CLINICAL RESEARCH PROTOCOL

DRUG:	SPI-1005
STUDY NUMBER(S):	SPI-1005-292
PROTOCOL(S) TITLE:	A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SPI-1005 IN SEVERE COVID-19 PATIENTS
IND NUMBER:	150553
NCT NUMBER:	NCT04483973
ORIGINAL PROTOCOL DATE:	28 July 2020
VERSION NUMBER:	2.0
VERSION DATE:	26 August 2022
CHEMICAL NAME:	2-phenyl-1,2-benzisoselenazol-3(2H)-one

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Evaluate the Safety and Efficacy of SPI-1005 in Severe COVID-19 Patients

Study No: SPI-1005-292

Original Protocol Date: 28 July 2020

Protocol Version No: 2.0

Protocol Version Date: 26 August 2022

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in The Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Approval of Clinical Protocol	
Name & Title	**Signature & Date**
Clinical Operations: Jacqueline Nguyen, VP, Clinical Operations	
Medical Lead: Jonathan Kil, MD, Chief Medical Officer	
Regulatory Affairs: Emily Harruff, Regulatory & Data Management	

SYNOPSIS OF CHANGES

SPI-1005-291 Protocol Version 2.0, 26 August 2022

Previous Approved Versions:

Previous version	Date
1.3	01 May 2021

Summary of Changes:

Section(s)	Description of Change
Page 1-8 Page headers	Administrative edits
Contact Information	Change of address for Lead Investigator
1.1 Synopsis	Increased number of study centers to 6-9 sites in the US
1.1 Synopsis	Increased study duration to >12 months
1.1 Synopsis	Revisions consistent with change to Section 5.2
1.3 Schedule of Assessments	Corrected a typo in footnote 6 regarding study treatment duration
1.3 Schedule of Assessments	Removed PK & PD testing from V5
1.3 Schedule of Assessments 7 Study Conduct	Amended Visit 4 to take place on Day 14±2. (Previous version had Visit 4 on Day 14 or date of discharge.)
1.3 Schedule of Assessments 7 Study Conduct	Visit 5: Clarified that patients should perform in-clinic visit if possible, and telehealth visit should only be performed when the patient cannot return to clinic.
1.3 Schedule of Assessments	Clarifications consistent with Section 7 & Section 8.
4.1 Overall Study Design	Revisions consistent with changes to Sections 1.3 & Section 7
5.2 Exclusion Criteria	Amended to exclude eGFR <60 mL/min/1.73m^2 (Previous version excluded eGFR <90 mL/min/1.73m^2)
6 Description of Study Treatment	Updated to reference to the most current Investigator's Brochure, V5.2
7.2.5 Visit 5 (Day 30)	Removed Pharmacokinetics and Pharmacodynamics from Visit 5
8.7 Pharmacodynamics	Amended to clarify that a sputum sample may be obtained instead of a saliva sample, if the saliva sample could not be obtained.

Statement of Confidentiality

The information contained in the Clinical Protocol, including unpublished data, is the property of Sound Pharmaceuticals, Inc., and is provided in strict confidence to investigators, potential investigators, or consultants for review. This information shall not be disclosed to third parties without prior written authorization from Sound Pharmaceuticals, Inc., except as necessary to obtain informed consent from study participants.

Statement of Compliance

This trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable United States (US) Code of Federal Regulations (CFR). The Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) Sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participant(s). All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator Brochure's for SPI-1005. I have read the Protocol SPI-1005-292 and agree to conduct the study as outlined. I agree to maintain compliance and confidentiality of all information received or developed in connection with this protocol.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

Contact Information

Table 1 Contact Information

Role in Study	Name	Address and Telephone number
Lead Investigator	Miriam Treggiari, MD, PhD, MPH, MA	Department of Anesthesiology Duke University 2301 Erwin Road Durham, NC 27710
Drug Safety Physician	Andrew Goodwin, MD	
24-Hour Emergency Contact	Andrew Goodwin, MD	

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ABBREVIATIONS

Table 2 A list of abbreviations and specialist terms found in clinical protocol

Abbreviation	Meaning
AE	Adverse Event
BID	Twice-daily dosing
CBC	Complete Blood Count
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPx	Glutathione Peroxidase
GSH	Glutathione
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
ICH	International Conference on Harmonization
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IEC	Institutional Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
LCMS/MS	Liquid Chromatography-Tandem Mass Spectrometry
mg	milligram
nCov2	SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2
ONOO-	Peroxynitrite
PI	Principal Investigator
PK	Pharmacokinetics
po	By mouth
PRN	As needed
RCT	Randomized Clinical Trial
ROS	Reactive Oxygen Species
RRT	Renal replacement therapy
SAE	Serious Adverse Event
SPI	Sound Pharmaceuticals, Inc.
SpO_2	Peripheral oxygen saturation
WHO	World Health Organization

1 PROTOCOL SUMMARY

1.1 Synopsis

SPI-1005-292: CLINICAL TRIAL SYNOPSIS	
Title	A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE ESCALATION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SPI-1005 IN SEVERE COVID-19 PATIENTS
Study Objective(s)	Primary objective: • Safety of SPI-1005 treatment compared to placebo Secondary objective: • Pharmacokinetic sampling, including plasma trough levels of ebselen and its major metabolite Exploratory objectives: • Improvement, stability, or worsening of clinical outcomes, as assessed by the WHO ordinal scale, comparing SPI-1005 with placebo • Improvement, stability, or worsening of respiratory status, as assessed by peripheral oxygen saturation (SpO_2) and degree of supplemental oxygen, comparing SPI-1005 with placebo • Pharmacodynamic testing, including reduction in inflammatory and cytokine storm-related biomarkers, comparing SPI-1005 treatment with placebo • Pharmacodynamic testing, including reduction in viral load, comparing SPI-1005 treatment with placebo
Study Design	This interventional study is a randomized, double-blind, placebo-controlled, dose escalation, multi-center clinical trial (RCT) of SPI-1005 in adult subjects with newly diagnosed COVID-19. All subjects will have a positive PCR test for novel SARS-CoV-2 (nCoV2) at enrollment. All safety and tolerability assessments will be performed at baseline or Day 1 before the start of dosing, at Day 3 and Day 7 of dosing, and at the end of dosing on Day 14 or on the day of discharge, whichever occurs earlier. Additional follow-up will occur on Day 30 or end of study. Dose escalation of SPI-1005 treatment from 400 mg BID to 800 mg BID will occur following completion of interim safety analysis and DSMB review.
Study Centers	Approximately 6-9 sites in the US.
Subjects	Approximately 60 adult men or women (≥18 years of age) with newly diagnosed COVID-19 within 7 days of symptom onset.

SPI-1005-292: CLINICAL TRIAL SYNOPSIS	
Inclusion Criteria	• Adults ≥18 years of age • Positive nCoV2 PCR test by nasopharyngeal, oral, saliva, or respiratory sample • Clinical signs, symptoms, and respiratory status consistent with severe COVID-19 o Score of 5-7 on the WHO Ordinal Scale • Onset of severe COVID-19 symptoms ≤7 days of study enrollment • Subject is in-patient at time of randomization to study treatment • Subject or legally authorized representative is willing and able to provide informed consent, and agrees for subject to comply with planned study procedures including reproductive requirements

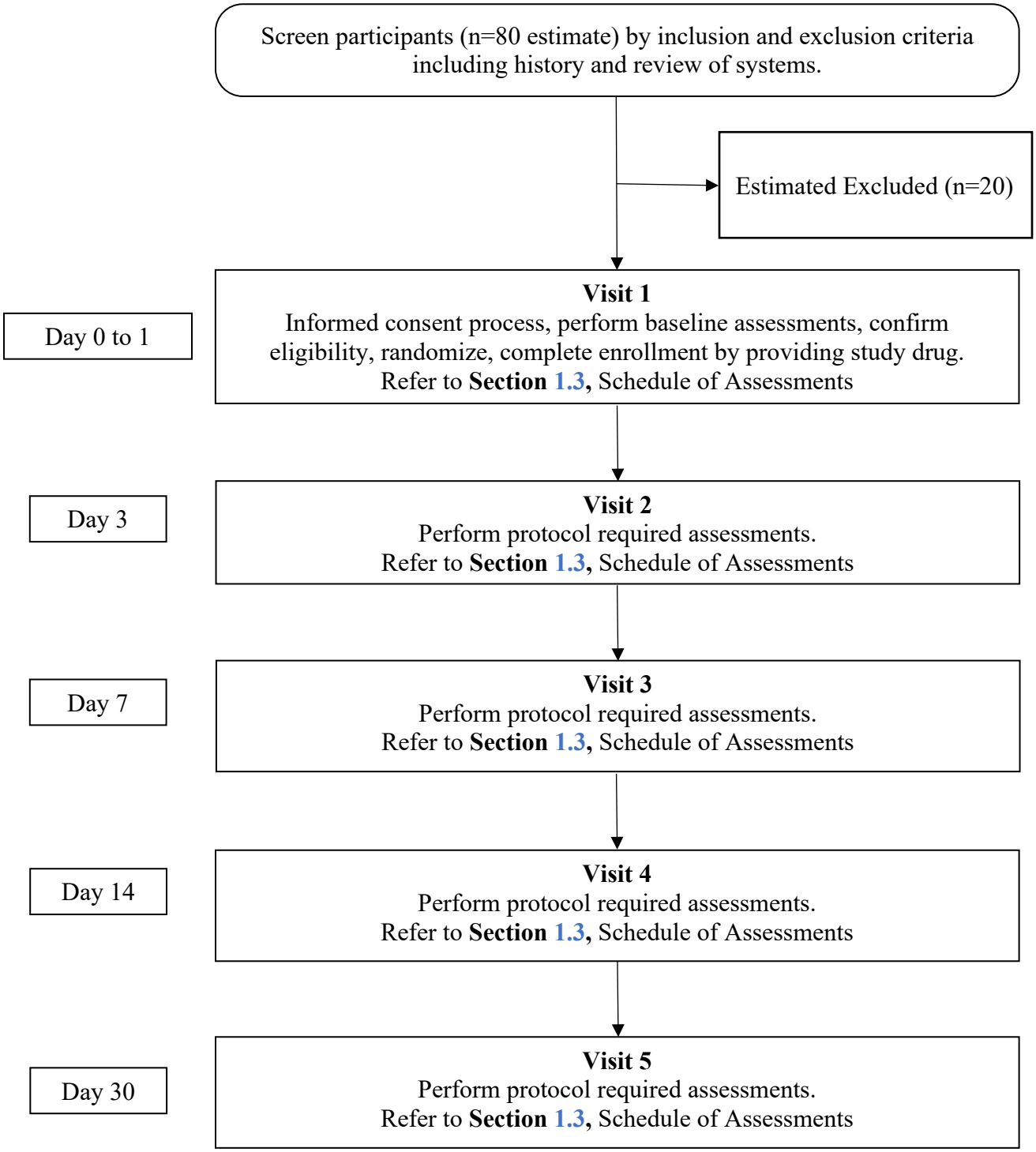
Exclusion Criteria	• Women who are pregnant or breastfeeding
	• Participation in another interventional investigational drug or device study concurrently or within 30 days prior to study consent
	• Patients with impaired hepatic or renal function
	  o ALT/AST >3 times the upper limit of normal; or
	  o eGFR <60 mL/min/1.73m^2; or
	  o History of hepatic impairment (cirrhosis) or renal impairment
	• Subject has any other illness or condition that, in the opinion of the investigator, would prohibit the subject from participating.

Study Duration	Estimated duration of >12 months.
Participant Duration	Participation for study subjects will be approximately 30 days.
Dose & Regimen	Subjects will be treated for 14 days, with SPI-1005 (400 or 800 mg BID), or matching placebo. AM and PM doses will be approximately 10-12 hours apart and before meals.
Safety & Tolerability Assessments	Physical examinations, vital signs, adverse events, hematology (CBC with differential) and serum chemistries (Chem 20) will encompass safety assessments. Adverse events will be coded using CTCAE (Version 5.0 or higher) and summarized by treatment group for the number of adverse events and compared. Vital signs and clinical laboratory results will be summarized for each treatment group and compared.
PK Assessments	The trough plasma levels of ebselen and its major metabolite (2-glucuronyl selenobenzanilide) will be determined using LC-MS/MS and the results will be summarized by treatment group.
PD Assessments	The saliva levels of viral load and plasma levels of inflammatory & cytokine storm-related biomarkers including high-sensitivity CRP, IL-1, IL-2, IL-6,

SPI-1005-292: CLINICAL TRIAL SYNOPSIS	
	TNF-alpha, and ferritin will be determined and the results will be summarized by treatment group.
Lead Investigator (s)	Miriam Treggiari, MD, PhD, MPH, MA

1.2 Schema

1.2.1 Consort Flow Diagram



1.3 Schedule of Assessments

Visit	V1	V2	V3	V4	V5[7,8]
Day	0-1	3	7	14	30
Visit Window	N/A	(±0)	(±0)	(±2)	(±2)
Informed Consent	X				
Demographics	X				
Medical History	X				
Physical Exam	X	X	X	X	X
Clinical Status[1]	X	X	X	X	X
Height & Weight	X				
Vital Signs[2]	X	X	X	X	X
Hematology	X	X	X	X	X
Chemistry	X	X	X	X	X
PK[3]	X	X	X	X	
PD (blood)[4]	X	X	X	X	
PD (saliva)[4]	X	X	X	X	
Urine Pregnancy[5]	X				
Concomitant Medications	X	X	X	X	X
Randomization	X				
Study Treatment[6]	X	X	X	X	
AE/SAE	X	X	X	X	X

(1) Clinical status will be assessed according to WHO Ordinal Scale for Clinical Improvement. In addition to study visits, clinical status will be assessed daily while patient is hospitalized.
(2) Vital signs to include O_2 saturation. Oxygen delivery method will also be captured.
(3) PK should be collected pre-dose, before any study treatment on the same day. PK comprises plasma specimens collected at trough for analysis of ebselen and major metabolite as well as total selenium.
(4) PD comprises testing for (a) nCov2 viral load, (b) inflammatory and cytokine storm biomarkers.
(5) Urine pregnancy test will be performed in women of childbearing potential.
(6) Study treatment (SPI-1005 400 or 800 mg BID or matching placebo BID for 14 days) will begin on Day 1 provided eligibility criteria have been reviewed and met.
(7) V5 should be conducted as an in-clinic visit with all study procedures performed per the Schedule of Assessments. Only if the patient has been discharged **and** it is not feasible for the patient to return to clinic, then a remote telehealth visit may be conducted.
(8) Subjects who do not show resolution of clinical status and/or laboratory results on Visit 5 (Day 30) may receive an additional follow-up visit, Visit 6 (Day 60), with the same procedures conducted as Visit 5.

2 INTRODUCTION

SARS-CoV-2 (nCoV2) has been identified as the viral etiology of COVID-19, a pandemic respiratory disease that has no effective treatment and growing morbidity and mortality. A groundbreaking study recently published in the journal Nature showed three major findings involving nCoV2 (Jin, Du et al., 2020). First, the authors crystalized the main protease (M^{pro}) structure, a critical enzyme responsible for viral replication. Second, they identified several potential pharmacologic agents or drugs that inhibit M^{pro} activity, utilizing a structure-based virtual screening of >10,000 compounds including approved and investigational drugs, and other pharmacologically active compounds. Among the six compounds that showed significant inhibition of M^{pro} activity, ebselen demonstrated the lowest half maximal inhibitory concentration (IC50). Third, they showed viral load reduction in an in vitro cell-based assay, where ebselen demonstrated the lowest half maximal effective concentration (EC50). M^{pro} may be the first identified specific nCoV2 drug target that, when inhibited, could reduce viral load or virulence, and potentially mitigate the devastating course of COVID-19.

Ebselen's ability to inhibit cellular protease activity through its covalent interaction with critical cysteine residues is not unique to Mpro in nCoV2. Many similar protein interactions have been identified and were recently summarized (Sies and Parnham, 2020). A number of studies have demonstrated the anti-inflammatory and cytoprotective effects of oral ebselen treatment in lung pathology. Multiple animal models have been tested including pulmonary inflammation induced by carrageenan, sephadex, ozone, cigarette smoke and endotoxin. In an LPS-induced model of lung inflammation, ebselen was shown to inhibit leukocyte infiltration in association with a lowered expression of ICAM-1 adhesion molecule and the inflammatory cytokines, TNFα and IL1β, in lung tissue that were recently summarized (Sies and Parnham, 2020). Importantly, the major organ affected during nCoV2 infection is the lung, which is the site of a pronounced inflammatory response.

Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one] is a mimic of GPx activity (Müller, Cadenas et al., 1984; Reiter & Wendel, 1984; Wendel, Fausel et al., 1984). It has strong activity against peroxynitrite (ONOO-), a reactive oxygen species (ROS) formed by the combination of two free radicals, superoxide anion and nitric oxide (Noguchi, Gotoh et al., 1994; Noguchi, Yoshida et al., 1992). Ebselen reduces cytochrome-C release from mitochondria and nuclear damage during lipid peroxidation (Namura, Nagata et al., 2001). Ebselen acts as a catalyst and is not consumed during detoxification reactions (Müller, Gabriel et al., 1988). SPI-1005, a novel anti-inflammatory, constitutes a new drug class and each capsule contains 200 mg of ebselen. SPI-1005 offers the potential for a safe, well tolerated, oral treatment for Meniere's disease, a disease for which there are currently no approved treatments.

Sound Pharmaceuticals has completed a Phase 1 study in healthy subjects (SPI-1005-101). In this Phase 1 study, 32 subjects were randomized to receive either a single oral dose of placebo or one of four different doses of SPI-1005, up to 1600 mg. There were no treatment- or dose-related trends in overall adverse events (AE) incidence when compared to placebo (Lynch & Kil, 2009). Pharmacokinetic analysis of ebselen and its metabolites supported twice daily dosing by oral route of administration. SPI has completed a Phase 2 study in healthy subjects (SPI-1005-202)

that were exposed to a Controlled Sound Challenge (CSC). In this Phase 2 study, 83 subjects were randomized to placebo or one of three doses of SPI-1005 capsules and treated for 4 days, twice daily by oral route of administration, up to 600 mg BID. There were no treatment- or dose-related trends in overall AE incidence when compared to placebo. SPI-1005 was found to be safe and effective in reducing the incidence and severity of the temporary threshold shift (TTS) induced by the CSC when compared to placebo (Kil, Lobarinas et al., 2017).

SPI has completed a Phase 1b safety and efficacy study in Meniere's Disease (MD) (SPI-1005-151). In this study, 40 adults with probable or definite MD were randomized to placebo or one of three doses (200, 400, or 600 mg, BID) of SPI-1005, and treated for 21 days by oral route of administration. No treatment- or dose related trends in overall AE incidence, nor selenosis, were observed. SPI-1005 was found to be safe and well tolerated during the three week course of treatment. SPI has also completed a Phase 2b safety and efficacy study in patients with MD (SPI-1005-251). In this study, 125 subjects with active probable or definite MD were randomized to placebo or one of two doses (200 or 400 mg, BID) of SPI-1005, and treated for 28 days by oral route of administration. SPI-1005 was found to be safe and well tolerated during the four week course of treatment.

In addition to these SPI sponsored studies in the US, Daiichi Pharmaceuticals sponsored three safety and efficacy studies testing ebselen in Japan for the indication of acute stroke. See the Investigator's Brochure for summaries of all non-clinical and clinical studies involving SPI-1005.

The objective of this study will be to evaluate the safety and explore the efficacy of SPI-1005 in the treatment of severe COVID-19 disease in adult patients.

3 STUDY OBJECTIVES

The objectives of this study are to evaluate the safety, efficacy, and PK of SPI-1005 capsules (400 or 800 mg BID), administered for 14 days compared to placebo in patients with severe COVID-19.

3.1 Primary Objective

The safety of SPI-1005 compared to placebo will be determined by examining the toxicities and frequency and severity of adverse events that are attributable to treatment. The safety evaluation will also include the physical exam, vital signs, and abnormal laboratory findings (CBC, serum chemistry). Changes in these laboratory values from baseline values will be averaged and compared between treatment groups.

3.2 Secondary Objective

The secondary objective of the study will be pharmacokinetic sampling including plasma trough levels of ebselen and its major metabolite.

3.3 Exploratory Objectives

The exploratory objectives of the study will include the following:

- Improvement, stability, or worsening of clinical outcomes, as assessed by the WHO ordinal scale, comparing SPI-1005 with placebo
- Improvement, stability, or worsening of respiratory status, as assessed by peripheral oxygen saturation (SpO_2) and degree of supplemental oxygen, comparing SPI-1005 with placebo
- Pharmacodynamic testing, including reduction in inflammatory and cytokine storm-related biomarkers, comparing SPI-1005 treatment with placebo
- Pharmacodynamic testing, including reduction in viral load, comparing SPI-1005 treatment with placebo

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This interventional study is a randomized, double-blind, placebo-controlled, dose escalation, multi-center clinical trial (RCT) of SPI-1005 in adult subjects with newly diagnosed COVID-19. Adults (age ≥18 years) with a positive PCR test for novel SARS-CoV-2 (nCoV2) and presenting within 7 days of clinical signs, symptoms, and respiratory status consistent with severe COVID-19 will be enrolled to the study. Positive PCR test may be performed by nasopharyngeal, oral, saliva, or respiratory sample.

Severe COVID-19 will be defined as:

- Clinical signs and symptoms consistent with COVID-19 disease
- Score of 5-7 on the WHO Ordinal Scale for Clinical Improvement

Following the informed consent and screening procedures, subjects will be evaluated by the Investigator for eligibility. Subjects must be hospitalized (inpatient) at the time of randomization to be eligible for study treatment. Eligible subjects will undergo baseline safety, pharmacokinetic, and pharmacodynamic assessments before initiating treatment.

Eligible subjects will be randomized by third party CRO to SPI-1005 (400 or 800 mg BID) or matching placebo (2:1) and treated for 14 days, starting on Day 1. The initial SPI-1005 dose level will be 400 mg BID, and this dose level will be escalated to 800 mg BID following the interim safety analysis. All safety, pharmacokinetic, and pharmacodynamic assessments will be performed on Day 3 and Day 7 of dosing, and on Day 14 at the end of dosing. Clinical status will be assessed daily according to the WHO Ordinal Scale while the subject is hospitalized. If the subject is discharged from the hospital, the discharge date and disposition will be captured. Additional follow-up will occur on Day 30 or end of study. If the subject is hospitalized on Day 30, all safety, pharmacokinetic, and pharmacodynamic assessments will be performed. If the subject is not hospitalized on Day 30, then the patient should return to the clinic for an in-clinic visit and undergo all safety, pharmacokinetic, and pharmacodynamic assessments per the Schedule of Assessments. If it is not feasible for the patient to return to clinic, then a remote telehealth visit may be conducted.

During the study, participants will be evaluated for safety (adverse events, physical exams, vital signs, clinical laboratory testing (CBC, serum chemistry)) according to the Schedule of Assessments in Section 1.3. Trough plasma levels of ebselen and its major metabolite will be determined using liquid chromatography-mass spectrometry (LCMS) at specified visits. The saliva levels of viral load and plasma levels of inflammatory & cytokine storm-related biomarkers including high-sensitivity CRP, IL-1, IL-2, IL-6, TNF-alpha, and ferritin will be determined at specified visits.

Dose escalation of SPI-1005 treatment from 400 mg BID to 800 mg BID will occur following completion of an interim safety analysis and DSMB review. The 400 mg BID dose has been tested in several other study populations for 21 and 28 days, and has been found to be safe and well-tolerated. For this reason, the 400 mg BID dose was chosen as the starting dose to test SPI-1005 in COVID-19 patients. The Cmax for the 400 mg BID dose is 92.0±43.9 ng/mL (mean±SD). The 800 mg BID dose was chosen as the high dose since it is twice the starting dose, and will result in a Cmax that is greater than that of the 600 mg BID dose of 150±57.9 ng/mL (mean±SD) documented in another study population. The 800 mg BID dose has not been tested in other study populations for 21 and 28 days, however a dose of 1600 mg/day has been tested in other study populations for 1-2 days. In this COVID-19 study population, 800 mg BID treatment will be limited to 14 days. Based on the *in vitro* findings of Jin, Du et al., 2020, a higher dose of ebselen may be required to inhibit M^{pro} activity *in vivo*.

All assessments will take place as specified according to the Schedule of Assessments in Section 1.3.

4.2 Safety Criteria for Stopping Dosing

If a study participant has an unanticipated, severe or serious adverse event potentially related to study treatment, the Investigator should contact the Sponsor to determine whether to discontinue study treatment. Regardless of communication with the Sponsor, the Investigator should make a determination about discontinuing the study treatment if it is in the best interest of the safety of the study participant. Study treatment may also be discontinued at the request of the study participant.

4.3 Criteria for Study Termination

Study participants who must discontinue study treatment for any reason should continue to complete the study through their study exit visit. If a study participant is not able to comply with study safety monitoring or is non-compliant with the study protocol and/or study treatment, the Investigator should contact the Sponsor about early termination of the study participant's study participation. Criteria for early termination are in Section 7.4, Early Termination of Participants.

5 STUDY POPULATION

Study participants will be required to meet all inclusion criteria to enroll in this study. If any exclusion criteria are met, enrollment will be declined.

5.1 Inclusion Criteria

- Adults ≥18 years of age

- Positive nCoV2 PCR test by nasopharyngeal, oral, saliva, or respiratory sample
- Clinical signs, symptoms, and respiratory status consistent with severe COVID-19
  - Score of 5-7 on the WHO Ordinal Scale
- Onset of severe COVID-19 symptoms ≤7 days of study enrollment
- Subject is in-patient at time of randomization to study treatment
- Subject or legally authorized representative is willing and able to provide informed consent, and agrees for subject to comply with planned study procedures including reproductive requirements.

5.2 Exclusion Criteria

- Women who are pregnant or breastfeeding
- Participation in another interventional investigational drug or device study concurrently or within 30 days prior to study consent
- Patients with impaired hepatic or renal function
  - ALT/AST >3 times the upper limit of normal; or
  - eGFR <90 mL/min/1.73m^2; or
  - History of hepatic impairment (cirrhosis) or renal impairment
- Subject has any other illness or condition that, in the opinion of the investigator, would prohibit the subject from participating.

6 DESCRIPTION OF STUDY TREATMENT

6.1 Compound

SPI-1005 is a formulation of ebselen, consisting of white, opaque hard gelatin capsules, each containing 200 mg of the active pharmaceutical ingredient ebselen and approximately 150 mg of the excipients: microcrystalline cellulose, sodium croscarmellose, and magnesium stearate. Placebo capsules contain only the excipients.

6.2 Dosing Levels

There are two dose levels: 400 or 800 mg BID of SPI-1005. The rationale for these dosing levels is summarized in Section 4.1.

6.3 Dosing Regimen

Eligible subjects will be randomized to SPI-1005 or placebo (2:1), and receive one of the following accordingly (2 capsules per dose):

- 400 mg po (2 active capsules each containing ebselen 200 mg) BID for 14 days;
- Placebo (2 placebo capsules) po BID for 14 days.

Following an interim safety analysis and DSMB review, the SPI-1005 treatment group will have the dose escalated from 400 mg BID to 800 mg BID. Eligible subjects will be randomized to SPI-1005 or placebo (2:1), and receive one of the following accordingly (4 capsules per dose):

- 800 mg (4 active capsules each containing ebselen 200 mg) po BID for 14 days;
- Placebo (4 placebo capsules) po BID for 14 days.

6.4 Dosage Form

#1 size opaque white capsule will contain either 200 mg of ebselen or matching placebo.

6.5 Manufacturer

SPI-1005 capsules are GMP manufactured by WuXi AppTech for Sound Pharmaceuticals, Inc.

6.6 Route of Administration

SPI-1005 capsules (or matching placebo) are orally administered with approximately 240 ml of water, 1-2 hours prior to food. Each dose will be administered approximately 10-12 hours apart, as two or four capsules in the morning and two or four capsules in the evening.

6.7 Packaging and Labeling

White size#1 hard gelatin capsules are supplied in white, opaque, high density polyethylene bottles, induction sealed, with a child-resistant white, opaque polypropylene cap.

SPI-1005 capsules (or matching placebo) are provided in bottles, each with a 14-day supply.

For additional information, refer to SPI-1005 Investigator's Brochure V5.2 dated December 01, 2021, or most recent version.

6.8 Storage

SPI-1005 capsules should be stored in a dry place at room temperature (20 to 25°C; 68-77°F). For additional information, refer to SPI-1005 Investigator's Brochure V5.2 dated December 01, 2021, or most recent version.

6.9 Study Drug Accountability

One bottle of study drug (SPI-1005 or matching placebo) will be dispensed after randomization on Visit 1. The bottle and any study drug that the subject has remaining in the bottle must be returned to the study personnel after the final dose of study treatment. Study personnel should examine the returned study drug in order to count and record the number of capsules dispensed, taken by the study participant, remaining, and lost. Subject testimony regarding missed doses should also be obtained.

Compliance with study treatment will be measured by subject's testimony and final remaining capsule count. Study staff should retain study treatment packaging and remainder of study drug capsules for drug accountability monitoring. Study drug accountability (e.g. bottle identifier, date of dispensation, number of capsules dispensed) will also be performed when dispensing any study treatment to the subject.

The subject should refrain from taking their morning dose of study treatment on the day of any study visit, until after the blood draw for pharmacokinetic analysis has been collected, in order to obtain trough plasma levels in the blood sample collection.

6.10 Study Drug Handling and Disposal

All study drug will be retained by the study site in an environment that is secure, limited access,

and is monitored daily for temperature. All study drug will be retained at the site until otherwise instructed by the Sponsor.

7 STUDY CONDUCT

7.1 Study Duration

The study component comprises a minimum of 5 scheduled interactions over a 30-day period

7.2 Study Procedures by Visit

7.2.1 Visit 1 (Day 0 to 1)

Informed consent for study participation must be obtained before study procedures are conducted.

Visit 1 comprises screening and baseline testing, determination of eligibility, and randomization and dispensation of study treatment for eligible subjects. Subjects should not be randomized or dispensed study treatment until all screening and baseline procedures have taken place, and the investigator has confirmed the subject is eligible for participation in the study.

For screening purposes, potential participants will have a positive nCoV2 PCR test (by nasopharyngeal, oral, saliva, or respiratory sample) which has been performed according to the study center's standard of care and will be documented in the CRF. Additionally, a baseline saliva sample will be obtained at Visit 1 for nCoV2 viral load testing by the central laboratory (see Section 8.7 Pharmacodynamics).

The following study procedures will be performed during Visit 1. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Informed Consent
- Demographics
- Medical History
- Physical Exam
- Clinical Status
- Height & Weight
- Vital Signs
- Blood & saliva sample collection for:
    - Clinical laboratory tests (CBC, chemistry)
    - Pharmacokinetics
    - Pharmacodynamics
- Urine pregnancy test, for women of childbearing potential only
- Concomitant medications
- Randomization (if eligibility criteria are met)
- Dispensation of study drug, study drug accountability
- Adverse Events

Following the informed consent process and confirmation of eligibility (inclusion/exclusion criteria), randomization will take place. Each study participant will be randomized to either SPI-1005 (400 or 800 mg) or matching placebo, double-blinded. The subject will be dispensed one bottle of study drug containing capsules of SPI-1005 or placebo. The date of first dose of study treatment will be recorded and is by definition Day 1. The subject will be instructed to refrain from taking their morning dose on the day of Visit 2.

7.2.2 Visit 2 (Day 3)

Visit 2 will take place on Day 3, which is 3 days after the start of study treatment.

The following study procedures will be performed during Visit 2. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Clinical Status
- Vital Signs
- Blood & saliva sample collection for:
    - Clinical laboratory tests (CBC, chemistry)
    - Pharmacokinetics
    - Pharmacodynamics
- Concomitant medications
- Study Treatment
- Adverse Events

The subject will be instructed to refrain from taking their morning dose on the day of Visit 2 until after the blood sample collection. The time and date of last dose prior to blood sample collection will be captured and recorded in the CRF.

7.2.3 Visit 3 (Day 7)

Visit 3 will take place on Day 7.

The following study procedures will be performed during Visit 3. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Clinical Status
- Vital Signs
- Blood & saliva sample collection for:
    - Clinical laboratory tests (CBC, chemistry)
    - Pharmacokinetics
    - Pharmacodynamics
- Concomitant medications
- Study Treatment

- Adverse Events

The subject will be instructed to refrain from taking their morning dose on the day of Visit 3 until after the blood sample collection. The time and date of last dose prior to blood sample collection will be captured and recorded in the CRF.

7.2.4 Visit 4 (Day 14)

Visit 4 will take place on Day 14 (± 2 day visit window). Day 14 will be the final day of study treatment dosing.

The following study procedures will be performed during Visit 4. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Clinical Status
- Vital Signs
- Blood & saliva sample collection for:
    - Clinical laboratory tests (CBC, chemistry)
    - Pharmacokinetics
    - Pharmacodynamics
- Concomitant medications
- Adverse Events

The subject will be instructed to refrain from taking their morning dose on the day of Visit 4 until after the blood sample collection. The time and date of last dose prior to blood sample collection will be captured and recorded in the CRF.

The time and date of last dose of study treatment will be captured and recorded in the CRF.

7.2.5 Visit 5 (Day 30)

Visit 5 will take place on Day 30 (± 2 day visit window) and will be the study exit visit.

The following study procedures will be performed during Visit 5. These procedures should be performed according to the descriptions detailed in Section 8, Description of Study Procedures, and Section 6.9, Study Drug Accountability.

- Physical Exam
- Clinical Status
- Vital Signs
- Blood sample collection for:
    - Clinical laboratory tests (CBC, chemistry)
- Concomitant medications
- Adverse Events

If the patient is not hospitalized at the time of Visit 5, then the patient should return to the clinic for an in-clinic visit and undergo the procedures (including safety assessments) described above. If it is not feasible for the patient to return to clinic, then a remote telehealth visit may be conducted. If a telehealth visit is conducted, the following procedures will be performed:

- Clinical Status
- Concomitant medications
- Adverse Events

7.3 Early Termination of Study Participants

Study participants may be discontinued from study treatment for any of the following reasons:

- Serious or life-threatening adverse event (AE) (see Section 9.3.6, Stopping Criteria);
- Failure or inability to comply with the dosing, evaluations, or other requirements of the study;
- Request of the study participant (study participants have the right to discontinue study treatment at any time for any reason);
- Pregnancy;
- Any situation or condition which may threaten the study participant's health or well-being by continuing in the study;
- Administrative (e.g., study termination).

It is the right and the duty of the investigator to interrupt study treatment of any study participant if he/she feels that study discontinuation is necessary to protect the study participant, or that there are unmanageable factors that may interfere significantly with the study procedures and/or the interpretation of results.

All study participants will be asked to complete the study assessments according to the Schedule of Assessments in Section 1.3, even if study treatment is discontinued for any reason. Additionally, if study treatment is discontinued, the following information will be documented:

- The reason for discontinuation of study treatment;
- The date of the last dose of test products from the trial;

Study withdrawal may occur due to withdrawal of consent or loss to follow-up. If a study participant prematurely withdraws from the study, the primary reason for the withdrawal will be obtained and documented. At the time of withdrawal, every effort (e.g., telephone contact, certified letter) should be made and documented, to ensure all procedures and evaluations scheduled for the study exit visit are performed.

At a minimum collect the following information when a study participant withdraws:

- The reason the study participant withdrew;
- The date of the last dose of test products from the trial;
- The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;
- (Serious) Adverse events;
- Compliance with the test product administration as specified in this protocol;

- Final Assessments: all procedures and evaluations scheduled for the study exit visit (Section 1.3: Schedule of Assessments)

All study participants receiving at least one study treatment dose will be included in the safety analysis, whether or not they complete the study. Reasons for dropouts will be reported and evaluated for possible introduction of bias into the analysis. Adverse events reported by study participants or revealed upon examination or lab testing will be included in the analysis.

8 DESCRIPTION OF STUDY PRODECURES

8.1 Informed Consent Procedures and Documentation

The investigator or qualified designee will explain the study and all study requirements to the subject or legally authorized representative, answer all of his/her questions, and obtain written informed consent using the most current IRB-approved ICF before performing any study-related procedure. A copy of the informed consent will be given to the subject.

8.2 Randomization and Blinding

The study is a randomized, double-blind, placebo-controlled study design. Appearance of active and placebo capsules is identical. Study center and sponsor personnel involved in the conduct and interpretation of the study will not have access to treatment codes. Laboratory personnel, and contracted designees of SPI who statistically analyze the data, will be blinded to the study treatment received by each study participant until after database lock. The bioanalytical staff analyzing PK samples will be provided randomization codes to facilitate PK analysis, but will not report unblinded data until after database lock. The sponsor's medical monitor will receive each treatment code in individual envelopes for use in emergency unblinding.

Study participants who are eligible for enrollment will be randomized according to the procedure established by the designated CRO. The designated CRO labeling the product maintains a confidential list of codes identifying the contents of each study drug dispensation.

Table 3 shows the number of SPI-1005 and placebo study participants in each study treatment group.

Table 3 Approximate number of study participants randomized to each dose

SPI-1005 *(400 mg BID)*	**SPI-1005** *(800 mg BID)*	**Placebo** *(BID)*
20	20	20

If a study participant experiences a serious adverse event that requires unblinding, the Investigator will request decoding of the study participant's group assignment and drug product information through SPI.

8.3 Medical History

A detailed medical history will be obtained by the investigator or designee. Medical history should include information on clinically significant personal medical history, including comorbidities, history of diseases, adverse medical events (e.g. seizures, arrhythmias), allergies

or reactions to medications or food, and previous surgeries.

8.4 Physical Exam

The investigator or designee (must be a licensed medical professional) will perform a physical examination of the following organ systems: Eyes, ears, nose, head, oropharynx, respiratory system, cardiovascular system, abdomen, skin, musculoskeletal reflexes, and extremities. For each abnormal finding, the investigator will comment on clinical significance (clinically significant or not clinically significant). Clinically significant changes from the baseline physical examinations will be recorded as adverse events.

8.5 Vital Signs

Vital signs will be obtained by the principal investigator or designee. Subjects will be in a seated or semi-recumbent position for at least 5 minutes. If the scheduled time for vital sign measurements coincides with a blood collection, the vital signs should be performed prior to the blood collection, or at least 5 minutes afterwards. This same timing for obtaining the vital signs (before or after the blood collection) should be used for all vital sign measurements.

Peripheral oxygen saturation (SpO_2) will be determined by pulse oximetry. Systolic and diastolic blood pressure (mmHg), pulse rate (bpm), body temperature (Celsius), SpO_2 (%), and the actual clock time (24:00) will be recorded in source and captured on the CRF.

Vital signs will be reviewed by the investigator for clinical significance (clinically significant or not clinically significant). Any clinically significant change from baseline for vital sign measurement (not associated with another adverse event) will be recorded in source as an adverse event and captured on the CRF.

8.6 Clinical Laboratory Tests

The clinical laboratory tests – hematology (CBC) and serum chemistry, as described in Table 4 – will be performed according to standard laboratory procedures. A central laboratory (CRO) will be used for the study, and a lab manual with detailed instructions for blood collection, processing, and shipping will be provided to study centers. All laboratory tests will be collected according to the schedule of assessments in Section 1.3. Results of laboratory tests will be provided to investigators and captured in the study database with reference ranges.

Table 4 SPI-1005-292 Clinical Laboratory Tests

Hematology	Chemistry	
RBC	Sodium	Albumin
Hematocrit	Potassium	AST (SGOT)
Hemoglobin	Chloride	ALT (SGPT)
Platelets	Bicarbonate	Total bilirubin
WBC	Glucose	Alkaline phosphatase
Neutrophils	Blood urea nitrogen (BUN) or Urea	Uric acid
Lymphocytes	Creatinine	LDH
Monocytes	Calcium	Cholesterol
Basophils	Magnesium	Triglycerides
Eosinophils	Inorganic phosphorus	Total protein

Clinical laboratory samples should be collected in the fasted state (after an overnight fast for morning sample collections and at least 4 hours without food for other samples) when feasible, or date and time of last meal recorded. Clinical laboratory test will be obtained prior to study drug administration.

The clinical laboratory test results will be reviewed by the investigator to determine clinical significance (clinically significant or not clinically significant). Any clinically significant change from baseline in a laboratory test will be recorded as an Adverse Event. The test should be repeated at appropriate time intervals until it returns to baseline or becomes a clinically insignificant finding. If the laboratory result does not return to clinically insignificant levels within a reasonable time, in the opinion of the Investigator, the subject may be discontinued from the study after discussion with the Medical Monitor.

8.7 Pharmacodynamics

Four (4) mL of blood will be collected for pharmacodynamics at the specified time points indicated in schedule of assessments in Section 1.3. Plasma levels of inflammatory & cytokine storm-related biomarkers including high-sensitivity CRP, pro-inflammatory analytes, and ferritin will be determined. The following pro-inflammatory analytes will be measured via a validated multiplex panel: IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNFα.

An additional two (2) mL of blood will be drawn at the specified time points for future analyses including immunological cellular assay and genetic sequencing of immune cells.

Saliva samples will be obtained to determine the levels of viral load and for viral sequencing of nCov2 at baseline and at follow-up visits according to the schedule of assessments in Section 1.3. If a saliva sample cannot be obtained, a sputum sample may be obtained instead.

The lab manual contains detailed instructions on collection, processing, and shipping of these samples. Sample collection times (actual clock time using 24:00) are to be recorded and will be captured in the CRF.

8.8 Pharmacokinetics

Three (3) mL of blood will be collected for pharmacokinetics at the specified time points indicated in schedule of assessments in Section 1.3. The lab manual contains detailed instructions on collection, processing, and shipping of these blood samples. Sample collection times (actual clock time using 24:00) are to be recorded and will be captured in the CRF.

The subject should refrain from taking their morning dose of study treatment on the day of any study visit, until after the blood draw for pharmacokinetic analysis has been collected, in order to obtain trough plasma levels in the blood sample collection. Trough plasma levels of ebselen and its major metabolite (2-glucuronyl selenobenzanilide) will be determined by LCMS/MS at specified visits.

A subset of subjects will provide additional PK sampling for peak plasma levels of ebselen and its major metabolite. An additional three (3) mL of blood will be collected 2 hours after the morning dose of study treatment during Visit 1, 2, and 3.

In prior ADME studies involving SPI-1005, the plasma half-life of ebselen is approximately 8-12 hours, 2-glucuronyl selenobenzanilide accounts for >90% of the metabolites, and it is cleared through the urine.

8.9 Clinical Status

While the patient is hospitalized, clinical status will be assessed daily and recorded. If the patient is not hospitalized, the clinical status will be assessed at the specified time points indicated in schedule of assessments in Section 1.3.

8.9.1 World Health Organization (WHO) Ordinal Scale for Clinical Improvement

Illness severity over time will be assessed by the WHO ordinal scale (see Appendix 1). The worst score the patient experiences on a particular day will be recorded.

The scale is as follows:

0. No clinical or virological evidence of infection;
1. Not hospitalized, no limitation of activities;
2. Not hospitalized, limitation of activities;
3. Hospitalized, no oxygen therapy;
4. Hospitalized, oxygen by mask or nasal prongs;
5. Hospitalized, non-invasive ventilation or high-flow oxygen;
6. Hospitalized, intubation and mechanical ventilation;
7. Hospitalized, ventilation + additional organ support – pressors, RRT, ECMO;
8. Death.

8.9.2 Measures of clinical support

The following measures of clinical support will be assessed and recorded in the CRF.

- Hospitalization
- Oxygen requirement
- Non-invasive mechanical ventilation (CPAP or BiPAP via mask) or high-flow nasal cannula
- Mechanical ventilation requirement (via endotracheal tube or tracheotomy tube)
- ECMO requirement
- RRT requirement

If the patient is receiving supplemental oxygen, the oxygen flow rate and/or fraction will be captured in the CRF.

8.10 Concomitant Medications

Each subject will be interviewed about concomitant medications, including over-the-counter medications and non-medicinal treatments or supplements, at the baseline visit and at each follow-up visit. All concomitant treatments will be recorded in the CRF and evaluated by the investigators.

8.10.1 Prohibited Medications

There are no prohibited medications based on prior drug-drug interaction studies or findings with SPI-1005.

8.11 Reproductive Requirements

- Males must be sexually inactive (abstinent) or use condoms throughout the study period and 90-days following study completion, even if not fertile.
- Females of childbearing potential must be sexually inactive (abstinent) for 14 days prior to screening and throughout the study; or use one of the following acceptable birth control methods:
  - IUD in place for at least 3 months prior to study; or
  - Barrier method (condom or diaphragm) with spermicide for at least 14 days prior to screening through study completion; or
  - Stable hormonal contraceptive for at least 3 months prior to study and through study completion; or
  - Surgical sterilization (vasectomy) of partner at least 6 months prior to study enrollment.
- Females of non-childbearing potential must be surgically sterile (bilateral tubal ligation with surgery at least 6 months prior to study enrollment; hysterectomy; or bilateral oophorectomy at least 2 months prior to study), or least 1 year since last menses.

9 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1 Definition of Adverse Event

Per the International Conference on Harmonization (ICH), an adverse event (AE) is defined as any untoward medical occurrence in a study participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this study treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

9.2 Definition of Serious Adverse Event

An adverse event (AE) or suspected 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 adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a study participant who received SPI-1005
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

  Examples of such events are:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
  - Development of drug dependency or drug abuse

9.3 Classification of an Adverse Event

Adverse events will be classified using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or higher.

9.3.1 Severity of Event

The following guidelines will be used to grade severity.

- **Grade 1 (Mild)** – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 (Moderate)** – Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

- **Grade 3 (Severe)** – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
- **Grade 4 (Life-threatening)** – Life-threatening consequences; urgent intervention required.
- **Grade 5 (Death)** – Death related to AE.

9.3.2 Relationship to Study Treatment

All adverse events must have their relationship to study intervention assessed by the Investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.3.3 Unanticipated Adverse Event

The Investigator will be responsible for determining whether an adverse event is unanticipated. An AE will be considered unanticipated if the nature, severity, or frequency of the event is not

consistent with the risk information previously described protocol and in the Investigator's Brochure.

9.3.4 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes the event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

9.3.5 Adverse Event Reporting

The investigator, along with delegated study staff, will record all adverse events with start dates occurring any time after informed consent is obtained until the end of study participation. At each study visit, the investigator will inquire about occurrence of AE/SAEs since the previous visit. Events will be followed for outcome until resolution or stabilization. The AE term should be reported in standard medical terminology when possible.

All SAEs must be reported to the Medical Monitor within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a scanned copy by email to the Medical Monitor [Andrew Goodwin, MD, goodwian@musc.edu].

Additional follow-up information, if required or available, should all be scanned and emailed within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Should a pregnancy occur, it must be reported and recorded in the study participant's medical record and recorded in the Medical History form in the CRF. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the study participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be dealt with as AEs.

Any serious or unanticipated adverse events must be reported to SPI, including death or life-threatening events, disabling or incapacitating conditions, or any event that requires hospitalization. Serious adverse events occurring during the duration of the study or within 28 days of the study participant's last dose must be reported within 24 hours the Medical Monitor [Andrew Goodwin, MD], even if the event appears unrelated to the study treatment.

Safety Reporting contact information:

Jonathan Kil, MD
Sound Pharmaceuticals, Inc.
4010 Stone Way North
Suite 120
Seattle, WA 98103
jkil@soundpharma.com
(206) 769-4820

Sound Pharmaceuticals is responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potentially serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Both SPI and investigators have the right to terminate this study at any time, and to arrange an appropriately agreed upon schedule for termination, if necessary. This information will be provided to each study participant during the informed consent process.

9.3.6 Stopping Criteria

An individual study participant will be discontinued from study treatment if either of the following stopping criteria are met:

- AE of severity grade 3 or higher which is possibly, probably, or definitely related to study drug; OR
- AE of severity grade 4 or higher, regardless of relationship to study drug

If any of the following study-wide criteria are met, study enrollment will be paused to allow the DSMB to review the safety data and determine whether or not the study may be allowed to proceed:

- Three patients develop the same severity grade 3 AE which is possibly, probably, or definitely related to study drug; OR
- Two patients develop the same severity grade 4 AE which is possibly, probably, or definitely related to study drug; OR

- One patient develops a severity grade 5 AE which is possibly, probably, or definitely related to study drug.

10 STATISTICAL CONSIDERATIONS

All study participants will be included in the analyses and include: all randomized study participants; all dosed study participants; and all evaluable study participants. The intent to treat and per protocol populations used for a given analysis will be detailed in the Statistical Analysis Plan.

The sample size for this study was established following the pre-IND meeting with FDA, to identify any early safety signals and to evaluate exploratory efficacy findings for future trials.

Adverse events will be coded using CTCAE (Version 5.0 or higher) and summarized by each treatment group (SPI-1005 400 or 800 mg BID, or placebo) for the number of adverse events.

Vital signs and clinical laboratory results will be summarized by each treatment group (SPI-1005 400 or 800 mg BID, or placebo). Comparisons will be made between baseline and all follow-up values. Abnormal values will be identified and categorized by severity.

Study data will be collected in the form of categorical and continuous variables. Categorical data will be analyzed using chi-square or Fisher's Exact test for small sample sizes. To estimate the effect of treatment longitudinally, data will be analyzed using mixed-effects models, using a linear or logit link for continuous or categorical variables respectively. Calculated p-values will be considered statistically significant at or below a two-sided alpha level of 0.05.

An interim safety analysis will be performed on patients receiving SPI-1005 400 mg BID vs placebo, prior to dose escalation to 800 mg BID(see Section 12.3 for further details).

The final analyses will involve comparisons of placebo to SPI-1005 400 mg BID, and SPI-1005 800 mg BID, and all subjects receiving SPI-1005 (400 mg or 800 mg BID). The placebo groups (matching 400 mg or 800 mg BID) will be pooled, such that final allocation will be 1:1:1.

The Statistical Analysis Plan will be provided separately and will contain detailed information for each primary and secondary endpoint on the main, supplementary, and sensitivity analysis methods, as well as methods for handling missing data.

11 INVESTIGATIONAL RECORD KEEPING

All study records including the disposition of the drug (i.e., dates, quantity, use by study participants, and unused supplies) and study participant Case Report Forms (CRFs), source documents, consent forms, and chart notes will be maintained and retained in accordance with federal regulations set forth by 28 CFR, Part 312.62. Each study participant case history will contain documentation confirming that informed consent was obtained from the study participant prior to participation in the study. All personnel associated with this study will make their best effort to ensure anonymity and confidentiality of study participant records.

Case histories and study records will be made promptly available upon request to SPI or FDA

personnel. SPI will furnish study progress reports annually to the FDA. Any alarming safety reports will be made available immediately to SPI and the FDA in accordance with regulatory requirements.

11.1 Protocol Deviations and Amendments

Any deviation from protocol deemed appropriate to prevent potential harm to an individual study participant does not require pre-approval from the clinical site IRB or authorities at SPI; however, such deviations must be reported to the IRB and SPI within five days of the occurrence.

If a deviation to the protocol is deemed appropriate for all study participants, a formal amendment must be entered for the study to reflect the change. If the deviation applies to only one study participant, the details and reasons for the change must be thoroughly documented in the study file.

Both SPI and clinical investigators must be in concurrence with any formal amendment to the protocol, and such an amendment must be approved by the IRB if it has the potential to impact a study participant's safety.

11.2 Publication Policy

The results of this clinical trial may be presented at scientific meetings or published. All published data, manuscripts, materials, and presentations are the joint property of Sound Pharmaceuticals, Inc. (SPI) and the appropriate clinical investigator(s). Authorship is determined by mutual agreement. Any data, manuscript, or abstract submitted for publication must be copied to all designated personnel at SPI and the appropriate clinical investigator(s) at least 30 days prior to submission so that proprietary information can be protected and all concerned parties will be able to make informed comments.

11.3 Study Monitoring

Before an investigational site can enter a study participant into the study, a representative of SPI will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of SPI or its representatives. This will be documented in a Clinical Trial Agreement between SPI and the investigator.

During the study, a monitor from SPI or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the study participant's medical records at the hospital or practice, and other

records relevant to the study. This will require direct access to all original records for each study participant (e.g., clinic charts).

- Data are entered into the CRFs in a timely manner.
- Record and report any protocol deviations not previously sent to SPI.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to SPI, and those SAEs that met criteria for reporting have been reported to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

The Investigator assumes ultimate responsibility for the conduct of the study and remains readily accessible throughout the duration of the study.

11.4 Audits and Inspections

Authorized representatives of SPI, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an SPI audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact SPI immediately if contacted by a regulatory agency about an inspection.

The Investigator agrees to allow the monitor to inspect the drug storage area, study drug inventory, drug accountability records, study participant charts and study source documents, and other records relative to study conduct.

11.5 Retention of Records

The Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for SPI or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records to ensure compliance with Good Clinical Practices and all applicable regulatory requirements, SPI may conduct a quality assurance audit.

11.6 Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Sponsor. However, authorized regulatory officials, IRB/IEC personnel, Sound Pharmaceuticals, Inc. and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, screening and/or treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

12 ETHICS AND RESPONSIBILITIES

The final clinical protocol, the final version of the Informed Consent Form, and recruitment materials must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must verify that IRB approval of the protocol, consent form and recruitment materials for the investigation is obtained prior to conducting study evaluations. The Investigator must maintain all IRB approvals and all materials approved by the IRB for this study including Informed Consent Form and recruitment materials and made available for inspection.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and biannually, as local regulations require.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. SPI will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

12.1 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

12.2 Data and Safety Monitoring Board (DSMB)

An independent and external Data Safety Monitoring Board (DSMB) will be used for this study. The DSMB charter and membership roster will be established by the independent DSMB with agreement by the Sponsor. DSMB members will be required to confirm they have no conflict of interest towards the integrity of oversight of this protocol.

12.3 Interim Safety Analysis

After the initial 30 eligible subjects have been randomized to the study, enrollment for the study will be paused. These subjects will have been randomized to receive either SPI-1005 400 mg BID or placebo (2:1) (refer to Section 6.3 for Dosing Regimen).

Then, an interim safety analysis with the independent, external DSMB will be conducted.

If the DSMB recommends that dose escalation may proceed, then enrollment for the study will resume, and 30 new eligible subjects will be enrolled and randomized to receive either SPI-1005 800 mg BID or placebo (2:1) (refer to Section 6.3 for Dosing Regimen).

If the DSMB does not recommend that dose escalation may proceed, then the study will be stopped.

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13 APPENDICES

13.1 APPENDIX I – WHO Ordinal Scale

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

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WHO R&D Blueprint
novel Coronavirus
COVID-19 Therapeutic Trial Synopsis
February 18, 2020, Geneva, Switzerland
https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis