A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF STI-5656 (ABIVERTINIB MALEATE) IN SUBJECTS HOSPITALIZED DUE TO COVID-19

STUDY INTERVENTION:	STI-5656
PROTOCOL NUMBER:	STI-5656-2001
Version	5.0
DATE FINAL:	07DEC2020
Amendment 1; V2.0	01JUL2020
Amendment 2; V3.0	08JUL2020
Amendment 3; V4.0	12NOV2020
IND NUMBER:	151327
SPONSOR NAME / ADDRESS:	Sorrento Therapeutics, Inc. 4955 Directors Place, San Diego, CA 92121 USA

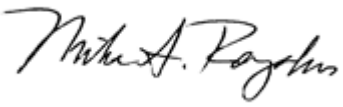
MEDICAL MONITOR/ EMERGENCY CONTACT

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF STI-5656 (ABIVERTINIB MALEATE) IN SUBJECTS HOSPITALIZED DUE TO COVID-19

Role in Study	Name	Address and Telephone number
Responsible Physician	Mike A. Royal MD JD MBA	mroyal@Sorrentotherapeutics.com +1 (858) 204 1112

SORRENTO THERAPEUTICS INC. APPROVAL

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF STI-5656 (ABIVERTINIB MALEATE) IN SUBJECTS HOSPITALIZED DUE TO COVID-19

	**07DEC2020**
Signature of Responsible Officer **Mike A. Royal MD JD MBA** **Chief Medical Officer, Sorrento Therapeutics, Inc.**	**dd mmm yyyy**
Printed Name of Responsible Officer and Title By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF STI-5656 (ABIVERTINIB MALEATE) IN SUBJECTS HOSPITALIZED DUE TO COVID-19

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:** _____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Sorrento Therapeutics Inc. representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

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A Phase 2, Randomized, Double-Blind, Placebo-controlled Study of the Safety and Efficacy of STI-5656 (Abivertinib Maleate) in Subjects Hospitalized Due to COVID-19
Protocol Number: STI-5656-2001, Version 4.0
Investigator(s)/ Study Centers This study will be conducted at multiple study centers located in the United States.
Phase: 2
Objectives **Primary Objective:** • To assess the efficacy of STI-5656 in subjects with severe coronavirus disease 2019 (COVID-19) **Secondary Objectives:** • To assess the safety and tolerability of STI-5656 in subjects with severe COVID-19 • To assess the pharmacokinetic profile in the study population
Endpoints **Primary Endpoint:** • Proportion of subject alive and free of respiratory failure at Day 28 Respiratory failure, is defined based on resource utilization of any of the following modalities: o Noninvasive positive pressure ventilation or continuous positive airway pressure o Endotracheal intubation and mechanical ventilation o Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) o Extracorporeal membrane oxygenation (ECMO) **Secondary Endpoints:** • Types, frequencies, and severities of adverse events (AEs) and the relationships of AEs to IP; includes serious adverse events (SAEs) • Proportion of subjects alive and free of respiratory failure at Day 60 • Change in clinical status (on a 0-8-point ordinal scale)[1] of subject at Day 7, Day 14 and Day 28

[1] 8-category ordinal scale of patient health status ranges: 0=no clinical or virological evidence of infection; 1=no limitation of activities; 2=limitation of activities; 3=hospitalized, no oxygen therapy; 4=oxygen by mask or nasal prongs; 5=non-invasive ventilation or high-flow oxygen; 6=intubation and mechanical ventilation; 7=ventilation + additional organ support – pressors, rapid response team (RRT), extracorporeal membrane oxygenation (ECMO); 8=death. See Section 14.2 for form.

- Proportion of subjects alive and discharged from Intensive Care Units (ICU) at Days 14 and 28
- Time from randomization to first occurrence of respiratory failure or death on study due to any cause up to Day 28
- Percent change from baseline in CRP at Days 3, 5, 7, 10, 14, 28
- Relative change from baseline in oxygenation index (PaO2/FiO2) up to Day 5
- All-cause mortality at Day 60 and Day 90
- Number of days alive and free of respiratory failure at Day 28
- Number of days with respiratory failure up to Day 28
- Number of days hospitalized up to Day 28
- Number of days in ICU (length of stay) up to Day 90
- Number of days alive outside of hospital up to Day 28
- Number of days alive outside of hospital up to Day 90
- Pharmacokinetics in the study population at 100 mg QD

Exploratory Endpoints:

- See Section 3.2.3

Subject Population

- ≥18 years with reverse transcriptase polymerase chain reaction (RT-PCR) confirmed infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- COVID-19 pneumonia (documented radiographically) requiring hospitalization; oxygen saturation level <94% on room air or subject requires supplemental oxygen.

Refer to Section 5 for complete eligibility details.

Investigational Product (IP) Description:

Investigational Product (IP) is STI-5656 (Abivertinib maleate)

Planned Sample Size

Approximately 80 subjects will be enrolled in this study, 40 will be randomized to each of two treatment arms.

Treatment Arms

All subjects will receive current standard of care (SOC) treatments.

In this setting, subjects will receive one of two treatments up to Day 14 or until hospital discharge (if sooner):

Arm 1: STI-5656 (100 mg QD starting dose)

Arm 2: Placebo QD

Duration of Study

For subjects, the total duration of the study will be up to 94 days (up to 4 days for the screening period plus up to 14 days for treatment and up to 90 days from randomization for follow-up).

The length of the study will be approximately 7 months (4 months for enrollment plus up to 90 days study duration).

Study Design

This is a Phase 2, randomized, double blind, placebo-controlled, 2-arm multicenter study to assess the safety and efficacy of STI-5656 (capsule administered orally) in the setting of current standard of care (SOC) in subjects with RT-PCR confirmed SARS-CoV-2 (COVID-19) infection and pneumonia (documented radiographically) requiring hospitalization. Subjects must have oxygen saturation levels < 94% on room air or subject requires supplemental oxygen.

Eighty (80) subjects meeting eligibility criteria will receive SOC treatment and will be randomized at a 1:1 ratio to one of two treatment arms

- Arm 1: STI-5656
- Arm 2: Placebo

The starting dose of STI-5656 is 100 mg PO QD administered up to 14 days or until hospital discharge whichever is sooner. Placebo follows the same schedule.

Subjects who discontinue at any time after randomization will not be replaced. There is no treatment crossover in this study.

Once subjects provide informed consent, they will have screening assessments performed (up to a 7-day screening window). Study Day 1 is the day of randomization. Subjects randomized should receive their first dose of STI-5656 or placebo on the day they are randomized (Day 1).

Subjects will be assessed daily while hospitalized. Subjects in both arms are assessed for adverse events and toxicities and all adverse events should be reported regardless of treatment arm assignment or causality.

PK samples will be collected from the first 20 subjects enrolled in this trial. For sampling time points please refer to the schedule of assessments.

Subjects will have an outpatient visit on Day 28 (for various study procedures) and a telephonic contact on Day 60 to collect any additional AEs and follow-up for unresolved AEs to resolution or to establishment of a new baseline.

SOC treatments will be collected in the electronic case report form (e-CRF) until hospital discharge. Continued outpatient treatment (concomitant medications) will be collected until Day 28. Any investigational medication received will be collected until Day 90.

Note: Investigational medicines other than STI-5656 are prohibited up to Day 28 or hospital discharge.

Discharged subjects will be contacted at Day 60 and Day 90 to collect survival, any experimental treatments and additional hospitalization information since the study hospital discharge.

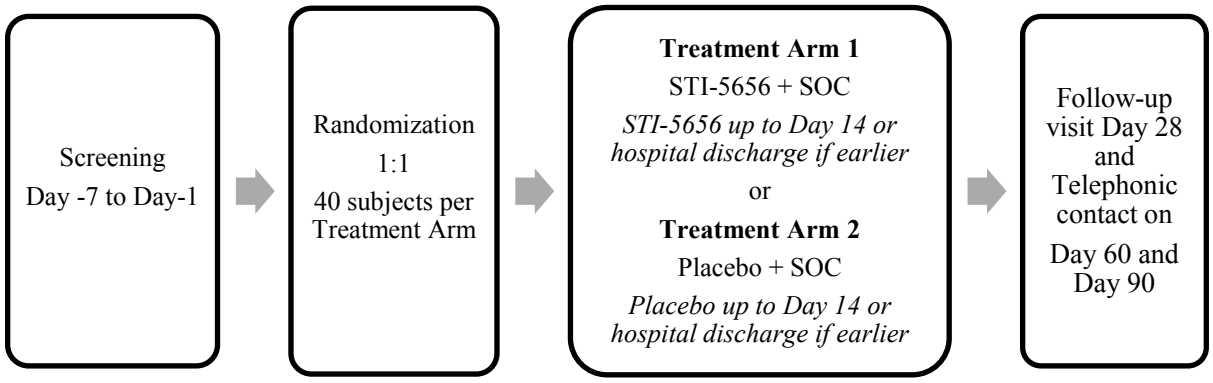
Subjects should be encouraged to remain in the study even if Study Drug is discontinued (for any reason).

Statistical Design

An evaluable sample size of 40 subjects per group (treatment arm) will provide 80% power (alpha=0.05, 2-sided) to detect a difference between groups in the number of subjects alive and free of respiratory failure at Day 28. This assumes that 95.7% of subjects who received STI-5656 plus SOC (group 1) and 70% of subjects who received only SOC (group 2) will be alive and free of respiratory failure at Day 28. This represents a treatment effect difference of approximately 26%.

All tests of significance will be assessed at alpha level=0.05, 2-sided.

Figure 1: Study Design



Schedule of Assessments (SOA)

See Table 1 for SOA

Data Monitoring Committee

An independent data monitoring committee (DMC) will be established under a charter for the trial and tasked to evaluate data from the study to ensure the ongoing safety of the study subjects and make recommendations to the Sponsor concerning safety and trial conduct. A blinded independent statistician will be used to facilitate DMC support. This statistician will have no role in the statistical assessments conducted for the study at its conclusion. Discussions with the independent statistician will be conducted during a closed session during the DMC deliberations. Sponsor, CRO and study site personnel will only participate in the open session. Unblinding of a given subject to assess an AE stopping rule trigger will be handled in a way to keep the Sponsor, CRO (and staff) and study site personnel blinded.

A futility analysis will be performed by an independent biostatistician after the first 40 subjects are enrolled.

Additional details may be found in the Statistical Analysis Plan (SAP) for this study.

2. SCHEDULE OF ASSESSMENTS (SOA)

Table 1: Schedule of Assessments

Assessments	Screening (Day -4 to -1)	Day 1 (Dose 1)[1]	Daily until hospital discharge	Hospital discharge or Early Term [2]	Outpatient visit: Day 28	Telephone Follow-up at Day 60 and 90
Informed Consent	X					
Assess eligibility	X	X				
Demographics[3]	X					
RT-PCR assay for SARS-CoV-2[4]	X					
Medical history (including COVID-19 history)	X					
Concomitant medications	X	X	X	X	X	
Physical exam, including weight; height[5]	X			X	X	
Vital signs[6]	X	X	X	X	X	
12-lead ECG (performed locally)[7]	X	X				
Pregnancy test for FCBP only[8]	X	X		X	X	
Urinalysis[9]	X	X	X		X	
Blood for hematology, coagulation and chemistry[10]	X	X	X	X	X	
Blood for CRP , serum ferritin, VEGF-A and cytokines[11] **Day 3, 5, 7, 10, 14 and 28 only**	X	X	X	X	X	
Respiratory Status[12]	X	X	X	X		
Adverse Events[13]	X	X	X	X	X	
Assess clinical status[14]	X	X	X	X		
IRT entry (at screening, randomization, then early termination or study completion	X	X		X		X
Study Drug administration (QD p.o.)		X	X[15]			

Assessments	Screening (Day -4 to -1)	Day 1 (Dose 1)[1]	Daily until hospital discharge	Hospital discharge or Early Term [2]	Outpatient visit: Day 28	Telephone Follow-up at Day 60 and 90
Sampling for pharmacokinetics[16]	X[16]	X[16]	X[16]			
Survival and additional experimental meds/ hospitalization/ICU status					X	X

Abbreviations: AEs: adverse events; ALC: Absolute lymphocyte count; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; BUN: blood urea nitrogen; CMP: complete metabolic panel; COVID-19: Coronavirus Disease 2019; D: day; ECG: electrocardiogram; ECMO: extracorporeal membrane oxygenation; ET: Early Termination; F: Fahrenheit; FCBP: female of childbearing potential; FiO_2: Fraction of inspired oxygen; IRT: Interactive Response Technology; IL: Interleukin; IFNγ: interferon gamma; QD: once daily; PaO_2: partial pressure of oxygen in arterial blood; p.o.: by mouth; RBC: red blood cells; rbc/hpf: red blood cells per high power field; RRT: rapid response team; RT- PCR: Reverse transcription polymerase chain reaction; TNFα: tumor necrosis factor alpha; WBC: white blood cells

[1] All assessments on Day 1 are to be performed prior to first dose of STI-5656. Day 1 laboratory results do not need to be available prior to randomization (and first dose of STI-5656 if assigned to that arm) if lab results are available from the previous 24 hours

[2] If the subject wishes to discontinue from the study prior to Day 28 or hospital discharge, every effort should be made to perform an Early Termination (ET) Visit within 7 days after the decision to discontinue the study.

[3] Demographics includes age, sex, race, ethnicity, date of birth.

[4] SARS-CoV-24 positive RT-PCR test results received more than 7 days prior to planned randomization may be used to confirm eligibility if the site is unable to obtain a repeat sample and confirm results prior to planned randomization day and if the subject has progressive disease consistent with COVID-19.

[5] Height at screening only

[6] Vital signs include body temperature (F), respiratory rate, radial pulse rate, systolic and diastolic blood pressure, and oxygen saturation (pulse oximetry). Pulse and blood pressure should be taken with subject in at least in a semi-recumbent position. It is preferred to collect vital signs approximately mid-afternoon each day. Vital signs may be obtained at additional times as deemed necessary by the Investigator.

[7] ECG to be performed at Screening, between 2 and 4 hours after study drug dosing, and as clinically indicated.

[8] Females of childbearing potential must have a negative pregnancy test at screening and within 24 hours before randomization (Day 1) unless the previous negative pregnancy test was within 72 hours of Day 1. Urine pregnancy test is acceptable. The test should be repeated at the time of the Day 28 visit.

[9] Urinalysis performed locally. Urinalysis includes protein, glucose, and blood (microscopic) – red blood cells per high power field (rbc/hpf).

[10] Laboratory tests performed locally.
Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count including differential.
Coagulation: INR, PTT.
Chemistry: performed locally. 14-analyte complete metabolic panel (CMP) : Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, total bilirubin (TBIL), blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, sodium, total protein, D-dimer, fibrinogen.

[11] Cytokines include TNFα, IFNγ, IL-6, IL-1β, IL-7, IL-8, IL-10, IL-12, IL-17, IL-18, IP 10, VEGF-A

[12]Record FiO_2 (and PaO_2) at the time of arterial blood gas sampling. If PaO2 is not available, use SPO_2. Other respiratory status data to collect includes oxygen supplementation status: mechanical ventilation, face mask, nasal cannula or room air. Radiographic findings will also be collected.

[13]AEs will be collected from the time of informed consent to Day 60. Any ongoing AEs at Day 28 will be followed until resolution or stabilization.

[14]An 8-category ordinal scale of patient health status ranges: 0=no clinical or virological evidence of infection; 1=no limitation of activities; 2=limitation of activities; 3=hospitalized, no oxygen therapy; 4=oxygen by mask or nasal prongs; 5=non-invasive ventilation or high-flow oxygen; 6=intubation and mechanical ventilation; 7=ventilation + additional organ support – pressors, rapid response team (RRT), extracorporeal membrane oxygenation (ECMO); 8=death. See Section 14.2 for form.

[15]STI-5656 or placebo administration up to Day 14 or hospital discharge, whichever is sooner for subjects in Treatment Arm 1. Study drug capsules should be taken orally with 200-250 mL of water following at least 2 hours of fasting.

[16]Samples will be collected from the first 20 subjects enrolled. Sampling timepoints are as follows: Day 1 (predose) and at 0.5, 1, 2, 4, 8, 12, postdose on dosing days 1 and 8.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective

To assess the efficacy of STI-5656 in subjects with severe COVID-19

3.1.2. Secondary Objectives

To assess the safety and tolerability of STI-5656 in subjects with severe COVID-19

To assess pharmacokinetics in the study population.

3.2. Endpoints

3.2.1. Primary Endpoint

- Proportion of subjects alive and free of respiratory failure at Day 28

  Respiratory failure, is defined based on resource utilization of any of the following modalities:

  – Noninvasive positive pressure ventilation or continuous positive airway pressure

  – Endotracheal intubation and mechanical ventilation

  – Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5)

  – Extracorporeal membrane oxygenation

3.2.2. Secondary Endpoints

- Types, frequencies, and severities of AEs and the relationships of AEs to IP; includes serious adverse events SAEs
- Proportion of subjects alive and free of respiratory failure at Day 60
- Change in clinical status (on a 0-8-point ordinal scale[2]) of subject at Day 7, Day 14, and Day 28
- Proportion of subjects alive and discharged from ICU at Days 14 and 28

[2] 8-category ordinal scale of patient health status ranges: 0=no clinical or virological evidence of infection; 1=no limitation of activities; 2=limitation of activities; 3=hospitalized, no oxygen therapy; 4=oxygen by mask or nasal prongs; 5=non-invasive ventilation or high-flow oxygen; 6=intubation and mechanical ventilation; 7=ventilation + additional organ support – pressors, rapid response team (RRT), extracorporeal membrane oxygenation (ECMO); 8=death.

- Time from randomization to first occurrence of respiratory failure or death on study due to any cause up to Day 28
- Percent change from baseline in CRP at Days 3, 5, 7, 10, 14, 28
- Relative change from baseline in oxygenation index (PaO2/FiO2) up to Day 5
- All-cause mortality at Day 60 and Day 90
- Number of days alive and free of respiratory failure at Day 28
- Number of days with respiratory failure up to Day 28
- Number of days hospitalized up to Day 28
- Number of days in ICU (length of stay) up to Day 90
- Number of days alive outside of hospital up to Day 28
- Number of days alive outside of hospital up to Day 90
- To assess the pharmacokinetic profile in the study population

3.2.3. Exploratory Endpoints

- Change from baseline in absolute lymphocyte counts at Days 3, 5, 7, 10, 14, 28
- Change from baseline in ferritin at Days 3, 5, 7, 10, 14, 28
- Change from baseline in VEGF-A at Days 3, 5, 7, 10, 14, 28
- Change from baseline for inflammatory cytokines (IL-6, TNF-α, IFNγ, IL1β, IL-7, IL-8, IL-10, IL-12, IL-17, IL-18, IP-10) at Days 3, 5, 7, 10, and 28

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, 2-arm multicenter study to assess the safety and efficacy of oral STI-5656 (or placebo) in the setting of current SOC in subjects with RT-PCR confirmed SARS-CoV-2 infection and COVID-19 pneumonia (documented radiographically) requiring hospitalization. Subjects must have oxygen saturation levels <94% on room air or subject requires supplemental oxygen.

Eighty (80) subjects meeting eligibility criteria will be randomized at a 1:1 ratio to one of two treatment arms in addition to SOC treatments:

- Arm 1: STI-5656
- Arm 2: Placebo

The STI-5656 dose is 100 mg p.o. QD administered up to 14 days or until hospital discharge if sooner.

SOC treatments will be collected in the electronic case report form (e-CRF).

Subjects who discontinue at any time after randomization will not be replaced. There is no treatment crossover in this study.

Once subjects provide informed consent, they will have screening assessments performed (up to 4-day screening window). Study Day 1 is the day of randomization. Randomized Subjects should receive their first dose of Study Drug on Day 1.

Subjects will be assessed daily while hospitalized. Subjects in both arms are assessed for adverse events (AEs) and toxicities and all AEs should be reported regardless of treatment arm assignment or causality. Subjects will be contacted on Day 28 to collect any additional AEs and follow-up for unresolved AEs,

SOC treatments will be collected in the electronic case report form (e-CRF) until hospital discharge. Continued outpatient treatment (concomitant medications) will be collected until Day 28. Any investigational medication received will be collected until Day 90. Note: Investigational medicines other than STI-5656 are prohibited up to Day 28 or hospital discharge.

Discharged subjects will be contacted at Day 60 and 90 to ensure survival and collect any experimental treatments and additional hospitalization information since the study hospital discharge. Subjects on Treatment Arm 1 (STI-5656) should be encouraged to remain in the study even if Study Drug is discontinued (for any reason).

An independent data monitoring committee (DMC) is established to evaluate the safety data from the study to ensure the ongoing safety of the study subjects and make recommendations to the Sponsor concerning safety and trial conduct (please refer to the DMC charter for details). A blinded independent statistician will be used to facilitate DMC support. This statistician will have no role in the statistical assessments conducted for the study at its conclusion. Discussions with the independent statistician will be conducted during a closed session during the DMC deliberations. Sponsor, CRO and study site personnel will only participate in the open session.

Unblinding of a given subject to assess an AE stopping rule trigger will be handled in a way to keep the Sponsor, CRO (and staff) and study site personnel blinded.

The study visit schedule and assessments are detailed in Table 1 Schedule of Assessment (SOA).

For subjects, the total duration of the study will be up to 94 days (up to 4 days for the screening period plus up to 14 days for treatment and up to 90 days from randomization for follow-up).

The length of the study will be approximately 7 months (4 months for enrollment plus up to 90 days study duration).

4.2. End of Trial Definition

The End of Trial is defined as either the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Subjects who are randomized but discontinue prior to the end of the study will not be replaced.

5.1. Subject Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Confirmed infection with SARS-CoV-2 per World Health Organization (WHO) criteria (including positive RT-PCR nucleic acid test of any specimen [eg, respiratory, blood, urine, stool, or other bodily fluid]) within 7 days of randomization. Positive RT-PCR test results more than 7 days prior to randomization is allowed if the site is unable to obtain a repeat sample and if the subject has progressive disease consistent with COVID-19.
2. COVID-19 pneumonia (documented radiographically) requiring hospitalization and oxygen saturation <94% on room air or subject requires supplemental oxygen.
3. Age ≥18 years at the time of signing the informed consent form
4. Subject or family member/caregiver must have provided written informed consent which includes signing the institutional review board approved consent form prior to participating in any study related activity. However, if obtaining written informed consent is not possible, other procedures as provided in the March 27th, 2020 FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, Question 10, may be used.
5. Able to swallow capsules
6. Willing to follow contraception guidelines

If a female, be sterile (surgically or biologically)* or at least one year post-menopausal**, or have a monogamous partner who is surgically sterile, or have a same sex partner, or if in a heterosexual relationship, must agree to do the following for at least 1 month after receiving IP:

- Practice abstinence
- Use at least 1 of the following medically acceptable methods of birth control:
  - Hormonal methods such as oral, implantable, injectable, vaginal ring, or transdermal contraceptives (must have started a minimum of 1 full cycle, based on the subject's usual menstrual cycle period, before IP dose
  - Intrauterine device
  - Double-barrier method (condoms, sponge, or diaphragm with spermicidal jellies or cream).

**Defined as having had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; or having a congenital or acquired condition that prevents childbearing*

[**]Defined as at least 12 months with no menses without an alternative medical cause) [can be confirmed with follicle stimulating hormone level (FSH) in the post-menopausal range (FSH levels ≥40 milli international units/mL (mIU/mL) at Screening) if the subject is not on hormonal replacement therapy]

If a male of reproductive potential*, unless he has a same sex partner, must agree to do the following for at least 1 month after receiving IP

- practice abstinence from heterosexual activity, or
- use (or have their partner use) acceptable contraception (see criterion above) during heterosexual activity

[*]Defined as having azoospermia, whether due to having had a vasectomy or due to an underlying medical condition.

5.2. Subject Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Known cardio-pulmonary resuscitation within 14 days of randomization
2. Pregnant or breast feeding
3. Suspected uncontrolled active bacterial, fungal, viral, or other infection (besides infection with SARS-CoV-2)
4. Alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) and total bilirubin > 2x ULN
5. QTcF prolongation >480 milliseconds
6. Uncontrolled or untreated symptomatic arrhythmias, myocardial infarction within the last 6 weeks, or congestive heart failure (NYHA Grade 3 or 4). Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll
7. Treatment with a strong cytochrome P450 (CYP3A4 inhibitor (within 14 days before first dose of study drug) or inducer (within 7 days before first dose of study drug).
8. Received anti-rejection or immunomodulatory drugs (eg, anti-cytokines, BTK inhibitors, JAK inhibitors, PI3K inhibitors) within 30 days before randomization on study
9. Concurrent participation in another clinical trial involving therapeutic interventions (observational study participation is acceptable).
10. Any condition that confounds the ability to interpret data from the study.
11. Relevant renal impairment (eGFR <60ml/min)
12. Any significant medical condition, laboratory abnormality or psychiatric illness that would interfere or prevent the subject from participating in the study.

5.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to

ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any SAE.

Individuals who meet all the screening criteria but were not selected for cohort may be re-screened to participate in a subsequent cohort. Screening laboratory tests and/or vital signs may be repeated once if, in the opinion of the Investigator, the out-of-range values are thought to be spurious and not indicative of an underlying disease or abnormality.

6. TREATMENT OF PARTICPANTS

6.1. Description of Investigational Product

Study treatment will be either STI-5656 (Investigational Product, or IP) or placebo.

6.2. Investigational Product Administration

Two STI-5656 or matching placebo capsules p.o. QD (two 50-mg capsules) administered up to 14 days or until hospital discharge if sooner.

Study drug capsules should be taken orally with 200-250 mL of water following at least 2 hours of fasting.

If vomiting occurs within 30 minutes after a patient takes the dose and the patients can tolerate the medication, the vomited dose should be made up.

If the subject is unable to swallow, the capsule contents may be flushed down a nasogastric or feeding tube with water.

6.3. Stopping Rule Triggers

Study drug dose should be paused per the guidelines in Table 2 (using the Common Terminology Criteria for Adverse Events, Version 5.0 [CTCAE] for severity grading).

Table 2: Stopping Rule Triggers

If any of the following possibly related AEs occur: • ≥ Grade 3 (G3) non-hematologic toxicities • ≥ G3 alanine aminotransferase (ALT) elevation **OR** ≥ any ALT and total bilirubin elevation in combination which meet Hy's Law criteria [i.e., any ≥ G3 hepatic impairment] • G3 thrombocytopenia with bleeding • G4 thrombocytopenia • G4 neutropenia • G3 neutropenia or thrombocytopenia in > 3 subjects • ≥ G3 renal impairment including acute kidney injury requiring hemodialysis • Any SUSAR (suspected unexpected serious adverse reaction)	At the first occurrence of any of the stopping rule triggers, discontinue Study Drug for the affected subject and pause further enrollment until DMC deliberations have been completed and a DMC decision that enrollment may be restarted has been rendered.

A DMC teleconference will be arranged within 5 business days of the stopping rule trigger. This should provide sufficient time for the CRO to prepare a blinded summary of the AE and the independent statistician to arrange to be unblinded to assist the DMC in its deliberations. Additionally, the DMC will be provided with tabular safety summaries at 25%, 50% and 75% enrollment for ongoing surveillance.

6.4. Dosing of Subjects Unable to Take Test Article PO

Subjects unable to take the capsules PO, for example after intubation may receive the drug or placebo via feeding tube. The formulation is blended powder filled in capsule allowing for

opening the capsules and dosing the content as is with water to flush the feeding tube. If this is not feasible, dosing should be discontinued.

6.5. Investigational Product Compliance

Subjects receive IP only while hospitalized and it is administered at the site; therefore, the site will monitor IP compliance.

6.6. Overdose

Any dose over the protocol-specified daily dose of STI-5656 will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the subject for any AE/SAE for at least 24 hours.
- Document the quantity of the excess dose.

6.7. Randomization and Blinding

Screening, randomization to one of two treatment arms (1:1 ratio), as well as study completion or study discontinuation will be registered by the site using an IRT system.

6.8. Emergency Unblinding

Emergency unblinding may be requested by the Investigator at any time if needed to properly assess the patient. The request should be submitted to the CRO and Sponsor's medical monitor.

6.9. Concomitant Medications

Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements), vaccine or transfusion that the subject received within 28 days prior to the Screening Visit and during the study up to hospital discharge must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Prohibited Concomitant Medications

The following medications are prohibited up to Day 28 or hospital discharge:

Anti-cytokines, other BTK inhibitors or other tyrosine kinase inhibitors (e.g. JAK or PI3K inhibitors as well as any immunosuppressive drugs (except steroids), such as anti-IL6 or anti-TNFα therapy.

7. IP MATERIALS AND MANAGEMENT

7.1. Investigational Product

IP	STI-5656 (Abivertinib maleate)	Placebo
Dose Formulation	Capsule for oral administration	Capsule for oral administration
Unit Dose Strength(s)	50 mg	n/a
Dose to be administered to subjects	200 mg QD (4 capsules once daily)	4 capsules once daily
Route of Administration	p.o. (by mouth)	p.o. (by mouth)
Use	Experimental	
Manufacturer	Shanghai Syn-The-All Pharmaceutical Co. Ltd. ("STA"), a wholly owned subsidiary of WuXi AppTec Co.	Shanghai Syn-The-All Pharmaceutical Co. Ltd. ("STA"), a wholly owned subsidiary of WuXi AppTec Co.
Sourcing	Provided centrally by Sorrento Therapeutics, Inc. or a Sorrento representative	Provided centrally by Sorrento Therapeutics, Inc. or a Sorrento representative
Packaging and Labeling	40 Capsules packaged inside an HDPE bottle and closed with a polypropylene cap.	40 Capsules packaged inside an HDPE bottle and closed with a polypropylene cap.

7.2. IP Packaging and Labeling

STI-5656 will be distributed to the investigational site's pharmacy. The site pharmacist will dispense STI-5656 to subjects in Treatment Arm 1.

The labels on the study drug bottles will include the following information:

- Protocol Number
- Lot Number
- Name of product and strength of each capsule
- Storage conditions
- Sponsor's name and address
- The statement: "Caution: New drug-limited by Federal Law to Investigational Use. Keep out of reach of children."

7.3. IP Storage

The shelf life of STI-5656 is at least 3 years when stored at room temperature (approximately 20º to 25°C [68º to 77°F]).

7.4. IP Accountability

The Principal Investigator (or designee) is responsible for accountability of all used and unused IP at the site.

The IP provided by the Sponsor must be made available for inspection by the Sponsor or its representatives and regulatory agency inspectors upon request.

7.5. IP Handling and Disposal

The Investigator must keep an accurate accounting of the number of bottles and capsules of STI-5656 delivered to the site, administered to subjects, and returned to the Sponsor/Sponsor representative or other disposition during and at the completion of the study.

The IP must be dispensed to subjects only by an appropriately qualified person. The IP is to be used in accordance with the protocol by subjects who are under the direct supervision of the Investigator. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all IP received at the site before final disposition.

All IP, including unused, partially used, and empty containers, should be disposed of in accordance with federal, state and local regulations and the institutional standard operating procedures (SOPs) or returned to the Sponsor/Sponsor representative as directed if destruction at the site is not possible.

8. STUDY PROCEDURES

Study procedures will be performed as described in the Schedule of Assessment Table 1.

Additional unscheduled visit/assessments may be performed at any time if clinically indicated and will be captured in the eCRFs if performed.

Protocol waivers or exemptions are not allowed, with the exception of immediate safety concerns. Such concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue the IP (subjects in Treatment Arm 1). Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

A subject may be re-screened once for the study if the defined screening period has been exceeded and the subject has not been randomized in the study.

8.1. Description of Procedures

8.1.1. Informed Consent

All subjects will review and sign an IRB-approved Informed Consent Form prior to performing any procedures specifically for this study.

8.1.2. RT-PCR assay for SARS-CoV-2

If RT-PCR confirmation of SARS-CoV-2 is not within 7 days prior to planned randomization, then positive RT-PCR test results more than 7 days prior to randomization is allowed to confirm eligibility if the site is unable to obtain a repeat sample and if the subject has progressive disease consistent with COVID-19.

8.1.3. Collection of Demographics, Medical History, Prior and Concomitant Medications

Demographics include age, sex, race, ethnicity, date of birth.

Current (active) medical conditions and relevant (non-active) medical history. Details of COVID-19 history should include COVID-19-related symptoms, time of onset of symptoms, date of first positive COVID-19 test result

Concomitant medications and prior medications taken within 28 days of informed consent

8.1.4. Vital Signs

Vital signs include body temperature (F), respiratory rate, radial pulse rate, systolic and diastolic blood pressure, and oxygen saturation (pulse oximetry). Pulse and blood pressure should be taken with subject in at least in a semi-recumbent position.

It is preferred to collect vital signs at approximately mid-afternoon each day. Vital signs may be obtained at additional times as deemed necessary by the Investigator.

8.1.5. Physical Exam

A physical exam should be performed at Screening and at hospital discharge or Early Termination Visit, whichever is later. Height (at screening) and weight (screening and discharge) should be recorded also.

8.1.6. 12-lead Electrocardiogram (ECG)

A 12-lead ECG is to be performed during Screening, between 2 and 4 hours after study drug dosing and at any time a subject complains of anything suggestive of a cardiac abnormality.

8.1.7. Clinical laboratory tests

Serum chemistry, hematology, coagulation, urinalysis and urine pregnancy tests are to be performed locally.

8.1.7.1. Serum Chemistry

Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, total bilirubin (TBIL), blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, sodium, total protein, D-dimer, fibrinogen.

8.1.7.2. Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count including differential.

8.1.7.3. Coagulation

International normalized ratio (INR), PTT.

8.1.7.4. C-reactive protein, serum ferritin, absolute lymphocyte count and cytokines

Blood should be collected for measuring C-reactive protein (CRP), serum ferritin, VEGF-A, and cytokines (IL-6, TNF-α, IFNγ, IL1β, IL-7,IL-8, IL-10, IL-12, IL-17, IL-18, IP10) should be measured on Days 3, 5, 7, 10, 14 and 28.

8.1.7.5. Urinalysis

Urinalysis to be performed locally. Urinalysis includes protein, glucose, and blood (microscopic) – red blood cells per high power field (rbc/hpf).

8.1.7.6. Urine Pregnancy Test

Urine pregnancy tests (B-HCG) will be performed (locally) for women of childbearing potential. FSH tests may be performed to confirm a woman is of non-childbearing potential if the subject is not on hormonal replacement therapy or not surgically sterile (refer to eligibility criteria for details).

8.1.8. Respiratory Status

Record FiO2 (and PaO2) at the time of arterial blood gas sampling. If PaO2 is not available, use SPO2. Other respiratory status data to collect includes oxygen supplementation status: mechanical ventilation, face mask, nasal cannula or room air. Radiographic findings will also be collected.

8.1.9. Clinical status using 8-category ordinal scale of patient health status

An 8-category ordinal scale of patient health status ranges will be used to collect subject clinical status where

0 = no clinical or virological evidence of infection;

1 = no limitation of activities;

2 = limitation of activities;

3 = hospitalized, no oxygen therapy;

4 = oxygen by mask or nasal prongs;

5 = non-invasive ventilation or high-flow oxygen;

6 = intubation and mechanical ventilation;

7 = ventilation + additional organ support – pressors, rapid response team (RRT), extracorporeal membrane oxygenation (ECMO);

8 = death.

See Section 14.2 for form.

8.1.10. IRT Registration, Randomization and Study Discontinuation or Completion.

Subjects will be registered in IRT after signing informed consent and will be randomized using the IRT on Day 1 to either Treatment Arm 1 (STI-5656 plus SOC) or Treatment Arm 2 (placebo plus SOC) using central integrated response technology (IRT). Subject study discontinuation or study completion should also be registered in the IRT.

8.1.11. Adverse Events

Adverse events will be collected from the time of signing the ICF through Day 60.

8.1.12. Follow-up contact

The subject will be seen on Day 28 to collect laboratory samples, report on any additional AEs and on the status of unresolved AEs. The subject will also be contacted at Day 60 and 90 to document survival (or collect date of death from family or subject's physician). In addition, any experimental medication, duration of any additional hospital or ICU admissions after the first "post-randomization" discharge will also be collected.

8.2. Procedures by Study Day

8.2.1. Screening

- Informed Consent
- Registration of screening in IRT
- RT-PCR assay for SARS-CoV-2 (if needed, see details in Section 8.1.2)
- Collection of Demographics, Medical History, Prior and Concomitant Medications
- Vital Signs
- Physical Exam
- 12-lead ECG
- Clinical laboratory tests per Section 8.1.7
- Respiratory Status
- Clinical status using 8-category ordinal scale of patient health status
- Assess eligibility

8.2.2. Study Day 1

- Vital Signs
- Clinical laboratory tests per Section 8.1.7
- Respiratory Status
- Collect adverse events since screening
- Collect con meds
- Clinical status using 8-category ordinal scale of patient health status
- Randomization in IRT
- Dispense STI-5656 or placebo capsules to subjects which should be taken orally with 200-250 mL of water following at least 2 hours of fasting.
- 12-lead ECG to be performed between 2 and 4 hours post study drug dosing

8.2.3. Daily until Hospital Discharge

- Vital Signs
- Clinical laboratory tests per Section 8.1.7. Note that the urine pregnancy test is performed only at Screening, prior to randomization on Day 1 and at hospital discharge.
- Respiratory Status
- Collect adverse events

- Collect con meds
- Clinical status using 8-category ordinal scale of patient health status
- Dispense Study Drug to subjects which should be taken orally with 200-250 mL of water following at least 2 hours of fasting.

8.2.4. Hospital Discharge or Early Termination from Study

- Physical Exam
- Vital Signs
- Clinical laboratory tests per Section 8.1.7
- Respiratory Status
- Collect adverse events
- Collect con meds
- Clinical status using 8-category ordinal scale of patient health status
- If early termination, register in IRT

8.2.5. Outpatient Follow-up Day 28

- Collect AEs, and update status on previously unresolved AE status
- Clinical laboratory tests per Section 8.1.7
- Collect survival, experimental medications since hospital discharge, any new hospitalizations/ ICU stays

8.2.6. Telephone Follow-up Day 60

- Update status on previously unresolved AEs
- Collect survival, experimental medications since hospital discharge, any new hospitalizations/ ICU stays

8.2.7. Telephone Follow-up Day 90

- Update status on previously unresolved AEs
- Collect survival, experimental medications since hospital discharge, any new hospitalizations/ ICU stays

8.3. Blood Volumes collected

Blood for hematology, coagulation and chemistry should be standard of care along with the addition of D-dimer and fibrinogen to the chemistry assessments. Blood collected for measuring CRP, serum ferritin and cytokines (IL-6, TNF-α, IFNγ, IL1β, IL-7, IL-10, IL-12, IL-17, IL-18 is approximately 6.5 mL per time point. Time points are Day 1 (baseline), Day 3, 7, 10, 14 and 28 (or at hospital discharge). The total blood volume collected for these measurements is approximately 60 mL per subject.

9. STATISTICS

9.1. Statistical Considerations

All tests of significance will be assessed at alpha level=0.05, 2-sided. All analyses and data presentations will be generated using SAS version 9.4, or higher (Cary, NC).

Subjects who are randomized to the study and discontinue before the end of the study will not be replaced. Missing values will not be imputed. For success/failure endpoints, subjects who discontinue prior to the specified time point will be included in the analysis as treatment failures and censored at the last day of follow-up for the time-to-event analysis. For all other endpoints, the mixed effect model repeat measurement (MMRM) analysis will be employed. The MMRM analysis only includes the available data. It has been demonstrated that the MMRM approach leads to estimators with comparatively small bias, and controls Type I error rates at a nominal level in the presence of missing completely at random (MCAR) or missing at random (MAR) and some possibility of missing not at random (MNAR) data (see https://pubmed.ncbi.nlm.nih.gov/19212876/).

9.2. Sample Size Estimation

An evaluable sample size of 40 subjects per group will provide 80% power (alpha=0.05, 2-sided) to detect a difference between groups in the number of subjects alive and free of respiratory failure at Day 28. This assumes that 95.7% of subjects who received STI-5656 plus SOC and 70% of subjects who received placebo plus SOC only will be alive and free of respiratory failure at Day 28. This represents a treatment effect difference of approximately 26%.

9.3. Analysis Population

The following analysis populations are planned:

- Safety population: All randomized subjects
- Full Analysis (FA) population: All randomized subjects
- Per-protocol (PP) population: Subset of the Full Analysis Set and excludes subjects with major protocol violations, entry criteria violations or missing visits. The results of the Full Analysis Set will be considered primary.

9.4. Data Analysis

9.4.1. Subject Disposition

The number and percentage of subjects included in each population, who completed the study, who discontinued study and reason for discontinuation will be presented for each cohort and treatment.

9.4.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be presented for each population by Treatment arm.

9.4.3. Primary Endpoints

For the primary endpoint, the proportion of subjects alive and free of respiratory failure at Day 28, the number and percentage of subjects will be presented by group. Possible differences between groups will be assessed using a generalized linear mixed model, assuming a binomial distribution and a logit link. The model will include group as a fixed effect. Subjects who discontinue the study prior to Day 28 will be considered treatment failures.

9.4.4. Secondary Endpoints (Safety)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by System Organ Class (SOC) and Preferred Term for each group. The first occurrence will be tabulated for an event that occurred more than once for a subject. Additionally, AEs will be tabulated by maximum severity and nearest relationship to IP. SAEs will be summarized similarly to AEs.

For continuous safety endpoints, descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum values) will be presented by group and study day. The changes from Day 1 to each subsequent day will be calculated for each subject and descriptive statistics will be presented. Possible differences between groups will be assessed using a mixed effect model repeat measurement (MMRM) analysis of covariance. The model will include the Day 1 value as a covariate, fixed effects of group, study day and group-by-study day interaction with subject as a random effect.

Categorical safety endpoints will be summarized as the number and percentage of subjects per category for each group.

Treatment-emergent adverse events (TEAE) will be defined as any AE occurring post first administration. Adverse events will be presented for each cohort and treatment by System Organ Class (SOC) and Preferred Term (PT):

- Treatment-emergent adverse events (TEAE): defined as any AE occurring postdose administration through 28 days following IP administration.
- IP related TEAEs
- SAEs
- IP related SAEs
- TEAEs (by grade and relationship to IP)
- Laboratory abnormalities by toxicity grade

9.4.5. Secondary Endpoints (Efficacy)

The proportion of subjects alive and discharged from the ICU at Day 14 and Day 28 and the proportion alive and free of respiratory failure at Day 60 and will be presented and analyzed as described for the primary efficacy endpoint. Subjects who discontinue from the study prior to each study day will be considered treatment failures.

Clinical Status will be assessed using a generalized linear mixed model, assuming a multinomial distribution. The model will include the Day 1 value as a covariate with fixed effects of group,

study day and group-by-study day interaction and subject as a random effect. If the group-by-study day interaction is found to be statistically significant then comparisons between groups at Day 7, Day 14 and Day 28 will be obtained from this model. Additionally, stacked bar charts will be presented for the proportion of subjects in each category by group and study day.

For the time from randomization to first occurrence of respiratory failure or death on study due to any cause, the Kaplan-Meier method will be applied. Subjects will be censored at the time of last follow-up. For each group, the 25th percentile, median and 75th percentile will be presented, if possible. Possible differences between groups will be assessed by the log-rank test.

The total number of deaths per group will be presented for All-cause mortality at Day 90.

9.4.6. Exploratory Endpoints

For all other efficacy endpoints, descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum values) will be presented by group and study day. The changes or percent changes from Day 1 to each subsequent day will be calculated for each subject and descriptive statistics will be presented. Possible differences between groups will be assessed using a MMRM analysis of variance\covariance. The model will include fixed effects of group, study day and group-by-study day interaction with subject as a random effect. The Day 1 value will be included when appropriate.

9.4.7. Interim Analysis

An interim futility analysis will be performed after 40 subjects have been enrolled. The analysis will be performed by an independent biostatistician who will have no contact with the study team.

10. ADVERSE EVENT DEFINITIONS AND PROCEDURE FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

10.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms. All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after hospital discharge. AEs that lead to study discontinuation should be followed until resolution or stabilization.

Serious Adverse Events (SAEs), regardless of relationship to investigational product, that occur from the time the subject signs informed consent until the last study visit and those made known to the Investigator at any time thereafter must be reported to Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;

- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to investigational product, action taken regarding investigational product, and outcome.

10.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity of AEs will be graded based upon the subject's symptoms according to CTCAE version 5.0 with unique clinical descriptions of severity for each AE based on this general guideline:

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

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with investigational product as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of study treatment, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study; or
- requires treatment, modification/ interruption of study treatment dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance

Regardless of severity grade (per CTCAE version 5.0), only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

Adverse Laboratory values that also meet the definition of SERIOUS, will be reported as SAEs.

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female of childbearing potential regardless of disease state) occurring while the subject is on investigational product, or within 1 month after last dose of investigational product, are considered immediately reportable events. Investigational product is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported Drug Safety immediately.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling. The Investigator will follow the female subject until completion of the pregnancy and must notify Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the investigational product should also be reported to Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant at any time up to one month after the male subject's last dose of IP, the male subject taking investigational product should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to the Sponsor or the Sponsor's representative within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to investigational product) that occur from the time the subject signs informed consent until the last study visit and those made known to the Investigator at anytime thereafter that are suspected of being related to investigational product. ALL SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to the Sponsor or the Sponsor's representative as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to the Sponsor or the Sponsor's representative.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the Sponsor or the Sponsor's representative and the IRB/EC.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, the Sponsor will determine the expectedness of events suspected of being related to STI-5656 based on the Investigator Brochure and determine regulatory reporting according to local Health Authority requirements and according to the Safety Management Plan for the protocol.

Events of e.g. disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed but will not be usually

reported as expedited safety reports to regulatory authorities unless they otherwise meet the requirements for expedited reporting.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of new serious and unexpected AE(s) or significant risks to subjects communicated by the Sponsor.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Drug Safety and the IRB/EC.

Sponsor or Sponsor's representative Contact Information for SAE reporting:

Please refer to the Serious Adverse Event Report Form.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor will pre-qualify 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 the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

As this study will be taking place during the COVID-19 pandemic, it is anticipated that most/all monitoring visits performed will be done remotely. This study will rely on the use of technology, either video or still camera pictures, to confirm facility requirements. The video or photo files will be stored in the Trial Master File.

During the study, a monitor from the Sponsor or its 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 IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's source records. This will require electronic access to all source records for each subject.
- Record and report any protocol deviations not previously sent to the Sponsor or it's representative.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor or it's representative and those SAEs that met criteria for reporting have been forwarded to the IRB.

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

11.2. Audits and Inspections

Authorized representatives of the Sponsor, 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 audit or inspection by the Sponsor or its representative 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 the Sponsor immediately if contacted by a regulatory agency about an inspection.

12. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor or its representative may conduct a quality assurance audit. Please see Section 11.2 for more details regarding the audit process.

13. ETHICS

13.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form (ICF), must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor or its representative before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients/subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. The Sponsor or its representative will provide this information to the Principal Investigator.

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

13.2. Ethical Conduct of the Study

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, applicable regulatory requirements and the Sponsor's policy on Bioethics.

13.3. Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

14. APPENDICES

14.1. List of Abbreviations and Definitions of Terms

The following abbreviations and specialist terms are used in this study protocol.

Table 3: Abbreviations

Abbreviation	Explanation
ADL	Activities of daily living
AE	Adverse Events
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AST	aspartate aminotransferase
B-hCG	Beta human chorionic gonadotropin
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus 2019
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events, Version 5.0
DMC	Data monitoring committee
EC	Ethics Committee
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
e-CRF	Electronic case report form
ET	Early Termination
F	Fahrenheit
FA	Full analysis
FDA	Food and Drug Administration
FCBP	Female of child-bearing potential
FiO_2	Fraction of inspired oxygen
FSH	Follicle stimulating hormone
G	Grade
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IRT	Interactive Response Technology

Abbreviation	Explanation
JAK	Janus kinase
L/min	Liters per minute
MedDRA	Medical Dictionary for Regulatory Activities
mIU	Milli international units
mL	Milliliters
PaO_2	Partial pressure of oxygen in arterial blood
PI3K	Phosphoinositide 3 kinase
p.o.	By mouth
PP	Per protocol
PT	Preferred term
QD	Once daily
RBC	Red blood cells
Rbc/hpf	Red blood cells per high power field
RRT	Rapid response team
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SOA	Schedule of Assessments
SOC	Standard of Care
SOC	System organ class
SOP	Standard operating procedures
TEAE	Treatment-emergent adverse events
ULN	upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cells
WHO	World Health Organization

14.2. Ordinal Scale for Clinical Improvement

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

Source: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf