A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, Multicenter Study to Evaluate the Efficacy and Safety of F-652 (IL-22:IgG2 Fusion Protein) in Patients with Moderate to Severe COVID-19

Investigational Product: F-652
Protocol Number: GC-652-04

NCT04498377

Original Protocol: 01 July 2020
Amendment: Version 2.0, 08 January 2021

CLINICAL STUDY PROTOCOL

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Protocol Number: GC-652-04

Sponsor:

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Original Protocol: 01 July 2020

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SIGNATURE PAGE

STUDY TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, Multicenter Study to Evaluate the Efficacy and Safety of F-652 (IL-22:IgG2 Fusion Protein) in Patients with Moderate to Severe COVID-19

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature

[redacted]

Date

01. 11. 2021

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Generon to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Generon and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Generon, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation, Multicenter Study to Evaluate the Efficacy and Safety of F-652 (IL-22:IgG2 Fusion Protein) in Patients with Moderate to Severe COVID-19

PROTOCOL NUMBER: GC-652-04

INVESTIGATIONAL PRODUCT: F-652

PHASE: 2

INDICATION: Treatment of moderate to severe coronavirus disease 2019 (COVID-19)

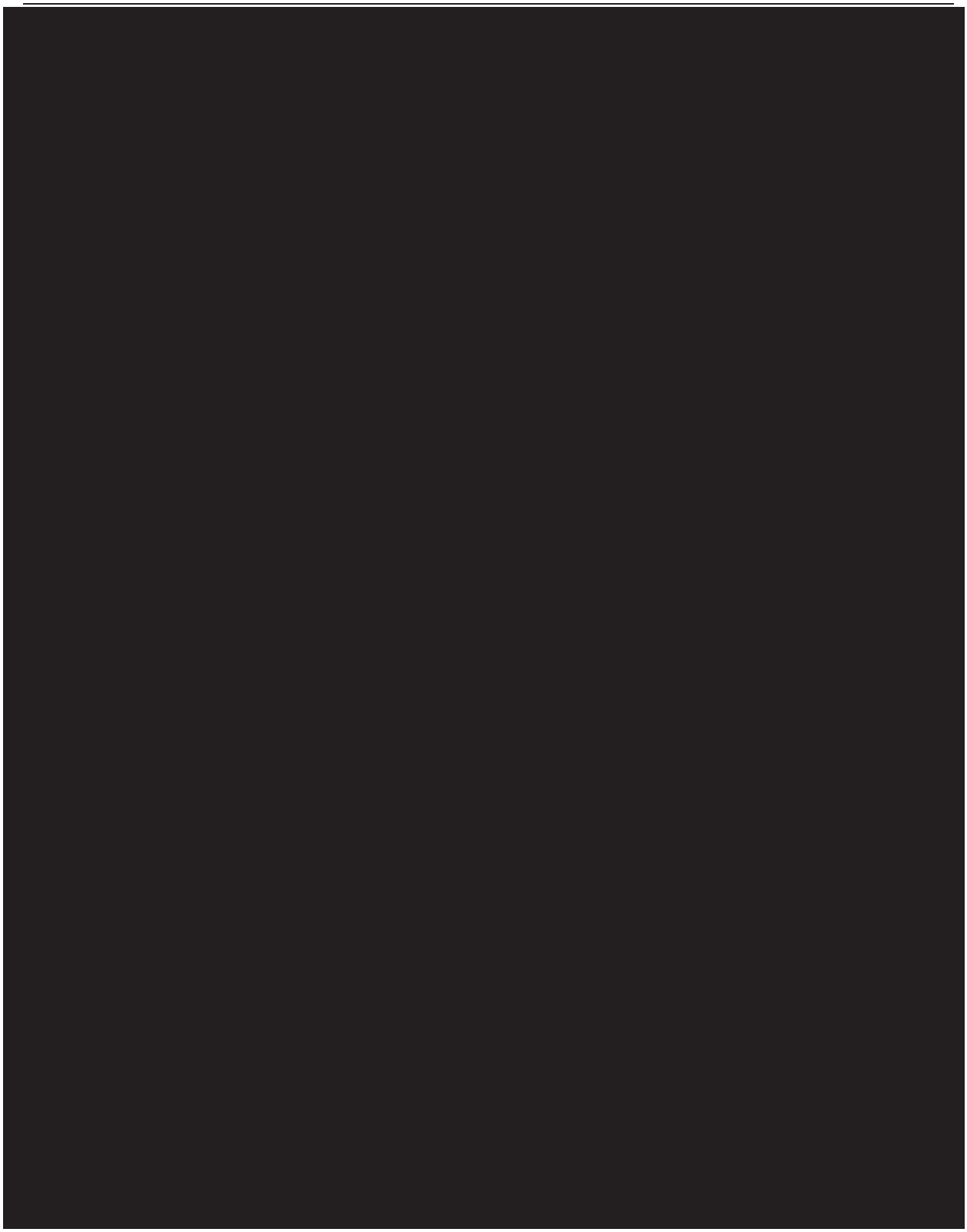
OBJECTIVES:

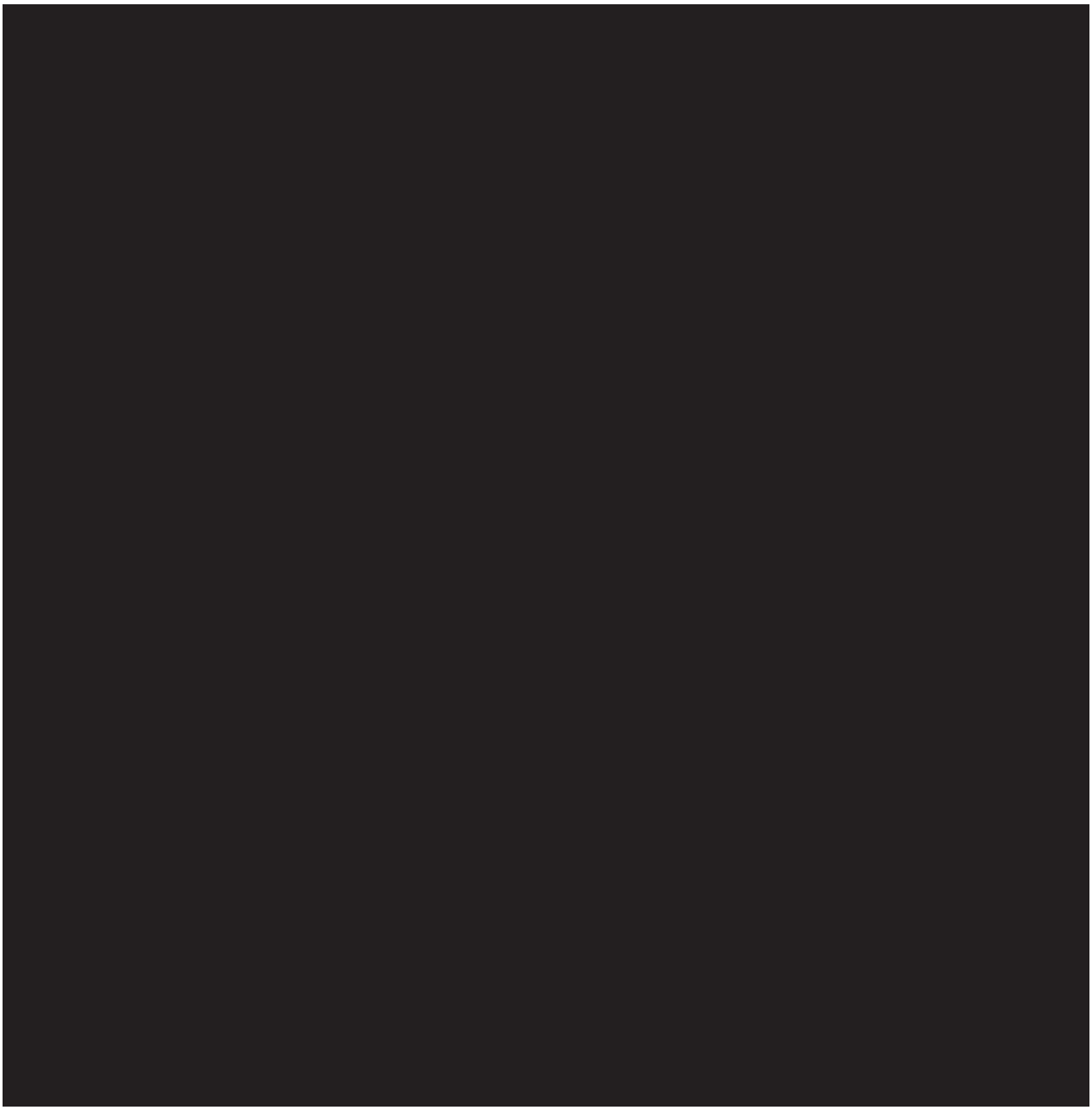
The primary objective is to evaluate the safety and efficacy of F-652 when intravenously (IV) administered in hospitalized, confirmed COVID-19 adult patients with moderate to severe symptoms.

The secondary objective is to evaluate the pharmacodynamics (PD) of F-652 when IV administered in hospitalized, confirmed COVID-19 adult patients with moderate to severe symptoms.

POPULATION:

Inclusion Criteria





STUDY DESIGN AND DURATION:

This is an interventional, multicenter, 2-arm, parallel-group, randomized, double-blind, placebo-controlled, dose-escalation, safety and efficacy study of F-652 treatment versus placebo in patients aged 18 years or older with a COVID-19 diagnosis confirmed by PCR. Eligible patients will have moderate to severe COVID-19 symptoms and will be hospitalized.

The study plans to include 4 cohorts, with enrolled patients being randomized 1:1 in a blinded manner on Day 1, following screening, to F-652 or placebo as follows:

- Cohort 1 (sentinel cohort): Four patients will receive either [redacted] or placebo. Two patients will receive F-652 and 2 patients will receive placebo. Upon completion of sentinel dosing (7 days after last patient last dose), the Data Monitoring Committee (DMC) will evaluate the safety and tolerability data of the sentinel patients and determine if it is acceptable to dose the remaining patients in this dosing group in Cohort 2.
- Cohort 2: Fourteen patients will receive either [redacted] or placebo. Seven patients will receive F-652 and 7 patients will receive placebo. Upon completion of Cohort 2, the DMC will convene and review all available safety data to determine if the study can proceed to the next dose level.
- Cohort 3 (sentinel cohort): Four patients will receive either [redacted] or placebo. Two patients will receive F-652 and 2 patients will receive placebo. Upon completion of sentinel dosing (7 days after last patient last dose), the DMC will evaluate the safety and tolerability data of the sentinel patients and determine if it is acceptable to dose the remaining patients in this dosing group in Cohort 4.
- Cohort 4: Sixteen patients will receive [redacted] or placebo. Eight patients will receive F-652 and 8 patients will receive placebo.

Treatment will begin on Day 1 following randomization. Patients assigned to active drug will receive a total of 2 doses of F-652 (1 IV infusion on Day 1 and 1 IV infusion on Day 8). Patients assigned to placebo will receive identical IV infusions of placebo vehicle on Days 1 and 8. If the patient is discharged from the site prior to Day 8, they will return for an outpatient visit to receive the second IV infusion and remain at the site for an approximate 2-hour observation period. All patients will receive available supportive and antiviral therapies as standard of care. Efficacy will be assessed on Days 15 and 29. Patients will be followed for safety until Day 60.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

[redacted]

EFFICACY ENDPOINTS:

Primary Efficacy Endpoint

The primary efficacy endpoint is the time to achieve a ≥2-point increase in the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale from baseline by Day 29.

The NIAID 8-point ordinal scale includes the following grades:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation;

3. Hospitalized, on non-invasive ventilation or high-flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplementation oxygen – requiring ongoing medical care (COVID-19 related or otherwise);
6. Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;
7. Not hospitalized, limitation on activities and/or requiring home oxygen; and
8. Not hospitalized, no limitations on activities.

Secondary Efficacy Endpoints

The secondary efficacy endpoints, listed in hierarchical order, include the following:

- Time to achieve a ≥2-point decrease in the NIAID 8-point ordinal scale;
- Length of hospital stay from first dosing (Day 1) and percentage of patients who have recovered and been discharged from the hospital by Days 15 and 29;
- Mortality rate by Days 15 and 29;
- Proportion of patients with a ≥2-point increase in the NIAID 8-point ordinal scale from baseline to Days 15 and 29;
- Alive and respiratory failure free days by Days 15 and 29;
- Percentage of patients progressed to severe/critical disease by Day 15; and
- Occurrence of any new infections during the study by Day 29.

SAFETY ENDPOINTS:

The safety endpoints include the following:

- All cause treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs);
- Change from screening (baseline) in clinical symptoms and abnormal vital signs, abnormal laboratory tests (e.g., complete blood count, serum chemistry, routine urinalysis, and coagulation function), and 12-lead electrocardiograms (ECGs); and
- Relationship of any observed adverse events (AEs) with F-652 treatment based on the Investigator's judgement.

[redacted]

STATISTICAL ANALYSES:

All computations will be performed using SAS® Version 9.4 or higher.

The following analysis populations will be defined for this study:

- Intent-to-Treat (ITT) Population: All patients who are randomized;
- Safety Population: All randomized patients who receive at least 1 dose of study drug; and
- Per Protocol (PP) Population: All patients in the ITT Population who finish the study as designed and without major protocol deviations.

Efficacy and safety data will be summarized by treatment arm. Data from all enrolled cohorts will be pooled together for analysis and sequentially analyzed by subgroups.

The ITT Population will be used to examine efficacy for both the primary and secondary endpoints, the Safety Population will be used to assess the safety endpoints, and the PP Population will be used as a secondary population for the analysis of the primary efficacy endpoint.

Efficacy Analyses

Primary efficacy endpoint

The time to achieve a ≥2-point increase in the NIAID 8-point ordinal scale from baseline by Day 29 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for the baseline NIAID 8-point ordinal scale. The NIAID 8-point ordinal scale will be assessed daily while the patient is hospitalized. If the patient remains hospitalized, the scale will also be assessed on Days 15 and 29. Any patient in the ITT Population with a missing primary endpoint result will be considered as a non-responder. The point estimates of the time to achieve a ≥2-point increase will be presented by treatment arm together with their 95% confidence intervals. The CMH odds ratio, associated 95% confidence interval, and p-value will also be presented.

Secondary efficacy endpoints

The time to achieve a ≥2-point decrease in the NIAID 8-point ordinal scale, proportion of patients with a ≥2-point increase in the NIAID 8-point ordinal scale from baseline to Days 15 and 29, mortality rate by Days 15 and 29, percentage of patients who have recovered and been discharged from the hospital by Days 15 and 29, and percentage of patients progressed to severe/critical disease by Day 15 will be analyzed using the same method as described for the primary efficacy endpoint.

The number of alive and respiratory failure free days by Days 15 and 29, the length of hospital stay from first dosing (Day 1) to discharge by Days 15 and 29, and occurrence of any new infections during the study by Day 29 will be summarized using descriptive statistics.

Exploratory Endpoints

The exploratory endpoints will be summarized using descriptive statistics.

Safety Analyses

All safety analyses will be performed on the Safety Population.

AEs will be coded using the Medical Dictionary for Regulatory Activities and summarized by system organ class, preferred term, and treatment arm as the number and percentage of patients

with an event. The following subsets will also be summarized by treatment arm: TEAEs, treatment-related AEs, treatment-related SAEs, and AEs leading to drug discontinuation.

Changes from baseline in clinical laboratory data, ECGs, vital signs, and physical examination findings will be summarized with descriptive statistics by treatment arm.

All demographic data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables.

A formal statistical analysis plan providing full technical details of the planned analyses will be finalized prior to database lock.

SAMPLE SIZE DETERMINATION:

The study plans to randomize 38 patients, with 4 patients in Cohort 1 (sentinel cohort), 14 patients in Cohort 2, 4 patients in Cohort 3 (sentinel cohort), and 16 patients in Cohort 4. The sample size is based on the purpose of the study and experience with similar proof-of-concept studies, and not based on statistical power calculation.

SITES: Approximately 10 sites in the United States and Russia

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE2	Angiotensin converting enzyme 2
AE	Adverse event
aGVHD	Acute graft versus host disease
AH	Alcoholic hepatitis
CBC	Complete blood count
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CoV	Coronavirus(es)
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
EOS	End of study
EV	Extracellular vesicle
FCBP	Female(s) of childbearing potential
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous(ly)
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease

Abbreviation	Definition
MERS	Middle East Respiratory Syndrome
NIAID	National Institute of Allergy and Infectious Diseases
PaO2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
QTcF	Heart rate-corrected QT interval using Fridericia's formula
Reg3	Regenerating islet-derived 3
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SpO_2	Peripheral capillary oxygen saturation
STAT3	Transcription 3
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile water for injection
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Epidemiology

Coronaviruses (CoV) are widely found in nature and possess the largest single-stranded positive-sense RNA genome known. They are divided into 4 genera: α, β, γ, and δ. All are well known causes of respiratory, enteric, and systemic infections in many species of mammals, birds, and fish.[1] Since 1960, 7 strains of community-acquired human β CoV have also been identified. Four of these are mildly pathogenic and cause cold-like upper respiratory infections in adults and children, while 2 of these (severe acute respiratory syndrome [SARS]-CoV-1 and Middle East Respiratory Syndrome [MERS]-CoV) cause severe viral pneumonia. SARS-CoV-1 emerged in 2002 in China and MERS-CoV emerged in 2012 in Saudi Arabia. The SARS-CoV-1 epidemic included about 8439 cases with 812 deaths (9.6% mortality), while the MERS-CoV epidemic claimed about 919 lives out of a total of 2521 cases (35% mortality).[2,3] Both SARS-CoV-1 and MERS-CoV showed wide areas of global emergence, high risk of human-to-human transmission, and presented as acute respiratory distress syndrome.

In December 2019, in Wuhan, China, the third highly pathogenic CoV, SARS-CoV-2, emerged in the human population.[4] It was identified as the causal pathogen in a cluster of 8 viral pneumonia cases of unknown etiology. SARS-CoV-2, officially named CoV disease 2019 (COVID-19), spread rapidly throughout China despite delayed quarantine, mandatory protective measures, and social distancing. On 30 January 2020, the World Health Organization declared the pandemic as a public health emergency of international concern.[5] As of 30 May 2020, there were 5,817,385 confirmed cases globally, with 362,705 deaths (6.2% mortality). In the United States, there have been 1,694,864 confirmed cases of COVID-19 with 100,304 deaths (5.9% mortality).[6]

The virus is zoonotic. Bats are believed to serve as the original reservoir of human pathogenic CoV, including SARS-CoV-1 and SARS-CoV-2, although other animals, such as camels in the case of MERS-CoV, may serve as an intermediate host from which the virus crosses the species barrier into humans.[7] The human host receptor to which SARS-CoV-2 binds is believed to be angiotensin converting enzyme 2 (ACE2).[7]

1.2 Clinical Features

Symptoms of COVID-19 appear from 2 to 14 days after exposure, with a median of 5 to 7 days, and range from mild to severe illness and death, although approximately 8% of infected humans develop no symptoms. Primary symptoms and their prevalence in order of frequency consist of fever >100.4°F (83% to 98% of patients); dry, hacking cough (76% to 82% of patients); fatigue and/or myalgia (11% to 44% of patients); and dyspnea (31% of patients).[8] Abnormal laboratory findings include lymphopenia (70% of patients), prolonged prothrombin time (58% of patients), and elevated lactate dehydrogenase (40% of patients).[9] The majority of infected healthy adults appear to develop mild symptoms. Adults who are immunocompromised (e.g., human immunodeficiency virus [HIV] infection) or over 65 years of age, particularly those with comorbidities such as hypertension, chronic obstructive pulmonary disease, moderate to severe asthma, diabetes, cardiovascular disease, chronic kidney disease undergoing dialysis, liver disease, or severe obesity (body mass index of 40 kg/m^2 or higher), are more susceptible to severe respiratory complications and pneumonia.[10]

Eighty percent of fatalities related to COVID-19 reported in the United States have been in adults ≥65 years of age. Of these, 10% to 27% of adults ≥85 years and 4% to 11% of adults 65 to 84 years of age have died. Hospitalization has been required in the United States for 31% to 70% of adults >85 years of age and 31% to 59% of adults 65 to 84 years of age.[6]

In those who develop severe lower respiratory symptoms, pulmonary infection is typically accompanied by a sustained extreme inflammatory response or cytokine storm, which can lead to severe complications such as respiratory distress syndrome and subsequent pulmonary edema, systemic hypoxia, septic shock, metabolic acidosis, and multiple organ failure.[6]

1.3 Treatment

No effective antiviral agents against COVID-19 have yet been confirmed. Current treatment focuses on standard of care symptomatic and respiratory support for viral pneumonia, including oxygen therapy, extracorporeal membrane oxygenation to patients with refractory hypoxemia, and mechanical ventilation if needed.[5]

Potential drug candidates include lopinavir/ritonavir (Kaletra®), nucleoside analogs, neuramidase inhibitors, remdesivir, umifenovir (Arbidol®), DNA (deoxyribonucleic acid) synthesis inhibitors (tenofovir disoproxil and lamivudine), chloroquine, ACE2-based peptides, 3C-like protease inhibitors, novel vinyl sulfone protease inhibitors, teicoplanin, and Chinese traditional medicine (ShuFengJieDu or Lianhuaqingwen capsules).[5,7,11,12]

1.4 Summary of Clinical Development of F-652

F-652 is a recombinant fusion protein consisting of human IL-22 and human immunoglobulin G2 Fc fragments. F-652 is produced in Chinese Hamster Ovary cells, with an immunoglobulin-like structure with 2 IL-22 molecules (recombinant human IL-22 dimer) at the N-terminal.

Similar to endogenous IL-22, F-652 was able to activate the STAT3 pathway. F-652 has been evaluated in vitro and in vivo in models of influenza and pneumococcal pneumonia lung infection and reported in the published literature.[16,18] Administration of F-652 following influenza infection promoted tight junction formation, reducing fluid buildup and inflammation. In a murine

pneumonia model, F-652 administration showed decreased lung, liver, and spleen bacterial burdens post-infection. Taken together, F-652 has the potential to be effective in promoting a protective response in the lungs following infection with COVID-19.

1.5 Rationale

F-652 has been postulated as a potential therapeutic candidate for treatment of patients with COVID-19, particularly in patients with moderate to severe symptoms. The overall aim of this exploratory study is to evaluate the safety and efficacy of F-652 when IV administered in hospitalized, confirmed COVID-19 adult patients with moderate to severe symptoms.

1.6 Risk/Benefit

The participation of patients with COVID-19 in this study can involve significant risks but there are expectations of medical benefits for the patients as well. The study population will include patients with moderate to severe COVID-19 who meet all the inclusion and none of the exclusion criteria that were developed based on safety and ethical considerations. Based on previous experience and understanding of F-652 and its demonstrated safety margin, the protocol will ensure the safety of enrolled patients.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the safety and efficacy of F-652 when IV administered in hospitalized, confirmed COVID-19 adult patients with moderate to severe symptoms.

2.2 Secondary Objective

The secondary objective is to evaluate the PD of F-652 when IV administered in hospitalized, confirmed COVID-19 adult patients with moderate to severe symptoms.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is an interventional, multicenter, 2-arm, parallel-group, randomized, double-blind, placebo-controlled, dose-escalation, safety and efficacy study of F-652 treatment versus placebo in patients aged 18 years or older with a COVID-19 diagnosis confirmed by polymerase chain reaction (PCR). Eligible patients will have moderate to severe COVID-19 symptoms and will be hospitalized. Figure 1 provides an overview of the study design.

AE = adverse event; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; NIAID = National Institute of Allergy and Infectious Diseases; PCR = polymerase chain reaction; PD = pharmacodynamic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TEAE = treatment-emergent adverse event.

The study plans to include 4 cohorts (see Table 1), with enrolled patients being randomized 1:1 in a blinded manner on Day 1, following screening, to F-652 or placebo as follows:

- Cohort 1 (sentinel cohort): Four patients will receive either [redacted] or placebo. Two patients will receive F-652 and 2 patients will receive placebo. Upon completion of sentinel dosing (7 days after last patient last dose), the Data Monitoring Committee (DMC) will evaluate the safety and tolerability data of the sentinel patients and determine if it is acceptable to dose the remaining patients in this dosing group in Cohort 2.
- Cohort 2: Fourteen patients will receive eithe[redacted] or placebo. Seven patients will receive F-652 and 7 patients will receive placebo. Upon completion of Cohort 2, the DMC will convene and review all available safety data to determine if the study can proceed to the next dose level.

- Cohort 3 (sentinel cohort): Four patients will receive either [redacted] or placebo. Two patients will receive F-652 and 2 patients will receive [redacted] mpletion of sentinel dosing (7 days after last patient last dose), the DMC will evaluate the safety and tolerability data of the sentinel patients and determine if it is acceptable to dose the remaining patients in this dosing group in Cohort 4.
- Cohort 4: Sixteen patients will receive eith[redacted] r placebo. Eight patients will receive F-652 and 8 patients will receive placebo.

Table 1. Dosing Strategy

Cohort	Number of Patients	Dosing
1 (sentinel)	4	[redacted]
2	14	
3 (sentinel)	4	
4	16	

Treatment will begin on Day 1 following randomization. Patients assigned to active drug will receive a total of 2 doses of F-652 (1 IV infusion on Day 1 and 1 IV infusion on Day 8). Patients assigned to placebo will receive identical IV infusions of placebo vehicle on Days 1 and 8. If the patient is discharged from the site prior to Day 8, they will return for an outpatient visit to receive the second IV infusion and remain at the site for an approximate 2-hour observation period. All patients will receive available supportive and antiviral therapies as standard of care. Efficacy will be assessed on Days 15 and 29. Patients will be followed for safety until Day 60.

[redacted]

3.3 Study Indication

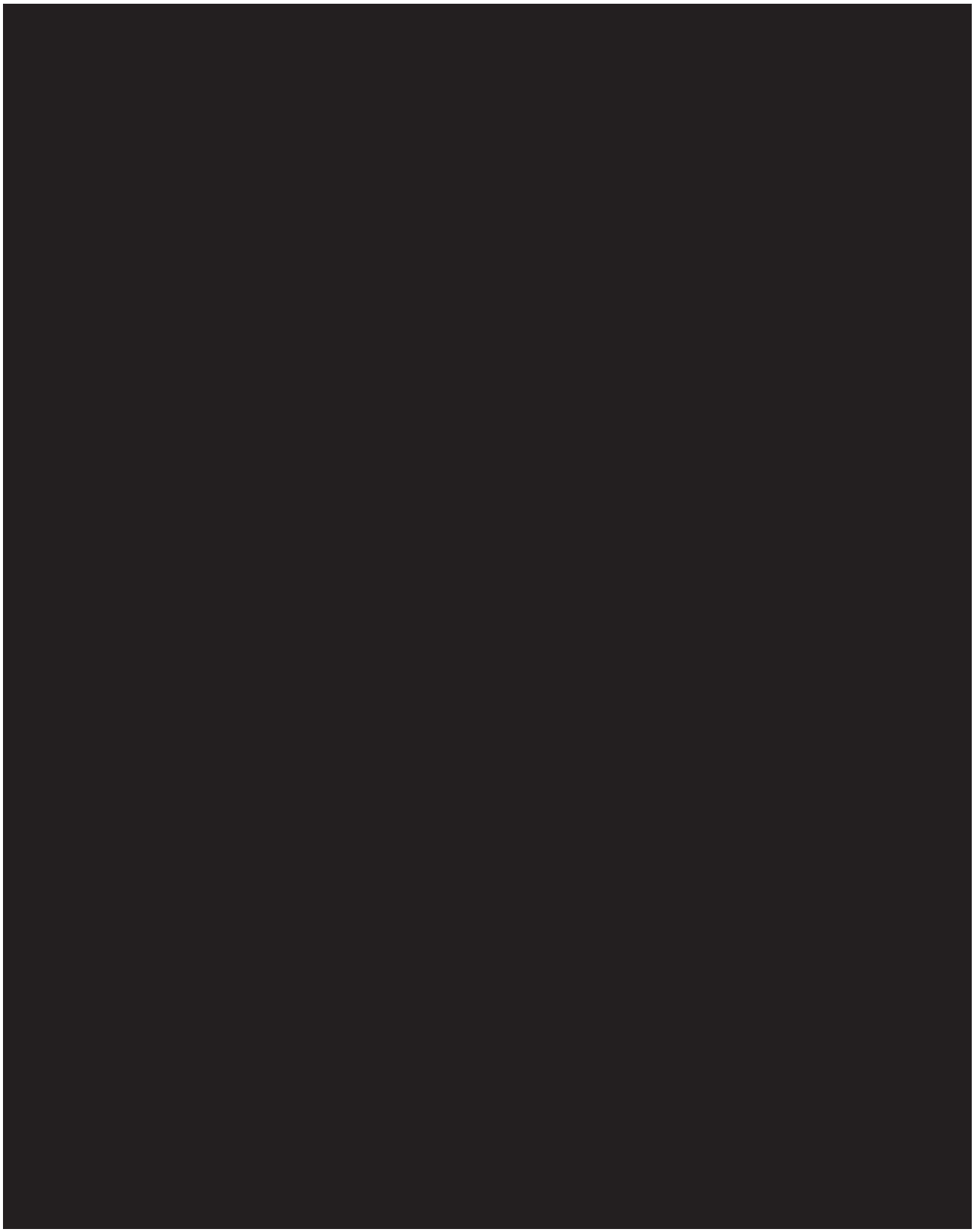
The indication for this study is the treatment of moderate to severe COVID-19.

4 SELECTION AND WITHDRAWAL OF PATIENTS

[redacted]

4.2 Exclusion Criteria

[redacted]



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4.3 Stopping Criteria

All AEs should be considered related to study drug unless clearly unrelated or if there is a clear etiology other than study drug such as a pre-existing medical condition, underlying disease, or concomitant medication.

4.3.1 Criteria for Discontinuation of Dosing in Individual Patients

Patients will be discontinued from dosing but will continue to be followed in the study if they experience any of the following:

- ≥Grade 3 (CTCAE v5.0) AE or clinically significant laboratory abnormality considered related to study drug;
- ≥Grade 3 (CTCAE v5.0) infusion reaction in the first 24 hours post-infusion;
- ≥Grade 2 (CTCAE v5.0) cytokine release syndrome;
- ≥Grade 2 skin-related AEs;
- Severe anaphylactic reaction, including bronchospasm; and/or
- Progression to acute respiratory distress syndrome.

For any patient who prematurely discontinues from study treatment, the reason and date of discontinuation will be documented in the electronic case report form (eCRF) and the patient should continue study visits and procedures as outlined in the Schedules of Procedures (Appendix A).

4.3.2 Criteria for Study Termination

In the event that any of the following are encountered, the DMC will convene as soon as possible to determine if the study must stop enrollment:

- SAE considered related to study drug;
- ≥Grade 3 (CTCAE v5.0) reaction considered related to study drug;
- ≥2 patients are discontinued from treatment for safety reasons pertaining to study drug per DMC decision;

- ≥2 patients experience similar SAEs or Grade 3 (CTCAE v5.0) AEs related to study drug per DMC decision; and/or
- ≥2 patients experience worsening of cytokine release syndrome related to study drug per DMC decision.

The following will not be considered as criteria for study termination:

- Grade 3 to 4 fever if present at study entry;
- Grade 3 nausea if it resolves to ≤Grade 1 within 72 hours;
- Grade 3 fatigue, malaise, or insomnia if it resolves to ≤Grade 1 within 72 hours; and/or
- ≤Grade 4 isolated electrolyte abnormalities that resolve with or without intervention to ≤Grade 2 within 72 hours.

4.4 Withdrawal Criteria

Participation of a patient in this study may be discontinued for any of the following reasons:

- Withdrawal of consent or request for discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Pregnancy;
- Use of prohibited concomitant medication;
- Patient failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

For patients who discontinue early from the study, the Investigator is responsible to ensure all safety assessments and final follow-up assessments scheduled for the end of study (EOS) visit, including follow-up for unresolved AEs (including SAEs), are completed prior to patient discontinuation. If the patient does not return for a scheduled visit, the Investigator must make every effort (documented telephone calls and registered letter, as allowed) to contact the patient. Patients will be deemed as lost-to-follow-up once the Investigator has completed a minimum of 3 telephone calls followed by a certified letter (as allowed) to the last known address of the patient or next of kin, as appropriate, with no response obtained. Attempts to contact the patient must be made and documented in the patient's medical records.

Patients who are consented but do not meet eligibility criteria will be considered screen failures. Patients withdrawn for safety reasons will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

The study drug will be administered only to patients who have given informed consent.

The patients will be randomly assigned to F-652 or placebo treatment in a 1:1 ratio in a blinded manner. Treatment will begin on Day 1 following randomization. All patients will receive available supportive and antiviral therapies as standard of care.

5.3 Randomization and Blinding

Patients will be randomized in a 1:1 ratio in a double-blind manner to receive F-652 or placebo.

An independent statistician from Medpace Inc., hereinafter Medpace, will generate the randomization schedule. Patients meeting eligibility criteria will be randomized on Day 1, following screening, in a 1:1 ratio to F-652 or placebo, respectively. Patients will be assigned a randomization number and treatment assignment according to the randomization schedule. This randomization schedule will be maintained by the investigative site pharmacist until it is appropriate to break the blind. The Investigator, investigative site personnel (except site-designated pharmacist and dedicated assistant), study monitors, vendors, Sponsor, and Medpace will remain blinded to treatment assignment.

Details of the emergency unblinding procedures are given in Section 5.4.

5.4 Breaking the Blind

Individual treatment assignments may be unblinded when immediate knowledge of the treatment assignment is needed to optimize the clinical management of the patient. The Investigator should contact the Medical Monitor to discuss the event prior to unblinding. In the event this is not possible, the Investigator should contact the Medical Monitor as soon as possible to discuss the event.

Randomization assignments will be prepared by the independent statistician and provided to the investigative site pharmacist to enable emergency code break procedures for individual patients without compromising the blind of the study. Documentation of the blind break, including the patient's identification, reason for breaking the blind, and the date and time of breaking the blind, must be retained in the patient's source documents at the sites in such a way as to avoid unblinding the treatment assignment to other site or Sponsor blinded personnel.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The lyophilized formulation of F-652 (5 mg/vial) will be provided to the investigative sites for patients' use. It is presented as a white or yellowish cake in a sterile 3 mL glass vial. The composition of the study drug is listed in Table 2.

[redacted]

5.5.3 Study Drug Administration

F-652 will be administered, based on the patient's most recent weight, at a dose [redacted] IV on Days 1 and 8. Placebo vehicle will be identical in appearance to the study drug and will be administered IV on Days 1 and 8. If the patient is discharged from the site prior to Day 8, they will return for an outpatient visit to receive the second IV infusion and remain at the site for an approximate 2-hour observation period. [redacted]

The definitions and management of infusion related reactions are described in Appendix C.

5.5.4 Treatment Compliance

Administration of the study drug will be performed by the investigative site staff and supervised by the Investigator or Sub-Investigator.

Details of the date and time when the study drug is administered, along with any deviation from the procedure described in this protocol, will be recorded in the patient's source documents and the eCRF.

[redacted]

Product technical complaints should be reported to the Sponsor. A product complaint is any report or complaint about a potential or alleged failure of the Sponsor's product to meet any of its quality specifications. These complaints may or may not represent a potential risk to the patient.

Product technical complaints may include:

- Quality defects as described in Section 5.5.2 and temperature excursions;
- Defects of containers and external wrappings; or
- Defects of labeling and packaging leaflets.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures (Appendix A).

7 EFFICACY ASSESSMENTS

7.1 Efficacy Endpoints

7.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the time to achieve a ≥2-point increase in the National Institute of Allergy and Infectious Diseases (NIAID) 8-point ordinal scale from baseline by Day 29.

The NIAID 8-point ordinal scale includes the following grades:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation;
3. Hospitalized, on non-invasive ventilation or high-flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen;
5. Hospitalized, not requiring supplementation oxygen – requiring ongoing medical care (COVID-19 related or otherwise);
6. Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care;
7. Not hospitalized, limitation on activities and/or requiring home oxygen; and
8. Not hospitalized, no limitations on activities.

7.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints, listed in hierarchical order, include the following:

- Time to achieve a ≥2-point decrease in the NIAID 8-point ordinal scale;
- Length of hospital stay from first dosing (Day 1) and percentage of patients who have recovered and been discharged from the hospital by Days 15 and 29;
- Mortality rate by Days 15 and 29;
- Proportion of patients with a ≥2-point increase in the NIAID 8-point ordinal scale from baseline to Days 15 and 29;
- Alive and respiratory failure free days by Days 15 and 29;
- Percentage of patients progressed to severe/critical disease by Day 15; and
- Occurrence of any new infections during the study by Day 29.

[redacted]

[redacted]

7.3 Mortality

Data collected for patient deaths will include whether the death occurred after withdrawal of care and, if so, the reason for withdrawal of care.

7.4 New Infections

Any new infections, regardless of the organism (e.g., viral or nonviral), should be captured on the eCRF. The site of infection and source of culture (e.g., sputum, blood, urine) should also be recorded.

[redacted]

8 SAFETY ASSESSMENTS

8.1 Safety Endpoints

The safety endpoints include the following:

- All cause TEAEs and SAEs;
- Change from screening (baseline) in clinical symptoms and abnormal vital signs, abnormal laboratory tests (e.g., complete blood count [CBC], serum chemistry, routine urinalysis, and coagulation function), and 12-lead electrocardiograms (ECGs); and
- Relationship of any observed AEs with F-652 treatment based on the Investigator's judgement.

8.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational therapeutic product, whether or not related to the investigational therapeutic product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent to Day 60 or until all drug-related toxicities have resolved, whichever is later. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment. Beginning at screening, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than the individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be

reported as an AE. Laboratory abnormalities or other abnormal clinical findings (e.g., ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgement of the Investigator.

8.2.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.2.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.2.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE according to the CTCAE grading system. The Investigator will also categorize each AE as to its potential relationship to study drug using the categories of yes or no.

The severity of all AEs should be graded according to the CTCAE v5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

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

<u>Causality assessment</u>

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.3 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled

or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

Events of progression of the patient's underlying COVID-19 diagnosis will be captured as efficacy endpoints; therefore, events clearly related to progression of the patient's underlying COVID-19 (signs/symptoms of progression) should not be reported as an SAE unless considered related to the study drug or the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during that timeframe, the event of "Progression of COVID-19" must be recorded as an SAE with a fatal outcome.

8.4 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence. After Day 60, any SAE that the Investigator considers related to study drug must be reported to Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.5 Pregnancy Reporting

If a patient becomes pregnant during the study, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA) and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational therapeutic product.

8.7 Clinical Laboratory Evaluations

CBC with differential will be performed at screening, Days 1, 3, 5, 7, 8, 10, 12, and 14. If the patient remains hospitalized, will also be performed on Days 15 and 29. If the screening assessment was obtained within 24 hours of Day 1 dosing, it is not necessary to repeat the CBC prior to Day 1 dosing.

Metabolic panel/chemistry assessments will be performed at screening, Days 1 and 8 (within 24 hours prior to dosing) and as clinically indicated. If the patient remains hospitalized, will also be performed on Days 15 and 29. If the screening assessment was obtained within 24 hours of Day 1 dosing, it is not necessary to repeat the chemistries prior to Day 1 dosing. Lactate dehydrogenase test should be repeated daily if elevated above the upper limit of normal.

Hemoglobin A1c will only be obtained at screening if the patient does not have a value within 90 days prior to screening.

Urine dipstick is acceptable and microscopic analyses can be performed if clinically indicated. If ≥2+ protein on urine dipstick, then a spot urine sample should be collected in order to calculate the urine protein to creatinine ratio or a 24-hour urine should be collected.

Clinical laboratory analytes are listed in Appendix B.

8.8 Viral Testing

A SARS-CoV-2 test will be performed on Day 1 (pre-dose), Day 4 (±1 day), Day 8 (pre-dose), Day 11 (±1 day), Day 14 (±1 day), and prior to discharge on Days 15 and 29. Patients will have a naso-pharyngeal swab collected at screening and analyzed using PCR. If possible, a central laboratory should be used to confirm local laboratory results.

8.9 Vital Signs

Vital signs will include systolic and diastolic blood pressure, respiration, pulse, and oral temperature, and should be taken prior to study drug infusion, every 15 minutes during the infusion, at the end of the infusion, and hourly post-infusion, for a minimum of 4 hours after each infusion within a window of ±5 minutes. Vital signs should be collected on a daily basis and may be collected more frequently if clinically indicated. Patients should be in a sitting position for at least 5 minutes prior to collection.

8.10 Electrocardiograms

Twelve-lead ECGs will be obtained at screening, Days 1 and 8 (pre-dose and 30 ±10 minutes after the end of infusion) and as clinically indicated within a window of ±10 minutes. If the patient remains hospitalized, will also be performed on Days 15 and 29. Whenever ECG and blood samples are specified to be collected at the same time, ECG will be obtained before the blood samples. ECGs should be obtained in digital format when possible and archived.

Patients should be in a supine position for at least 10 minutes prior to the ECG measurement. The ECG measurements will include heart rate, RR-interval, PR-interval, QT-interval, QRS-complex, and QTcF.

8.11 Physical Examinations

A physical examination will be performed at screening, Days 1 and 8. If the patient remains hospitalized, will also be performed on Days 15 and 29. A complete physical examination will be performed at screening and Day 29 if the patient is hospitalized, while a symptom-directed physical examination will be conducted on Days 1 and 8, and Day 15 if the patient is hospitalized.

The physical examination will consist of assessments of general condition, skin, eyes/ears/nose/mouth/throat, neck/thyroid, chest/lungs, heart, vascular system, lymph nodes, abdomen, extremities, nervous systems/reflexes, musculoskeletal, and spine.

The patient's weight will be measured within 12 hours prior to dosing on each day of study drug administration.

8.12 Lung Function Assessments

Lung function will be assessed daily by peripheral capillary oxygen saturation (SpO_2) in ambient air (if possible), SpO_2 with oxygen supplementation (if applicable), documentation of oxygen delivery method, highest oxygen delivery flow rate (if receiving noninvasive oxygen), highest fraction of inspired oxygen (% FiO_2) (if on positive pressure ventilation), highest positive end-expiratory pressure (if on positive pressure ventilation), and lowest partial pressure of oxygen (PaO2):fraction of inspired air (FiO_2) ratio if arterial blood gas is obtained and the patient is on positive pressure ventilation.

8.13 Echocardiogram

An echocardiogram (ECHO) is not necessary unless otherwise indicated. An up-trending troponin-I with hemodynamic compromise or other concerning cardiovascular symptoms/signs should prompt consideration of obtaining an ECHO.

9 STATISTICS

9.1 Analysis Populations

All computations will be performed using SAS® Version 9.4 or higher.

The following analysis populations will be defined for this study:

- Intent-to-Treat (ITT) Population: All patients who are randomized;
- Safety Population: All randomized patients who receive at least 1 dose of study drug; and
- Per Protocol (PP) Population: All patients in the ITT Population who finish the study as designed and without major protocol deviations.

Efficacy and safety data will be summarized by treatment arm. Data from all enrolled cohorts will be pooled together for analysis and sequentially analyzed in subgroups.

The ITT Population will be used to examine efficacy for both the primary and secondary endpoints, the Safety Population will be used to assess safety endpoints, and the PP Population will be used as a secondary population for the analysis of the primary efficacy endpoint. A list of patients with major protocol deviations leading to exclusion from the PP Population will be finalized prior to unblinding the randomized treatment assignments. All timepoints for analysis purposes will be collected from the day of randomization.

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

9.2.1.1 Primary efficacy endpoint

The time to achieve a ≥2-point increase in the NIAID 8-point ordinal scale from baseline by Day 29 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusting for the baseline NIAID 8-point ordinal scale. The NIAID 8-point ordinal scale will be assessed daily while the patient is hospitalized. If the patient remains hospitalized, the scale will also be assessed on Days 15 and 29. Any patient in the ITT Population with a missing primary endpoint result will be considered as a non-responder. The point estimates of the time to achieve a ≥2-point increase will be presented by treatment arm together with their 95% confidence intervals. The CMH odds ratio, associated 95% confidence interval, and p-value will also be presented.

9.2.1.2 Secondary efficacy endpoints

The time to achieve a ≥2-point decrease in the NIAID 8-point ordinal scale, proportion of patients with a ≥2-point increase in the NIAID 8-point ordinal scale from baseline to Days 15 and 29, mortality rate by Days 15 and 29, percentage of patients who have recovered and been discharged from the hospital by Days 15 and 29, and percentage of patients progressed to severe/critical disease by Day 15 will be analyzed using the same method as described for the primary efficacy endpoint in Section 9.2.1.1.

The number of alive and respiratory failure free days by Days 15 and 29, the length of hospital stay from first dosing (Day 1) to discharge by Days 15 and 29, and occurrence of any new infections during the study by Day 29 will be summarized using descriptive statistics.

9.2.2 Exploratory Endpoints

The exploratory endpoints will be summarized using descriptive statistics.

9.2.3 Analysis of Safety

All safety analyses will be performed on the Safety Population.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment arm as the number and percentage of patients with an event. The following subsets will also be summarized by treatment arm: TEAEs, treatment-related AEs, treatment-related SAEs, and AEs leading to drug discontinuation.

Changes from baseline in clinical laboratory data, ECGs, vital signs, and physical examination findings will be summarized with descriptive statistics by treatment arm.

All demographic data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables.

A formal statistical analysis plan providing full technical details of the planned analyses will be finalized prior to database lock.

9.2.4 Interim Analysis

Interim analysis is not planned for this study.

9.2.5 Sample Size Determination

The study plans to randomize 38 patients, with 4 patients in Cohort 1 (sentinel cohort), 14 patients in Cohort 2, 4 patients in Cohort 3 (sentinel cohort), and 16 patients in Cohort 4. The sample size is based on the purpose of the study and experience with similar proof-of-concept studies, and not based on statistical power calculation.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- MedDRA (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous or data that are missing will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study drug, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study. Patients alive at the end of the study who require further follow-up may be entered into a separate long-term follow-up study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Ethics Review

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or a patient's legal guardian must be approved by the IRB/IEC.

No study drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with

the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to the Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

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APPENDIX A: SCHEDULE OF PROCEDURES

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Blood urea nitrogen or urea
Calcium	Chloride
Creatine kinase	Creatinine
Estimated glomerular filtration rate (eGFR)	Glucose
Lactate dehydrogenase	Lipase
Magnesium	Phosphorus or phosphate
Potassium	Sodium
Total bilirubin	Uric acid

Additional Chemistry Parameters

Arterial blood gas [1]	Hemoglobin A1c [2]

1. Only if clinically indicated.
2. Obtained only if the patient does not have a value within 90 days prior to screening.

Endocrinology

Beta human chorionic gonadotropin (β-HCG) [1]

1. Serum β-HCG pregnancy test for females of childbearing potential.

Hematology

Absolute neutrophils [1]	Basophils
Eosinophils	Hematocrit
Hemoglobin	Lymphocytes
Monocytes	Platelets
White blood cell count and differential [2]	

1. Neutrophils plus bands.
2. Manual microscopic review will be performed only if white blood cell count and/or differential values are out of reference range.

Additional Hematology

Erythrocyte sedimentation rate (ESR)

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Microscopy is performed only as needed based on positive urine dipstick test results.

[redacted]

[redacted]

APPENDIX C: DEFINITIONS AND MANAGEMENT OF INFUSION-RELATED REACTIONS

In the event of infusion-related reactions, Investigators should institute treatment measures according to best medical practice. Any event of infusion-related reaction, generally defined as clinically significant deviations in blood pressure, heart rate, respiratory rate, and oxygen saturation, will be recorded.

In the event of infusion-related allergic reaction, and if flushing, sudden rash, or difficulty breathing occur, the infusion will be stopped immediately and affected patients will be monitored until the infusion-related allergic reaction has resolved.

The following treatment guidelines may be employed at the discretion of the treating physician:

- Grade 1 infusion-related reaction (Common Terminology Criteria for Adverse Events [CTCAE] v5.0): Mild transient reaction; infusion interruption not indicated; intervention not indicated;
- Grade 2 infusion-related reaction (CTCAE v5.0): Therapy or infusion interruption indicated, but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤24 hours;

  Treatment of Grade 1 or Grade 2 infusion-related reactions:

  1. Decrease infusion rate by 50%, administer antihistamines, corticosteroids, etc., as medically indicated and monitor for worsening condition;
  2. Stop infusion if infusion-related symptoms continue despite number 1;
  3. Administer bronchodilators, oxygen, antihistamines, corticosteroids, etc., as medically indicated;
  4. Resume infusion at 50% of previous rate once reaction has decreased to Grade 1 in severity. Monitor closely for any worsening; and
  5. If the reaction reoccurs, stop infusion. Study treatment will be discontinued;
- Grade 3 infusion-related reaction (CTCAE v5.0): Characterized as prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; or
- Grade 4 infusion-related reaction (CTCAE v5.0): Characterized as life-threatening consequences; urgent intervention indicated;

  Treatment of Grade 3 or Grade 4 infusion-related reactions:

  1. Stop the infusion immediately and disconnect infusion tubing from the patient;
  2. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, IV fluids, vasopressor agents, oxygen, etc., as medically indicated;
  3. Immediately contact Medical Monitor and report serious adverse event; and
  4. Study treatment will be discontinued.