A Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ampligen® in Patients with Post-COVID Conditions

Protocol Number:	**AMP-518**
Version:	**Version 4.0**
Date:	**23-Aug-2023**

Sponsor: **AIM ImmunoTech Inc.**
2117 SW Highway 484
Ocala, FL 34473, USA
[redacted]

Clinical Trials.gov Identifier: NCT05592418

Confidentiality Statement

PROTOCOL APPROVAL PAGE

Protocol Number:	**AMP-518**
Version:	**Version 4.0**
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We, the undersigned, have reviewed this protocol and agree that it contains all relevant information required to meet FDA, GCP and all applicable regulatory guidelines and statutes.

PROTOCOL APPROVAL FOR USE

Program Director; Amarex Clinical Research, LLC	Signature	Date
Pharmacovigilance; Amarex Clinical Research, LLC.	Signature	Date
Biostatistics; Amarex Clinical Research, LLC.	Signature	Date
Medical Writing; Amarex Clinical Research, LLC.	Signature	Date
Chief Scientific and Medical Officer; AIM ImmunoTech Inc.	Signature	Date

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number:	**AMP-518**
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I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with US Food and Drug Administration (FDA) regulations and Investigational Review Board/Institutional Ethics (IRB/IEC) requirements for testing on human subjects. I agree to ensure that the requirements for obtaining informed consent are met.

Principal Investigator's Signature _____ Date _____

Print Name _____

Site Number _____

SPONSOR INFORMATION

Sponsor Office:

AIM ImmunoTech Inc.
2117 SW Highway 484
Ocala, FL 34473, USA
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CONTRACT RESEARCH ORGANIZATION INFORMATION

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: AIM ImmunoTech Inc.	
Name of Study Product: Ampligen®	
Protocol Number: AMP-518	**Indication:** Post-COVID Conditions
Title of Study: A Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ampligen® in Patients with Post-COVID Conditions	
Study Center: Up to 10 centers in the United States. Centers must have the capability of implementing appropriate infection-control measures to prevent infection of study staff and others who share the clinical site space. The facility should be adequately staffed by medical personnel and equipped with a "crash cart" in the event of acute allergic reaction or requirement for advanced cardiac life support.	
Planned Number of Subjects: 80 subjects	**Study Development Phase:** Phase 2
Indication for Use: Ampligen® is being evaluated for treatment of adult patients with Post-COVID Condition of fatigue	
Objective: The purpose of this study is to assess the efficacy and safety of Ampligen® administered twice weekly by intravenous (IV) infusions in subjects experiencing the Post-COVID Condition of fatigue.	
Study Outcomes: **Primary Outcome Measure:** • Change from baseline to week 13 in PROMIS® Fatigue Score (T-Score). **Secondary Outcome Measures:** • Change from baseline to week 6 in PROMIS® Fatigue Score (T-Score). *Note: Additional PROMIS® Fatigue Score analysis (change from baseline) at week 6 and 13 will be performed excluding response to item, "How often did you have enough energy to exercise strenuously?"* • Change from baseline to week 6 and 13 in distance traveled during a 6-minute walk test. • Proportion of subjects with minimal clinically important difference (MCID), defined as at least 54 m, in the Six-Minute Walk Test (6MWT) at the end of 12-week treatment phase. • Change from baseline to week 6 and 13 in PROMIS® Cognitive Function Score (T-Score). • Change from baseline to week 6 and 13 in PROMIS® Sleep Disturbance Score (T-Score). **Exploratory Outcome Measures**	

Name of Sponsor/Company: AIM ImmunoTech Inc.	
Name of Study Product: Ampligen®	
Protocol Number: AMP-518	**Indication:** Post-COVID Conditions

- Changes from baseline in COVID-19-related symptoms using Symptom Burden Questionnaire for Long COVID (SBQ-LC) during the course of the treatment phase.

[redacted]

- Change from baseline in cognitive function as measured by Montreal Cognitive Assessment (MoCA) at week 4, 8, and 13 during the treatment phase.
- Incidence of hospitalization during the treatment phase.
- Duration (days) of hospitalization during the treatment phase.
- Evaluation of lymphocyte profile by flow cytometry in patients with post-COVID-19 conditions.
- Identification and evaluation of plasma protein biomarkers in patients with post-COVID-19 conditions.

Safety Outcome Measures:

- Incidence of treatment-related adverse events.
- Incidence and severity of treatment-emergent adverse events (TEAEs).
- Incidence of serious adverse events (SAEs).
- Incidence of TEAEs and SAEs leading to discontinuation of study medication.
- Changes in blood chemistry and hematology results.
- Changes in vital signs including temperature, pulse, respiratory rate, systolic and diastolic blood pressure.
- Changes in physical examination results.
- Change in electrocardiogram (ECG) results.

Trial Design:

This is a Phase 2, two-arm, randomized, double blind, placebo controlled multicenter study to evaluate the efficacy and safety of Ampligen® in patients experiencing the Post-COVID Condition of fatigue. Patients will be randomized 1:1 to receive twice weekly IV infusions of Ampligen® or placebo.

The study will have three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

Note: During visits conducted at the study clinic, subjects and site personnel will use appropriate protective gear (e.g., masks, gloves) to prevent the spread of the infection.

Name of Sponsor/Company: AIM ImmunoTech Inc.	
Name of Study Product: Ampligen®	
Protocol Number: AMP-518	**Indication:** Post-COVID Conditions

Screening Phase (up to 1 week):

All subjects will provide written informed consent and have a Screening visit (V1) within 7 days prior to first treatment visit (V2) to determine eligibility for subject participation.

All subjects who fail to meet eligibility criteria are considered screen failures and are exited from the study without further evaluation.

Treatment Phase (12 weeks):

Ampligen® and placebo will be administered via twice weekly infusions (Example: Monday/Thursday or Tuesday/Friday schedule) for 12 weeks [redacted]

Table 0-1: Study Drug Dose and Duration of Infusion

Visit/Day/Week/ Dose	Cumulative Dose Number	Dose Amount	Duration of Infusion
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Follow-Up Phase (2 weeks):

Name of Sponsor/Company: AIM ImmunoTech Inc.	
Name of Study Product: Ampligen®	
Protocol Number: AMP-518	**Indication:** Post-COVID Conditions

Follow-Up Visit 1 (V26):

A safety follow-up visit will be performed 3 to 4 days after the End of Treatment (EOT) visit (V25).

Follow-Up Visit 2 (V27):

A second safety follow-up visit will be performed 2 weeks after the End of Treatment (EOT) visit (V25).

Investigational Product Administration:

This is a double-blind study. The investigator and staff, subjects and Sponsor/CRO staff directly related to study conduct will be blinded to the treatment assignment. [redacted]

Study Duration:

- **Screening Phase** (Screening to Baseline): Up to 7 days (1 Week)
- **Treatment Phase**: 12 weeks
- **Follow-Up Phase**: 2 weeks

Total Study Duration: up to 15 weeks

Inclusion Criteria:

1. Male or female adult between 18 to 60 (inclusive) years of age at time of enrollment.
2. Prior confirmed COVID-19 diagnosis by standard RT-PCR assay or equivalent testing at least 12 weeks prior to baseline.

   Note: For subjects with COVID-19 symptoms who were not tested for the presence of SARS-CoV-2, a positive serum antibody test for SARS-CoV-2 will be sufficient in subjects not vaccinated for COVID-19 or it can be shown that the positive antibody cannot be associated with the COVID-19 vaccination.

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3. Laboratory confirmed negative SARS-CoV-2 (COVID-19) infection by a government approved test / kit at time of enrollment.
4. Subject meets for the criteria of fatigue per the 1994 CDC Case Definition for Chronic Fatigue Syndrome (CFS): Unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities. The fatigue must have persisted or recurred during 3 or more consecutive months of illness and must not have preceded the onset of the COVID-19 symptoms.
5. PROMIS® Fatigue - Short Form 7a response total raw score of ≥ 21 at screening and baseline.
6. Electrocardiogram (ECG) with no clinically significant findings as assessed by the Investigator.

   Note: Below are the examples of clinically significant ECG abnormalities:

   - *Previous documented evidence of myocardial infarction or recent significant change in the resting EKG suggesting infarction or other acute cardiac events.*
   - *Current symptoms of coronary insufficiency (i.e. - angina pectoris and/or ST segment depression on EKG).*
   - *Evidence of uncontrolled atrial or frequent or complex ventricular ectopy, or myocardial conduction defect which would increase the risk of syncope (for example, second degree or higher A-V block).*
7. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
8. Men and women of childbearing potential and their partner must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, bilateral tubal occlusion, or vasectomy) or must practice complete sexual abstinence for the duration of the study (excluding women who are not of childbearing potential and men who have been sterilized).
9. Females of child-bearing potential must have a negative urine pregnancy test at Screening Visit and prior to receiving the first dose of study drug; and Male participants must agree to use contraception and refrain from donating sperm for at least 90 days after the last dose of study intervention.
10. Subject is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions.

Exclusion Criteria:

Name of Sponsor/Company: AIM ImmunoTech Inc.	
Name of Study Product: Ampligen®	
Protocol Number: AMP-518	**Indication:** Post-COVID Conditions

1. Inability to provide informed consent or to return to the Investigator's site for scheduled infusions and evaluations.
2. Exhibiting signs of moderate or severe pulmonary disease (such as COPD, asthma, or pulmonary fibrosis).
3. Ongoing requirement of oxygen therapy.
4. Pulse oxygen saturation (SpO2) of <94% on room air at the time of screening.
5. Thrombocytopenia (platelets $<100\times10^9$/L), anemia (hemoglobin <9.0 g/dL), or leukopenia (WBC $<3\times10^9$/L) on screening labs
6. History of splenectomy.
7. Known hypercoagulable state or at increased risk of thrombosis (e.g., due to immobility)
8. Liver cirrhosis or patient showing signs of clinical jaundice at the time of screening.
9. Transaminase (ALT or AST) >3X ULN or total bilirubin >2X ULN at screening
10. Chronic kidney disease stage 4 or requiring dialysis at the time of screening.
11. Estimated GFR <60 mL/min/1.73 m^2 at the time of screening.
12. NYHA Class III or IV congestive heart failure (CHF).
13. Exhibiting signs of uncontrolled hypo-or hyper-thyroidism at the time of Screening.
14. Diagnosis of autoimmune disease (e.g., SLE, rheumatoid arthritis, psoriasis) at the time of screening.
15. Uncontrolled rheumatologic disorders at the time of screening.
16. Diagnosis of sleep apnea (central or obstructive) at the time of screening.
17. History of organ transplantation or are candidates for organ transplantation at the time of screening.
18. History of Chronic Fatigue Syndrome prior to COVID-19 infection.
19. History of fibromyalgia prior to COVID-19 infection.
20. History of major psychiatric disorder including psychotic or melancholic features, bipolar disorders, schizophrenia of any subtype, schizoaffective disorder, major depression, delusional disorders of any subtype, dementias of any subtype, anorexia nervosa or bulimia nervosa.
21. Any malignancy within the past 5 years, excluding successfully treated basal cell carcinoma or squamous cell carcinoma without evidence of metastases.
22. Any other clinically significant serious systemic diseases, chronic or intercurrent active medical disorder and other reasons which would interfere with study conduct or study results interpretation per the Investigator.

Name of Sponsor/Company: AIM ImmunoTech Inc.	
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23. Chronic or intercurrent acute medical disorder or disease making implementation or interpretation of the protocol or results difficult or unsafe per the investigator.
24. Therapy with interferons, interleukins, or other cytokines or investigational drugs within 6 weeks of beginning study medication. Subjects must give written informed consent prior to discontinuation of investigational drugs.
25. Treatment with any of the following therapies within the eight (8) weeks immediately preceding the start of study baseline or during baseline: systemic glucocorticoids (i.e., hydrocortisone, prednisone, etc.) or mineralocorticoids (i.e., fludrocortisone (Florinef), etc.), interferons, interleukin-2, systemic antivirals, gamma globulin or investigational drugs or experimental agents not yet approved for use in the United States.
26. Prior participation in an Ampligen® study.
27. Medical necessity, as determined by the patient's primary doctor or the principal investigator, to continue aspirin (ASA) or non-steroidal anti-inflammatory (NSAID) drugs for 20 consecutive days or for more than 10% of the study duration.
28. History of congestive heart failure, suspected or known dissecting aneurysm, recent systemic or pulmonary embolus or myocardial infarction (≤ 6 months), severe valvular heart disease, ventricular aneurysm, active or suspected myocarditis or pericarditis, thrombophlebitis or intracardiac thrombi, or acute infection.
29. Evidence of moderate or severe obstructive pulmonary disease.
30. Resting diastolic blood pressure > 115 mm Hg or resting systolic blood pressure > 200 mm Hg.
31. Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, or myxedema).
32. Concurrent use of any beta blockers and/or bronchodilators which cannot remain at a stable dosage level during baseline and the study.
33. History of alcohol or other substance abuse within two (2) years before the onset of acute COVID-19 or at any time afterward.
34. History of suicide attempt, suicidal behavior, or suicidal ideation, within two (2) years of baseline. A score of 10 or greater on the PHQ-9 at Baseline indicates symptoms of depression and will exclude subject. A score of greater than zero on question nine (9) of the PHQ-9 at Baseline indicates suicidal ideation and will exclude subject.
35. Pregnant or breast feeding.
36. Participation in another study for an investigational treatment.

Statistical Considerations:

Name of Sponsor/Company: AIM ImmunoTech Inc.	
Name of Study Product: Ampligen®	
Protocol Number: AMP-518	**Indication:** Post-COVID Conditions

Sample Size Determination and Rationale

A total of 80 subjects will be randomized 1:1 in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this exploratory study.

Analysis Populations

[redacted]

Efficacy Analysis

[redacted]

Safety Analysis

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BSL	Baseline
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CFS	Chronic Fatigue Syndrome
CHF	Congestive Heart Failure
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DIS	Diagnostic Interview Schedule
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ETT	Exercise Tolerance Testing

Abbreviation	Term
FDA	U.S. Food and Drug Administration
FUV	Follow-up Visit
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HCT	Hematocrit
HEENT	Head, Ears, Eyes, Nose, and Throat
HIPAA	Health Insurance Portability Accountability Act
HPF	High Power Field
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention to Treat
IWRS	Interactive Web Based Response System
IV	Intravenous
KPS	Karnofsky Performance Score
LAR	Legally Authorized Representative
LDH	Lactate dehydrogenase
MoCA	Montreal Cognitive Assessment
MCID	Minimal Clinically Important Difference
ME	Myalgic Encephalomyelitis
ORF	Open-Reading Frames
PEM	Post Exertional Malaise
PCR	Polymerase Chain Reaction
PHQ	Patient Health Questionnaire
PI	Principal Investigator
RBC	Red Blood Cells
RNA	Ribonucleic Acid

Abbreviation	Term
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SAS	Statistical Analysis System
SBQ-LC	Symptom Burden Questionnaire for Long COVID
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
SOP	Standard Operating Procedure
SV	Screening Visit
TEAE	Treatment Emergent Adverse Event
TLR3	Toll like receptor 3
TRS	Transcription-Regulating Sequences
TV	Treatment Visit
ULN	Upper Limit of Normal
USA	United States of America
WBC	White Blood Cells

1 INTRODUCTION AND BACKGROUND

1.1. STATEMENT OF INTENT

The design, conduct and reporting of this study shall be conducted in compliance with the protocol, International Conference on Harmonization/Good Clinical Practice (ICH/GCP), and all appropriate regulatory requirements. Investigator(s) participating in this study will have documented training in GCP. Independent monitoring of the trial will be accomplished utilizing a Contract Research Organization (CRO).

1.2. BACKGROUND OF THE COVID-19 DISEASE

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral cause of coronavirus disease 2019 (COVID-19) was first identified in late 2019 in Wuhan, Hubei province, China. On 11 March 2020, the World Health Organization declared the disease a global pandemic. The global burden of SARS CoV-2 infection continues to increase with estimates of more than 200 million people infected and over four million deaths as of September 2021.

While some individuals infected with SARS-CoV-2 may be asymptomatic, many people display symptomatic disease varying from mild to critical in severity. Severe-to-critical illness is typically marked by hypoxemic respiratory failure requiring ventilatory support. Morbidity and mortality rates are elevated among patients with pre-existing co-morbidities such as cardiovascular disease, diabetes mellitus, chronic respiratory disease, hypertension and cancer. The observed case fatality ratio (CFR) varies considerably from country to country and over time. However, the CFR in the USA has been estimated at 2.8%. While public discourse on COVID-19 has largely centered around patients with severe or fatal illness, it has become apparent that a growing number of patients experience mild to moderate symptoms for a prolonged period of time.

Patients and survivors of COVID-19 from the Body Politic COVID-19 Support Group created and analyzed a survey targeted at patients experiencing symptoms for over two weeks. Responses from 640 patients were collected between April 21 and May 2, 2020 (https://patientresearchcovid19.com/research/report-1/).

Key findings were symptoms are not limited to cough, fever, and shortness of breath. Other widely reported symptoms span neurological, gastrointestinal, cardiovascular, and other systems and include fatigue (reported by 81.3% of respondents), chills/sweats (75.9%), body aches (73.9%), headache (72.2%), brain fog and concentration issues (68.6%), gastrointestinal issues (66.9%), trouble sleeping (66.1%), and dizziness (60.6%). An elevated temperature under 100.1°F was reported by 72.2% of respondents while a fever over 100.1°F was reported by only 47.8% of respondents. The other key finding was recovery is volatile, includes relapses, and can take six or more weeks. At the time respondents took the survey, 90.6% reported not being recovered and were, on average, on day 40 of experiencing symptoms. 89% of respondents said that their symptoms fluctuated in intensity and frequency, and 70% reported new symptoms appearing at

different stages of their illness. Based on textual responses and anecdotes from the support group, patients may feel better for days or weeks only to relapse into old or new symptoms soon after.

1.2.1. Post-COVID Conditions

The abundance of symptoms described above have now been narrowed and characterized by the CDC as nineteen Post-COVID Conditions [Post-COVID Conditions CDC]. Although most people with COVID-19 get better within weeks of illness, some people continue to experience these post-COVID conditions. Post-COVID conditions are a wide range of new, returning, or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19. Even people who did not experience COVID-19 symptoms in the days or weeks after they were infected can have post-COVID conditions.

These conditions can present as various types and combinations of health problems for different lengths of time. Unlike some of the other types of post-COVID conditions that tend only to occur in people who have had severe illness, these symptoms can happen to anyone who has had COVID-19, even if the illness was mild, or if they had no initial symptoms. People commonly report experiencing different combinations of the following symptoms:

- Difficulty breathing or shortness of breath
- Tiredness or fatigue that interferes with daily life
- Symptoms that get worse after physical or mental activities (also known as post-exertional malaise)
- Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
- Cough
- Chest pain
- Stomach pain
- Headache
- Fast-beating or pounding heart (also known as heart palpitations)
- Joint or muscle pain
- Pins-and-needles feeling
- Diarrhea
- Sleep problems
- Fever
- Dizziness on standing (lightheadedness)
- Rash
- Depression or anxiety
- Change in smell or taste

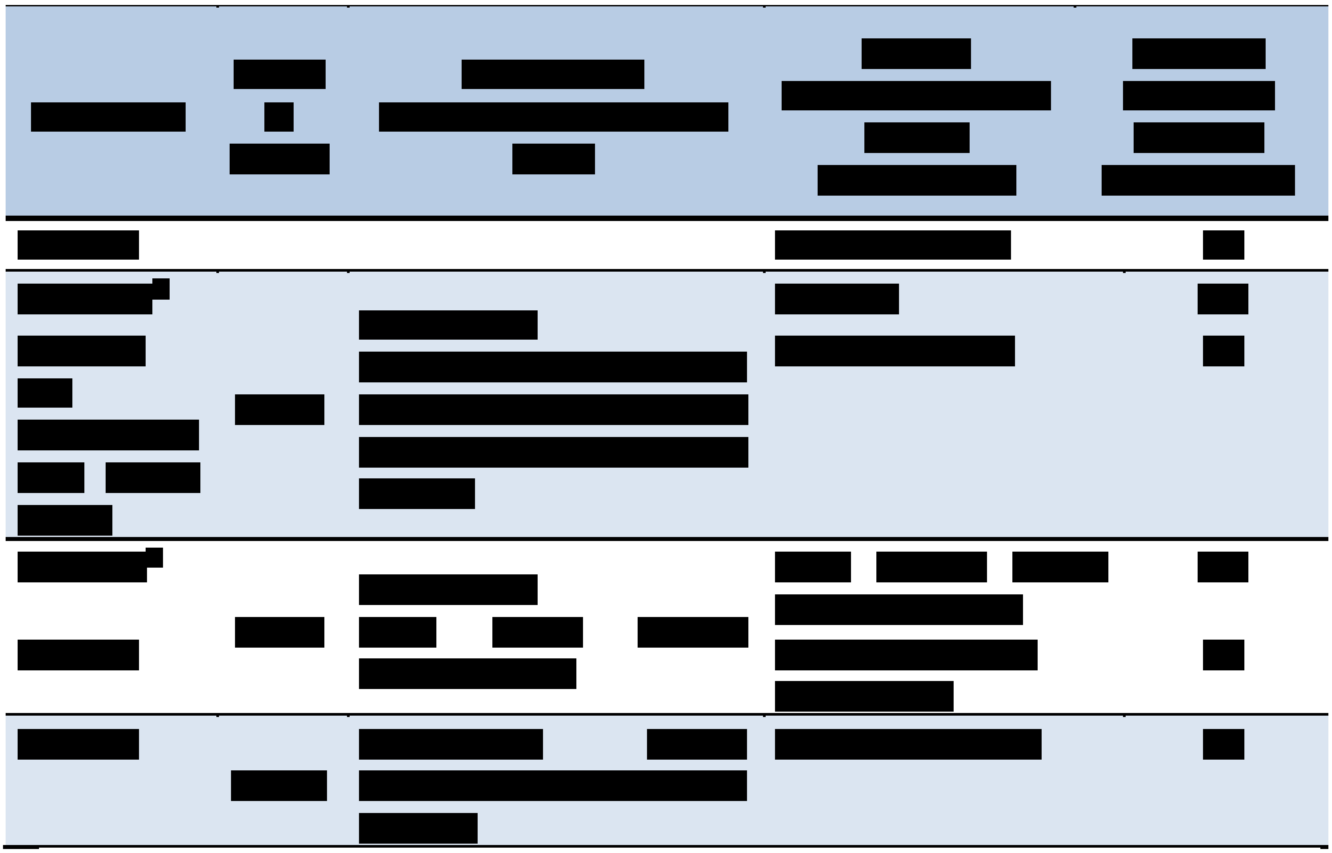
- Changes in menstrual period cycles

1.3. NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

The name of the investigational product is Rintatolimod (Trade Name: Ampligen®). [redacted]

Figure 1-1: Ampligen® Efficacy Potential

1.4. SUMMARY OF PRIOR PRE-CLINICAL AND CLINICAL STUDIES



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2. STUDY OBJECTIVES AND OUTCOME MEASURES

2.1. STUDY OBJECTIVES

2.1.1. Primary Objective

The purpose of this study is to assess the efficacy and safety of Ampligen® administered twice weekly by IV infusions in subjects experiencing the Post-COVID Condition of fatigue.

2.2. STUDY OUTCOME MEASURES

2.2.1. Primary Outcome Measure

- Change from baseline to week 13 in PROMIS® Fatigue Score (T-Score).

2.2.2. Secondary Outcome Measures

- Change from baseline to week 6 in PROMIS® Fatigue Score (T-Score).

  Note: Additional PROMIS® Fatigue Score analysis (change from baseline) at week 6 and 13 will be performed excluding response to item, "How often did you have enough energy to exercise strenuously?"

- Change from baseline to week 6 and 13 in distance traveled during a 6-minute walk test.
- Proportion of subjects with minimal clinically important difference (MCID), defined as at least 54 m, in the Six-Minute Walk Test (6MWT) at the end of 12-week treatment phase.
- Change from baseline to week 6 and 13 in PROMIS® Cognitive Function Score (T-Score).
- Change from baseline to week 6 and 13 in PROMIS® Sleep Disturbance Score (T-Score).

2.2.3. Exploratory Endpoints

- Changes from baseline in COVID-19-related symptoms using Symptom Burden Questionnaire for Long COVID (SBQ-LC) during the course of the treatment phase.

  Note: A set of common COVID-19-related symptoms (see Symptom Burden Questionnaire for Long COVID (SBQ-LC)) will be evaluated at each scheduled study visit by the patient regardless of which symptoms a subject had at baseline, as new symptoms may appear following the baseline assessment.

- Change from baseline in cognitive function as measured by Montreal Cognitive Assessment (MoCA) at week 4, 8, and 13 during the treatment phase.
- Incidence of hospitalization during the treatment phase.
- Duration (days) of hospitalization during the treatment phase.
- Evaluation of lymphocyte profile by flow cytometry in patients with post-COVID-19 conditions.

- Identification and evaluation of plasma protein biomarkers in patients with post-COVID-19 conditions.

2.2.4. Safety Outcome Measures

- Incidence of treatment-related adverse events.
- Incidence and severity of treatment-emergent adverse events (TEAEs).
- Incidence of serious adverse events (SAEs).
- Incidence of TEAEs and SAEs leading to discontinuation of study medication.
- Changes in blood chemistry, hematology, and coagulation parameter results.
- Changes in vital signs including temperature, pulse, respiratory rate, systolic and diastolic blood pressure.
- Changes in physical examination results.
- Change in electrocardiogram (ECG) results.

3. STUDY DESIGN

This is a Phase 2, two-arm, randomized, double blind, placebo controlled multicenter study to evaluate the efficacy and safety of Ampligen® in patients experiencing the Post-COVID Condition of fatigue. Patients will be randomized 1:1 to receive twice weekly IV infusions of Ampligen® or placebo.

3.1. STUDY CENTER

Up to 10 centers in the United States. Centers must have the capability of implementing appropriate infection-control measures to prevent infection of study staff and others who share the clinical site space. The facility should be adequately staffed by medical personnel and equipped with a "crash cart" in the event of acute allergic reaction or requirement for advanced cardiac life support.

3.2. STUDY POPULATION

The study population for the study will be adult patients with the Post-COVID Condition of fatigue.

3.3. ELIGIBILITY CRITERIA

3.3.1. Inclusion Criteria

Potential subjects are required to meet all of the following criteria for enrollment into the study:

1. Male or female adult between 18 to 60 (inclusive) years of age at time of enrollment.
2. Prior confirmed COVID-19 diagnosis by standard RT-PCR assay or equivalent testing at least 12 weeks prior to baseline.

   Note: For subjects with COVID-19 symptoms who were not tested for the presence of SARS-CoV-2, a positive serum antibody test for SARS-CoV-2 will be sufficient in subjects not vaccinated for COVID-19 or it can be shown that the positive antibody cannot be associated with the COVID-19 vaccination.
3. Laboratory confirmed negative SARS-CoV-2 (COVID-19) infection by a government approved test / kit at time of enrollment.
4. Subject meets for the criteria of fatigue per the 1994 CDC Case Definition for Chronic Fatigue Syndrome (CFS): Unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities. The fatigue must have persisted or recurred during 3 or more consecutive months of illness and must not have preceded the onset of the COVID-19 symptoms.

5. PROMIS® Fatigue- Short Form 7a response total raw score of ≥21 at screening and baseline.
6. Electrocardiogram (ECG) with no clinically significant findings as assessed by the Investigator.

   Note: Below are the examples of clinically significant ECG abnormalities:

   – *Previous documented evidence of myocardial infarction or recent significant change in the resting EKG suggesting infarction or other acute cardiac events.*

   – *Current symptoms of coronary insufficiency (i.e. - angina pectoris and/or ST segment depression on EKG).*

   – *Evidence of uncontrolled atrial or frequent or complex ventricular ectopy, or myocardial conduction defect which would increase the risk of syncope (for example, second degree or higher A-V block).*
7. Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
8. Men and women of childbearing potential and their partner must agree to use two medically accepted methods of contraception (e.g., barrier contraceptives [male condom, female condom, or diaphragm with a spermicidal gel], hormonal contraceptives [implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings], or one of the following methods of birth control (intrauterine devices, bilateral tubal occlusion, or vasectomy) or must practice complete sexual abstinence for the duration of the study (excluding women who are not of childbearing potential and men who have been sterilized).
9. Females of child-bearing potential must have a negative urine pregnancy test at Screening Visit and prior to receiving the first dose of study drug; and Male participants must agree to use contraception and refrain from donating sperm for at least 90 days after the last dose of study intervention.
10. Subject is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures and study restrictions.

3.3.2. Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded from enrollment:

1. Inability to provide informed consent or to return to the Investigator's site for scheduled infusions and evaluations.
2. Exhibiting signs of moderate or severe pulmonary disease (such as COPD, asthma, or pulmonary fibrosis).
3. Ongoing requirement of oxygen therapy.

4. Pulse oxygen saturation (SpO2) of <94% on room air at the time of screening.
5. Thrombocytopenia (platelets $<100\times10^9$/L), anemia (hemoglobin <9.0 g/dL), or leukopenia (WBC $<3\times10^9$/L) on screening labs
6. History of splenectomy.
7. Known hypercoagulable state or at increased risk of thrombosis (e.g., due to immobility)
8. Liver cirrhosis or patient showing signs of clinical jaundice at the time of screening.
9. Transaminase (ALT or AST) >3X ULN or total bilirubin >2X ULN at screening
10. Chronic kidney disease stage 4 or requiring dialysis at the time of screening.
11. Estimated GFR <60 mL/min/1.73 m^2 at the time of screening
12. NYHA Class III or IV congestive heart failure (CHF).
13. Exhibiting signs of uncontrolled hypo-or hyper-thyroidism at the time of Screening.
14. Diagnosis of autoimmune disease (e.g., SLE, rheumatoid arthritis, psoriasis) at the time of screening
15. Uncontrolled rheumatologic disorders at the time of screening.
16. Diagnosis of sleep apnea (central or obstructive) at the time of screening.
17. History of organ transplantation or are candidates for organ transplantation at the time of screening.
18. History of Chronic Fatigue Syndrome prior to COVID-19 infection.
19. History of fibromyalgia prior to COVID-19 infection.
20. History of major psychiatric disorder including psychotic or melancholic features, bipolar disorders, schizophrenia of any subtype, schizoaffective disorder, major depression delusional disorders of any subtype, dementias of any subtype, anorexia nervosa or bulimia nervosa.
21. Any malignancy within the past 5 years, excluding successfully treated basal cell carcinoma or squamous cell carcinoma without evidence of metastases.
22. Any other clinically significant serious systemic diseases, chronic or intercurrent active medical disorder and other reasons which would interfere with study conduct or study results interpretation per the Investigator.
23. Chronic or intercurrent acute medical disorder or disease making implementation or interpretation of the protocol or results difficult or unsafe per the investigator.
24. Therapy with interferons interleukins, or other cytokines or investigational drugs within 6 weeks of beginning study medication. Subjects must give written informed consent prior to discontinuation of investigational drugs.

25. Treatment with any of the following therapies within the eight (8) weeks immediately preceding the start of study baseline or during baseline: systemic glucocorticoids (i.e., hydrocortisone, prednisone, etc.) or mineralocorticoids (i.e., fludrocortisone (Florinef), etc.), interferons, interleukin-2, systemic antivirals, gamma globulin or investigational drugs or experimental agents not yet approved for use in the United States.
26. Prior participation in an Ampligen® study.
27. Medical necessity, as determined by the patient's primary doctor or the principal investigator, to continue aspirin (ASA) or non-steroidal anti-inflammatory (NSAID) drugs for 20 consecutive days or for more than 10% of the study duration.
28. History of congestive heart failure, suspected or known dissecting aneurysm, recent systemic or pulmonary embolus or myocardial infarction (≤ 6 months), severe valvular heart disease, ventricular aneurysm, active or suspected myocarditis or pericarditis, thrombophlebitis or intracardiac thrombi, or acute infection.
29. Evidence of moderate or severe obstructive pulmonary disease.
30. Resting diastolic blood pressure > 115 mm Hg or resting systolic blood pressure > 200 mm Hg.
31. Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, or myxedema).
32. Concurrent use of any beta blockers and/or bronchodilators which cannot remain at a stable dosage level during baseline and the study.
33. History of alcohol or other substance abuse within two (2) years before the onset of acute COVID-19 or at any time afterward.
34. History of suicidal ideation, suicide attempt, or suicidal behavior within two (2) years of baseline. A score of 10 or greater on the PHQ-9 at Baseline indicates symptoms of depression and will exclude subject. A score of greater than zero on question nine (9) of the PHQ-9 at Baseline indicates suicidal ideation and will exclude subject.
35. Pregnant or breast feeding.
36. Participation in another study for an investigational treatment.

4. STUDY SCHEDULE

The study Schedule of Assessments is presented in Table 4-1 and Table 4-2.

The study will have three phases: Screening Phase, Treatment Phase, and Follow-Up Phase.

Note: During visits conducted at the study clinic, subjects and site personnel will use appropriate protective gear (e.g., masks, gloves) to prevent the spread of the infection.

Screening Phase (up to 1 week):

All subjects will provide written informed consent and have a Screening visit (V1) within 7 days prior to first treatment visit (V2) to determine eligibility for subject participation.

All subjects who fail to meet eligibility criteria are considered screen failures and are exited from the study without further evaluation.

Treatment Phase (12 weeks):

Ampligen® and placebo will be administered via twice weekly infusions (Example: Monday/Thursday or Tuesday/Friday schedule) for 12 weeks. [redacted]

Follow-Up Phase (2 weeks):

Two safety follow-up visits will be performed 3 to 4 days and 2 weeks after the End of Treatment (EOT) visit (V25).

Table 4-1: Schedule of Assessments V1 to V14

Procedure/Assessments	Screening Visit	Treatment Visits												
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Week	Week 0	1(Day 0)	1	2	2	3	3	4	4	5	5	6	6	7
Window Period		Within 7 days of SV												
[redacted]	X													
[redacted]	X	X												
[redacted]	X													
[redacted]	X	X												
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X										X		
[redacted]	X	X										X		
[redacted]	X	X		X		X		X		X		X		X
[redacted]		X		X		X		X		X		X		X
[redacted]		X		X		X		X		X		X		X
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X	X		X		X		X		X		X	
[redacted]	X	X		X		X		X		X		X		X
[redacted]		X						X						
[redacted]	X					X						X		
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
[redacted]	X													
[redacted]	X	X										X		
Bio[redacted]	X	X										X		
[redacted]	X	X						X	X					
[redacted]	X	X										X		

Procedure/Assessments	Screening Visit	Treatment Visits												
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Week	Week 0	1(Day 0)	1	2	2	3	3	4	4	5	5	6	6	7
[redacted]		X										X		
[redacted]		X												
[redacted]														
[redacted]		X												
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

[redacted]

Table 4-2: Schedule of Assessments V15 to V27

Procedure/Assessments	Treatment Visits											Follow-up 1	Follow-up 2
Visit	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	Visit 26	Visit 27
Week	7	8	8	9	9	10	10	11	11	12	12	Week 13 (3 to 4 days after EOT)	Week 14
Window Period													± 3 days
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]										X			X
[redacted]										X			X

Procedure/Assessments	Treatment Visits											Follow-up 1	Follow-up 2
Visit	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	Visit 26	Visit 27
Week	7	8	8	9	9	10	10	11	11	12	12	Week 13 (3 to 4 days after EOT)	Week 14
Window Period													± 3 days
[redacted]		X		X		X		X		X		X	
[redacted]		X		X		X		X		X		X	
[redacted]		X		X		X		X		X		X	
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X		X		X		X		X		X		
[redacted]		X		X		X		X		X		X	X
[redacted]		X										X	
[redacted]				X								X	
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X	X	X	X	X	X		
[redacted]													
[redacted]												X	X
[redacted]												X	X
[redacted]		X	X							X			X
[redacted]												X	X
[redacted]												X	
[redacted]												X	
[redacted]													

Procedure/Assessments	Treatment Visits											Follow-up 1	Follow-up 2
Visit	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	Visit 26	Visit 27
Week	7	8	8	9	9	10	10	11	11	12	12	Week 13 (3 to 4 days after EOT)	Week 14
Window Period													± 3 days
[redacted]	X	X	X	X	X	X	X	X	X	X	X		

[redacted]

[redacted]

4.1. SCREENING PHASE

Screening phase is designed to determine whether subjects are eligible to proceed to the treatment phase of the study.

4.1.1. Screening Visit (V1)

Screening assessments will commence at Visit 1 (V1) after obtaining signed informed consent, and will include:

[redacted]

All subjects who fail to meet eligibility criteria are considered screen failures and are exited from the study without further evaluation.

[redacted]

[redacted]

4.2. TREATMENT PHASE

4.2.1. Randomization (V2)

Visit 2 (Day 0) defined as day of first Ampligen® or placebo administration.

Subjects who meet the eligibility criteria will have completed the following evaluations and assessments at V2:

- [redacted]

[redacted]

4.2.2. Subsequent Treatment Visits (V3-V25)

The following assessments will be performed:

[redacted]

[redacted]

4.3. FOLLOW-UP PHASE

4.3.1. Follow-Up visit 1 (V26)

Follow-Up visit (V26) will be performed 3 or 4 days after the End of Treatment (EOT) visit (visit 25). The following assessments will be performed at V26:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

4.3.2. Follow-Up visit 2 (V27)

Follow-Up visit 2 will be performed at 2 weeks after the End of Treatment (EOT) visit (visit 25). The following assessments will be performed at V27:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

4.4. UNSCHEDULED VISITS

In the event that the subject will return to clinic at a time other than a regularly scheduled study visit, the visit will be regarded as an unscheduled visit. Assessments at unscheduled visits are at the discretion of the Investigator. All pertinent findings, including adverse events or changes in medications, will be noted in the eCRF.

5. SUBJECT COMPLETION, WITHDRAWAL AND CRITERIA FOR STOPPING THE STUDY

5.1. SUBJECT COMPLETION

A subject who completes the Treatment Phase will be considered as having completed the study.

Note: Subjects who discontinue treatment (voluntarily or involuntarily) or withdrawn from study participation prior to completing visit 25 are considered as having not completed the study.

5.2. SUBJECT TREATMENT DISCONTINUATION

Patients who fail to comply with the requirements of the study will be discontinued from the study treatment. Reasons for treatment discontinuation may include but are not limited to the following:

- Lost to Follow-up
- Voluntary patient or guardian withdrawal.
- Protocol violation, such as failure to comply with the requirements of the study or use of prohibited concomitant medications.
- Physician decision, such as significant intercurrent illness or surgery, as determined by the Investigator which prevents the patient from taking the study medication, or which requires administration of drugs disallowed in this study.
- Adverse event, such as toxicity grading of 3 or 4 or serious adverse event (SAE) felt by the investigator to be related to the study medication.

5.3. SUBJECT WITHDRAWAL FROM STUDY

Subjects should only be considered withdrawn from the study if they withdraw consent.

5.4. DATA COLLECTED FROM TREATMENT DISCONTINUED/WITHDRAWN STUDY SUBJECTS

Every attempt should be made to collect follow-up information for the subjects who discontinued the treatment or were withdrawn from the study. [redacted]

[redacted]

5.5. Dose Escalation Stopping Criteria

[redacted]

5.6. Study Stopping Criteria

[redacted]

The FDA and other global regulatory authority will be consulted for any protocol amendment before restarting the trial if a stopping rule is met.

6. STUDY TREATMENT

6.1. DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

The investigational product is Ampligen®. [redacted]

6.1.1. Packaging and Labeling

[redacted]

Study treatment will be labeled, according to the regulatory guidelines, as an investigational product to ensure that it will not be used outside of the clinical investigation. The Sponsor, protocol number, expiry date and time, if required, and any additional relevant information will appear on the pack label.

6.1.2. Storage and Handling

Ampligen® (rintatolimod) liquid solution should be stored under refrigeration at 2-8°C.

All study treatment materials will be stored in their original packaging in a safe and secure location at the investigational site. Study treatment material will be disposed of in accordance with institutional and /or local requirements.

Additional details on the procedures for receiving, storing, and using rintatolimod can be found in a separate document entitled "Pharmacy Manual".

6.2. ADMINISTRATION

Ampligen® and placebo will be administered via twice weekly infusions (Example: Monday/Thursday or Tuesday/Friday schedule) for 12 weeks. [redacted]

Table 6-1: Study Drug Dose and Duration of Infusion

Visit/Day/Week/ Dose	Cumulative Dose Number	Dose Amount	Duration of Infusion
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Visit/Day/Week/ Dose	Cumulative Dose Number	Dose Amount	Duration of Infusion
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

Table 6-2: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

[redacted]

[redacted]

[redacted] up to 90 to 120 minutes if needed at the reduced dose to mitigate infusion related intolerance.

6.2.1. Study Personnel

This is a double-blind study. The investigator and staff, subjects and Sponsor/CRO staff directly related to study conduct will be blinded to the treatment assignment. [redacted]

[redacted]

6.3. DRUG COMPLIANCE

Ampligen® Drug Accountability (DA) procedures will be reviewed with the study staff and DA will be conducted at interim monitoring visits and the close out visit. The site will maintain accurate DA logs.

The site will maintain and file all copies of the drug requests and shipping receipts to assist with accountability efforts. Access to study drug will be limited to persons identified in the site's delegation log at all times. The site will maintain proper temperature log documentation for all refrigerated study drug.

6.4. CONCOMITANT MEDICATIONS

[redacted]

7. DESCRIPTION OF PROTOCOL ASSESSMENTS AND PROCEDURES

7.1. INFORMED CONSENT

A written informed consent will be obtained for this study by the Investigator or designee from all subjects prior to performance of any protocol-specific procedure. This study will be conducted in accordance with the provisions of the Declaration of Helsinki.

The Investigator must comply with applicable regulatory requirements and must adhere to the Good Clinical Practice (GCP) in the process of obtaining and documenting the informed consent. The Investigator, or designee, must also inform subjects of all pertinent aspects of the study. Before written informed consent is obtained from the subject, the Investigator or a person designated by the Investigator, must provide the subject enough time and opportunity to inquire about the details of the study and to decide whether or not to participate in the trial. All questions addressed by the subject about the study must be answered to the satisfaction of the subject. Prior to the subject's participation in the trial, the written informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Authorization for release of protected health information must also be obtained, as per local policies.

7.2. ASSESSMENT OF ELIGIBILITY

The Investigator must assess subject continued eligibility for the study as per the Inclusion and Exclusion criteria, during the Screening Phase. The eligibility criteria are described in Section 3.3.1 (Inclusion Criteria) and Section 3.3.2 (Exclusion Criteria). In the event that the subject is not suitable or eligible for the study, the subject will be considered "screen failure".

7.2.1. Re-screening

A subject who signed a consent form but did not meet the inclusion/exclusion criteria is classified as a screen failure.

[redacted]

7.3. DEMOGRAPHIC INFORMATION

In this study the demographic information will include:

- Dates of ICF signature
- Date of birth
- Gender
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, or Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, or Unknown)
- Use of tobacco products

7.4. MEDICAL HISTORY

A medical history will be recorded during the Screening Phase and will include:

- All ongoing medical conditions
- All previously resolved medical conditions that are relevant in the judgment of the Investigator
- Any prior medical conditions that have resolved within the last year

Events that emerge prior to first dose of study medication on Day 1 will be recorded in the medical history and not as AEs. Aside from being used to determine subject eligibility, this information will permit the Investigator to record the nature, duration, and severity of any ongoing baseline medical conditions prior to the subject's receiving investigational product treatment.

For each relevant history, the following will be documented:

- Disease/disorder/condition
- Date of diagnosis
- History status (resolved or ongoing).

7.5. PHYSICAL EXAMINATION

The physical examination will include routine examinations for the following:

- Constitutional/General Appearance
- Head, Ears, Eyes, Nose, Throat (HEENT)
- Neurologic
- Cardiovascular

- Musculoskeletal and Extremities
- Dermatologic
- Respiratory
- Gastrointestinal
- Genitourinary
- Lymphatic
- Psychiatric

Each abnormality will be recorded, and the Investigator will record an assessment of its clinical significance.

7.6. VITAL SIGNS, HEIGHT AND WEIGHT

The following will be collected:

- Systolic Blood Pressure
- Diastolic Blood Pressure
- Heart Rate (Pulse)
- Temperature
- Respiratory Rate
- Height (Screening only)
- Weight
- Body Mass Index

Note: During days of Ampligen® or Placebo administration, pre-infusion vitals (before the start of infusion) and post-infusion vitals (after the end of infusion) will be measured. Post-infusion vitals will be limited to blood pressure and pulse only.

Note: During study visits when the 6MWT is performed, vitals should be collected before and after 6MWT (i.e., pre 6MWT, and post 6MWT), as clinically indicated per the discretion of the Investigator or designee. These should be documented in the source records as standard of care assessments; however, they will not be captured as a protocol assessment.

Note: During study visits when the 6MWT and study drug administration is performed (i.e., Visit 6, 12, and 18), vitals should be collected as follows: pre 6MWT and post 6MWT, if clinically indicated per the discretion of the Investigator or designee. Subjects should be rested

for at least 10 minutes after completing the 6MWT before pre-infusion vitals are taken. Post-infusion vitals should be taken after the completion of the study administration.

7.7. 30 Minute Site Check

Subjects will be monitored for 30 minutes after every infusion for evaluation of any unexpected adverse events.

7.8. Concomitant Medication

The subject may take any medications judged necessary by the Investigator, provided such medications are not listed in Section 6.4.1.

All medications and therapies administered or taken by the subject beginning 30 days prior to Screening Visit and throughout the study will be recorded in the source documents and on the appropriate page of the case report form (CRF). Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter medication and topical medication.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose).
    - **Note:** *Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.*
- Route of dosing
- Indication for use
- The start date
- The stop date (if medication/therapy is not ongoing).

7.9. Clinical Laboratory Assessments

Blood samples will be collected for analysis of the following parameters described in Table 7-1 (local lab) and Table 7-2 (central lab).

[redacted]

The blood sample for an Exploratory Analysis-plasma protein biomarker samples will be collected, processed and stored at the site, and later transferred to a central lab.

All laboratory reports will be reviewed by the Investigator. Abnormal results that are new and are considered by the Investigator to be clinically significant will be recorded as adverse events. If in the Investigator judgment, in order to make the determination of clinical significance the testing may be needed to be repeated. Validated, quality-controlled laboratory data will be transferred to the main database for analyses.

Table 7-2: [redacted]

[redacted]
[redacted]

[redacted]

[redacted]

[redacted]

7.10. Pulse oxygen saturation (SpO2)

Pulse oxygen saturation (SpO2) will be recorded at all visits. [redacted]

7.11. [redacted]

[redacted]

7.12. [redacted]

[redacted]

7.13. Viral Testing for SARS-CoV-2

Nasal swab samples (or another current acceptable collection method for sample) will be performed at baseline for all subjects.

7.14. ELECTROCARDIOGRAM

A 12-lead electrocardiogram (ECG) will be performed per the site standard procedures. [redacted]

7.15. [redacted]

[redacted]

7.16. [redacted]

[redacted]

7.17. [redacted]

[redacted]

8. STATISTICAL ANALYSIS

This Section presents general information about statistical considerations and concepts and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this study will be in a separate document, i.e., the Statistical Analysis Plan (SAP).

8.1. TREATMENT GROUPS

The following treatment groups will be assessed in the study:

- Ampligen®
- Placebo (normal saline)

8.2. DESCRIPTION OF STUDY OUTCOMES AND ESTIMAND

Refer to Section 2.2 for description of study outcome measures.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

8.3. SAMPLE SIZE DETERMINATION AND RATIONALE

The sample size of 80 subjects will be used in this study. The sample size is based on clinical judgment. No statistical power calculation is used to establish the sample size for this proof-of-concept study.

8.4. RANDOMIZATION AND STRATIFICATION

A total of 80 subjects (40 per group) will be randomized in a 1:1 ratio (Ampligen®: placebo). [redacted]

- [redacted]
- [redacted]

[redacted]

8.5. BLINDING

This is a double-blind study. The investigator and staff, subjects and Sponsor/CRO staff directly related to study conduct will be blinded to the treatment assignment. [redacted]

[redacted].

[redacted]

8.6. TIME TO UNBLINDING

8.6.1. Emergency Unblinding

Breaking the blind prematurely will be allowed only if the subject's well-being requires knowledge of the subject's treatment allocation. Every attempt will be made to maintain the blind throughout the study.

[redacted]

8.7. INTERIM ANALYSIS

There is no planned interim analysis for this early phase study.

8.8. GENERAL STATISTICAL CONSIDERATIONS

All collected study data will be presented in subject data listings. [redacted]

8.8.1. Analysis Populations

[redacted]

[redacted]

8.8.2. Covariates

For efficacy analyses important prognostic factors that need adjustment will be specified in the Statistical Analysis Plan (SAP) for the study.

8.8.3. Missing Data

All efforts will be made to avoid missing data; however, there will be no imputation of missing data for this early phase study and primary analysis of efficacy data will be based on observed data only.

[redacted]

8.8.4. Multiplicity

No adjustment of multiplicity will be done for the efficacy analysis of the data for this early phase study.

8.9. ANALYSIS METHODS

A Statistical Analysis Plan (SAP) will be developed and approved before the database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the data from this trial.

8.9.1. Subject Disposition

The disposition of all subjects who signed an ICF will be provided. [redacted]

8.9.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group using appropriate descriptive statistics.

Medical history will be presented as by-subject listing.

8.9.3. Concomitant Medications/Therapies

Concomitant medications/therapies will be summarized separately for the Safety population. All prior and concomitant medications recorded in the case report form will be coded to matching Anatomic Therapeutic Classification codes using the most recent version of the WHO Drug Dictionary. Descriptive summaries by treatment group will be prepared using the coded term. All concomitant medications/therapies recorded in the case report form will be listed.

8.9.4. Efficacy Analyses

8.9.4.1. Primary Analysis

[redacted]

[redacted]

8.9.5. Safety Analyses

8.9.5.1. Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent version of MedDRA dictionary.

[redacted]

8.9.5.2. Clinical Laboratory Data

[redacted]

8.9.5.3. Vital signs

[redacted]

8.9.5.4. Physical Examination

[redacted]

8.9.5.5. ECG

[redacted]

9. SAFETY REPORTING

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this Section of the protocol.

9.1. ADVERSE EVENT (AE) DEFINITION

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the patient to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant (CS) to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

9.2. REPORTING OF ADVERSE EVENTS

Report initiation for all AEs and SAEs will begin at the time of the first treatment visit and continue until the end of final study visit. All events will be followed to resolution or until the subject completes the study. A final assessment of outcome will be made at that time.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is considered to be an SAE (see Section 9.3), the impact the event had on study treatment (see Section 9.2.1), the Common Terminology Criteria for Adverse Events (CTCAE) grade (intensity) of the event (see Section 9.2.2), the causality of the event (see Section 9.2.3), whether treatment was given as a result of the event (see Section 9.2.4), and the outcome of the event (see Section 9.2.5)

9.2.1. Impact on Study Treatment

The impact the event had on the study treatment will be assessed as either: dose increased, dose not changed, dose rate reduced, dose reduced, drug interrupted, drug withdrawn, not applicable, or unknown. The "not applicable" assessment will be used only when the subject is no longer in the Treatment Phase of the protocol.

9.2.2. CTCAE Grade (Intensity) Assessment

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 9-1: CTCAE v5.0 General Guidelines

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

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017

9.2.3. Causality Assessment

AEs will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

1. **Definitely related**: This category applies to those AEs that the Investigator feels are incontrovertibly related to the study treatment. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study treatment; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it follows a known response pattern to treatment with the study treatment.
2. **Probably related:** This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study treatment. An AE may be considered probable if or when (must have three): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.
3. **Possibly related**: This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are judged unlikely but cannot be ruled out with certainty to the study treatment. An AE may be considered possible if or when (must have two): (1) it follows a reasonable temporal sequence from administration of the study treatment. (2) It could not

readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It follows a known response pattern to treatment with the study treatment.

4. **Unlikely related**: In general, this category can be considered applicable to those AEs which, after careful medical consideration at the time they are evaluated, are judged likely to be unrelated to the study treatment. An AE may be considered unlikely if or when (must have two): (1) it does not follow a reasonable temporal sequence from administration of the study treatment. (2) It could not readily have been produced by subject's clinical state, environmental or toxic factors, or other therapies administered to the subject. (3) Disappears or is decreased upon discontinuation of the study treatment. (4) It does not follow a known response pattern to treatment with the study treatment.
5. **Unrelated**: This category applies to those AEs which, after careful consideration at the time they are evaluated, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and determined with certainty to have no relationship to the study treatment.

9.2.4. Treatment Given as a Result of the Event

The event impact in terms of treatment provided will be as either: none, medication administered, non-drug therapy administered, surgery performed, hospitalization, or other (with a specification).

9.2.5. Outcome Assessment

The outcome of the event will be assessed as either: fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

9.3. SERIOUS ADVERSE EVENT (SAE) DEFINITION

An SAE is defined as any AE that:

- Results in death
- Is life threatening (the subject is at immediate risk of dying from the adverse experience)
- Requires subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse effect when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.4. REPORTING OF SERIOUS ADVERSE EVENTS

The Investigator is required to report all SAEs that occur during the time period specified in Section 9.2. Once the Investigator becomes aware of an SAE, he/she must report the SAE to Medical Monitor within 24 hours.

Medical Monitor	[redacted]

The Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, electrocardiogram [ECG] reports, discharge summary, hospital notes, etc., if applicable. Additional follow-up information as it becomes available must be reported to the Medical Monitor.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified.

9.4.1. SAE Follow-Up

All subjects experiencing an SAE, including the discontinued subjects, must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator (i.e., recovery, return to baseline status, no further improvement expected, or death).

For each SAE indicated as an unresolved event on the initial report, regardless of whether the subject completed the study or withdrew, the site should submit a follow-up report with updated information.

9.5. EXPECTED/ANTICIPATED EVENTS

Refer to Investigator Brochure for the expected/anticipated events.

9.6. PREGNANCY REPORTING

To ensure patient safety, any pregnancy that occurs after the first treatment visit until the end of final study visit should be recorded using a Pregnancy Notification Form and reported immediately to Sponsor within 24 hours of learning of the pregnancy.

If a subject becomes pregnant during the study before the end of treatment phase, they will be a discontinued subject. If a subject becomes pregnant during the study after the end of treatment during the follow up portion, they can complete the remaining scheduled follow up unless there is a medical contraindication.

9.6.1. AE and SAE Reporting

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs.

9.6.1.1. Abortions

An induced elective abortion to terminate a pregnancy without medical reason is not regarded as an AE. However, an induced therapeutic abortion to terminate a pregnancy because of complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion in a study subject is always considered an SAE.

9.6.2. Informed Consent

The ICF will include information regarding reporting of pregnancy to the Sponsor and collection of information through the end of pregnancy that occurs in either a female subject or in a female partner of a male subject. If a female partner becomes pregnant, the Investigator will request consent from the partner to collect this information.

9.6.3. Pregnancy Follow-Up

The pregnancy will be followed-up to determine the outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) and should include an assessment of the possible relationship to the study treatment of any pregnancy outcome. This information should also be documented on the Pregnancy Outcome Form and reported to the Sponsor.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Subjects will be identified on eCRFs by a unique subject identification number and on source documents by name and date of birth. No personal identifier will be used in any publication or communication used to support this research study. The subject identification number will be used if it becomes necessary to identify data specific to a single subject.

The local IRB, FDA, the monitors, auditors, and personnel authorized by the Sponsor are eligible to review the medical and research records related to this study as part of their responsibility to protect human subjects in clinical research. They will be given direct access to source data and documentation (e.g., medical charts/records, printouts etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Access to electronic medical records may be governed by institution policy. The study site will be required to ensure access while remaining compliant with institutional requirements.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. MONITORING REQUIREMENTS

The specific obligations outlined in 21 Code of Federal Regulations (CFR) and ICH guidelines require the Sponsor to maintain current personal knowledge of the progress of a study. Therefore, the Sponsor's designated monitor will visit the site during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable, and that protocol adherence is satisfactory.

As delineated above, the Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the eCRF. In addition to the original medical records, these data may include but are not limited to study, laboratory reports, etc.

In accordance with federal regulations, site inspections will serve to verify strict adherence to the protocol and the accuracy of the data that is being entered on the case report forms. A Monitoring Log will be maintained at each study site. The Monitoring Log will be signed by the monitor, dated, and stated the type of visit. The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA or other regional regulatory authority.

11.2. ACCEPTABILITY OF CASE REPORT FORMS (CRFS)

For each subject who has signed an informed consent form, a CRF must be completed. For subjects who are screen failures, this would be limited to the screen failure CRF page. All source documents and CRFs will be completed as soon as possible after the subject's visit and corrections to data on the CRFs will be documented, if applicable. The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs will be reviewed by the Sponsor’s or designated CRO’s monitor, who will make a decision as to their acceptability.

11.3. MODIFICATION OF PROTOCOL

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator’s IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject’s participation in the trial.

An amendment may also require modification of the informed consent form. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor. An amendment must be provided in writing, and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities and notify other Investigators using this protocol.

11.4. REPORTING PROTOCOL DEVIATIONS

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the subject will continue in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

11.4.1. Major Protocol Deviation or Violation

A major protocol deviation or violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. Examples of this include:

- Failure to obtain informed consent prior to initiation of study-related procedures
- A research subject does not meet the protocol's eligibility criteria but was enrolled without prior approval from the sponsor.
- A research subject received the wrong treatment or incorrect dose.
- A research subject met withdrawal criteria during the study but was not withdrawn.
- A research subject received a prohibited concomitant medication.
- Failure to treat research subjects per protocol procedures that specifically relate to primary efficacy outcomes.
- Changing the protocol without prior sponsor and IRB approval.
- Multiple minor violations of the same nature after multiple warnings.

11.4.2. Minor Protocol Deviation or Violation

A minor protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that has not been approved by the IRB and which DOES NOT have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy, and reliability of the study data. Examples of this include:

- Follow-up visits that occurred outside the protocol required time frame because of the participant’s schedule.

- Blood samples obtained at times close to but not precisely at the time points specified in the protocol.

12. ETHICS AND REGULATORY REQUIREMENTS

This study is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, GCP, 21 CFR, ICH E6, HIPAA regulations in 45 CFR Part 164 (US only), and the Belmont Principles of respect for persons, beneficence, and justice. No protocol changes will be implemented without the prior review and approval of the IRB, except when the modification does not involve the subject's participation in the trial or where it may be necessary to eliminate an immediate hazard to a research subject. In the latter case, the change will be reported to the IRB as soon as possible, according to IRB regulations.

Additionally, the study product used in this study is manufactured, handled, and stored in accordance with applicable GMP. The study product provided for this study will be used only in accordance with this protocol.

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

The Principal Investigator (PI) at each site will provide the Institutional Review Board/Independent Ethics Committee (IRB/IEC) with all appropriate materials as required by their IRB/IEC, including but not limited to the clinical study protocol, informed consent form, and any advertising materials. The study will not be initiated until the IRB/IEC provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IRB or IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB/IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB/IEC and must agree to share all such documents and reports with the Sponsor.

No changes from the final approved protocol will be initiated without the IRB/IEC's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the modification does not involve the subject's participation in the trial.

12.2. INVESTIGATOR'S RESPONSIBILITIES

The Investigators are responsible for performing the study in full accordance with the protocol and the current revision of the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline, approved by the ICH, and any applicable national and local laws and regulations.

Information regarding to the study center participating in this study that cannot comply with these standards will be documented.

12.3. SUBJECT INFORMED CONSENT REQUIREMENTS

All subjects participating in this study will be given to by the Investigator and/or designee, written and oral information about the study in a language understandable by the subject. Written informed consent will be obtained from each subject prior to any procedures or assessments that would not otherwise be required for the care of the subject are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained and the subject has been given sufficient time to ask questions and consider participation in the study. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. It is permissible for a third person (e.g., a family member) to be present during the explanation of the study.

The written Informed Consent Form (ICF) will be in compliance with CFR 21 Part 50.27 and GCP guidelines. The Sponsor and/or designated CRO will approve the ICF and all amendments to the ICF prior to submission to the IRB/IEC. A copy of the ICF to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the study. The study site must provide the Sponsor with an unsigned copy of IRB/IEC-approved ICF along with applicable documentation to support this approval. The original signed ICF is retained in the subject's study records, and a copy is provided to the subject. A second copy may be filed in the subject’s medical record, if allowed by institutional policy.

13. DATA HANDLING AND RECORD KEEPING

13.1. RECORDING AND COLLECTION OF DATA

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the Investigator(s), the medical record and the research records will be considered the source documents for the purposes of auditing the study.

Applicable source data will be manually transcribed to approve case report forms (CRF). The Investigator is ultimately responsible for the accuracy of the data transcribed on the forms. All source documents and CRFs will be completed as soon as possible after the subject's visit.

The Investigator will review the CRFs to indicate that, to his/her knowledge, they are complete and accurate. Designated source documents will be signed and dated by the appropriate study personnel. The Investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

All research data will be entered, either electronically or manually, into a computerized database. The clinical database will be designed by the clinical data manager in accordance with 21 CFR Part 11 and based on protocol requirements defined by the Sponsor.

The Investigator will maintain a confidential list of study subjects that will include each subject's study number, name, date of birth, and unique hospital identification number if applicable. This list will be kept by the Investigator and will not be collected by the Sponsor. A notation will be made in the subject's case history/medical chart that he/she is participating in a clinical study and has provided a signed and dated ICF as well as a release for protected health information as required by local policies. The Investigator must also maintain a separate screening log of all the subjects screened for participation in the study; it should include gender, age, eligibility status, reason for ineligibility, if applicable; and study allocated subject number, if applicable.

13.2. CLINICAL DATA MANAGEMENT

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's or the CRO's SOPs as well as provisions of the study-specific Data Management Plan.

13.3. ARCHIVING

All study documentation at the Investigator site and Sponsor site will be archived in accordance with ICH GCP E6 and the Sponsor's quality standards and SOPs.

The Investigator will maintain all research records, reports, and case history reports for a period of two (2) years after regulatory approval of the investigational product. If no application is filed or if the application is not approved, records must be maintained for two (2) years after all investigations have been completed, terminated or discontinued and the FDA has been notified.

These documents should be retained for a longer period however, if required by the applicable regulatory requirements or if needed by Sponsor or its authorized representative (as per GCP 5.5.11).

At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study)
- Completed CRFs
- Signed protocols and protocol amendments
- Laboratory results, ranges, and certifications
- IP and accountability records
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee, and IRB
- Investigator and sub-investigator CVs
- Signed informed consent and protected health information consent forms
- Subject screening
- SAE reports
- IRB approval and re-approval letters
- Completed quality of life questionnaire
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the Investigator so that the conduct of the study can be fully documented and monitored.

Study records should not be transferred from site or destroyed without prior written agreement between the Sponsor and the study Investigator. Study records are subject to inspection by applicable health and regulatory agencies at any time.

14. PUBLICATION PLAN

All information supplied by AIM ImmunoTech Inc. in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigator's Brochure, clinical protocol, case report forms and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of AIM ImmunoTech Inc., shall not be disclosed to others without the written consent of AIM ImmunoTech Inc., and shall not be used except in the performance of this study.

It is understood by the Investigator that the Sponsor will use the information collected in this clinical trial in connection with the development of AIM ImmunoTech Inc. Therefore, this information may be disclosed as required to other Investigators or appropriate regulatory authorities. By agreeing to participate in this clinical trial, the Investigator understands that he/she has an obligation to provide the Sponsor with complete test results and all data developed during this trial.

Publication and Disclosure: The site and Investigator agree to submit any proposed manuscript, presentation, or other public disclosure regarding the study to Sponsor for review at least thirty (30) days prior to submitting such proposed manuscript to a publisher or delivering or making such presentation or other public disclosure to any third party. Within thirty (30) days of its receipt, Sponsor shall advise the site and/or Investigator, as the case may be, in writing of any information contained therein that is confidential information (other than research results included in a proposed manuscript) or that may impair Sponsor's ability to obtain patent protection. Sponsor shall have the right to require the site and/or Investigator, as applicable, to remove specifically identified confidential information (but may not require removal of research results from a proposed manuscript) and/or to delay the proposed submission or delivery of the proposed manuscript or presentation, or other public disclosure, for an additional sixty (60) days to enable Sponsor to seek patent protection. The site and Investigator shall not publish, publicly disclose, present or discuss any results of or information pertaining to the site's and Investigator's activities prior to completion of the trial, even if the study is terminated before its completion and the final clinical study report is signed off, or with respect to any endpoints or analyses other than those specified in this protocol.

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16. APPENDIX

16.1. APPENDIX 1: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.03

For complete detailed information please refer to the link below:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

16.2. APPENDIX 2: PROMIS® SLEEP DISTURBANCE – SHORT FORM 4A

Appendix 2 found here.

16.3. APPENDIX 3: PROMIS® COGNITIVE FUNCTION- ABILITIES SHORT FORM 8A

Appendix 3 found here.

16.4. APPENDIX 4: PROMIS® FATIGUE SCALE

Appendix 4 found here.

16.5. APPENDIX 5: SYMPTOM BURDEN QUESTIONNAIRE FOR LONG COVID (SBQ-LC)

Appendix 5 found here.

16.6. APPENDIX 6: PHQ-9 PATIENT DEPRESSION QUESTIONNAIRE

Appendix 6 found here.

16.7. APPENDIX 7: 6-MINUTE WALK TEST

For complete detailed information please refer to the link below:

https://neuropt.org/docs/default-source/cpgs/core-outcome-measures/core-outcome-measures-drafts--march-2018/6mwt_protocol_final.pdf?sfvrsn=36cd5443_4

16.8. APPENDIX 8: MONTREAL COGNITIVE ASSESSMENT (MOCA)

[redacted]

16.9. APPENDIX 9: HOLIDAY/VACATION WEEK VISIT SCHEDULING GUIDANCE DOCUMENT

Appendix 9 found here.