 APPENDIX 1

Respiratory Symptom Inventory

Symptom	Screen	W1	W2	W3	W4	W5	W6	W7	W8	M3	M4	M5	M6
Cough													
Fever >100.4													
Shortness of breath													
Sore throat													
Gastrointestinal symptoms													
Malaise													
Headache													
Muscle pain													
Loss of taste and/or smell													
Other (describe)													