Sironax

A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study to Assess Safety and Efficacy of SIR1-365 in Patients with Severe COVID-19

Study Number: **SIR365-US-101**

Study Phase: [redacted]

Compound Name: **SIR1-365, a Receptor-Interacting Protein 1 (RIP1) Inhibitor**

Sponsor Name: **Sironax USA, Inc, a Subsidiary of Sironax, Ltd (Sironax)**

Sponsor Medical Representatives: [redacted]

Protocol Version History: **Version 2.4 Issued on April 8th, 2021**

The Main Changes Made to Version 2.3 to Generate V 2.4

1. Appendix 6: “Medications that are mainly metabolized by CYP450 2C19” has been revised to eliminate some medications that are metabolized partially by CYP450 2C19 and/or the impact of CYP450 2C19 inhibitors on the pharmacokinetic profile of these medications is minor or unknown.

The Main Changes Made to Version 2.2 to Generate V 2.3

1. Inclusion criterion #4, “Patients with plasma CRP level > 50 mg/L at screening” has been changed to “Patients with plasma CRP level > 50 mg/L or 4x upper limit of normal range at screening”. **Rationale for the change**: In this study, CRP level is measured at local laboratories. Since each laboratory uses different methods with different normal range, it is reasonable to use 4x upper limit of normal range as another cut-off in case a local laboratory has high normal range.

2. Exclusion criterion #1, “oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fracture of delivered oxygen ≥0.5)” has been changed to “oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fracture of delivered oxygen ≥0.5. However, periodically delivered at flow rates >20 L/min with fracture of delivered oxygen ≥0.5 is allowed)”. **Rationale for the change**: Some severe COVID patients may need oxygen delivered at flow rates >20 L/min with fracture of delivered oxygen ≥0.5 for a short period of time to maintain sufficient oxygen level.

3. Exclusion criterion #5, the following sentence has been added to the end of this criterion: “One dose of dexamethasone at >6 mg but ≤12 mg or equivalent is allowed, provided baseline CRP level is measured 24 hours after the dexamethasone dosing at >6 mg but ≤12 mg”. **Rationale for the change**: Change on CRP level induced by one dose of dexamethasone at >6 mg but ≤12 mg or equivalent is limited 24 hours after the dosing.

4. Exclusion criterion #13, “suspected or known systemic bacterial or fungal infections” has been changed to “sepsis induced by systemic bacterial or fungal infections”. **Rationale for the change**: Sepsis induced by systemic bacterial or fungal infections will cause hyperinflammation.

5. Prohibited medications, the following sentence has been added after the Janus kinase inhibitor Baricitinib: “Baricitinib at ≤4 mg/day for less than 7 days prior to screening is allowed. However, this medication should be discontinued after enrollment)”. **Rationale for the change**: Based on the information listed in the FDA approved label, baricitinib-induced reduction on CRP level were seem one week after treatment.

The Main Changes Made to Version 2.1 to Generate V 2.2

1. Summary of phase 1a studies conducted in healthy volunteers in Australia has been added to provide the up-to-date clinical data to the investigators.
2. To prioritize clinical treatments for patients and to reduce the burden on patients and clinical staff, the time to perform some clinical assessments has been changed from before morning (1^{st}) dose to before the afternoon (2^{nd}) dose.
3. To reduce the burden on patients and workload on clinical staff, the frequency of CRP and ferritin tests has been reduced from daily testing during the 14-day treatment period to 5 tests on days 1, 3, 7, 10 and 14. Similarly, the frequency of blood tests for coagulopathy and cardiac panels has been reduced from 9 tests on days 1-7, 10 and 14 to 5 tests on days 1, 3, 7, 10 and 14.
4. To fit into the clinical practice of treating patients with severe COVID-19, screening visit and baseline visit can be combined in some patients. In that case, the number of dosing could be less than 3 times on that day. ECG, laboratory test and other test results obtained within 24 hours prior to consent can be used as baselines.
5. For those patients who are qualified to be discharged before Day 14 determined by investigators, study drug will not be administered after discharge.
6. [redacted]
7. If the routine tests at a local laboratory [redacted] can be measured instead.
8. Some editorial changes to improve the reading and quality of the document

Sironax

Product Name: SIR1-365

Study Number: SIR365-US-101

Protocol Approval

Protocol Title	A Multicenter, Randomized, Double-blinded, Placebo-controlled Study to Assess Safety and Efficacy of SIR1-365 in Patients with Severe COVID-19
Protocol Number	SIR365-US-101
Protocol Date	April 8th, 2021

Version 2.4 accepted and approved by:

Signature _____ Date Apr 8, 2021

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A multicenter, randomized, double-blinded, placebo-controlled study to assess safety and efficacy of SIR1-365 in hospitalized patients with severe COVID-19."

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Version 2.4 issued on April 8th, 2021, the International Council on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Sironax or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Sironax.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

Table of Contents

1. Protocol Synopsis

Study Title: A multicenter, randomized, double-blinded, placebo-controlled study to assess safety and efficacy of SIR1-365 in patients with severe COVID-19
Sponsor: Sironax USA, Inc, a Subsidiary of Sironax, Ltd (Sironax)
Study Number: SIR365-US-101
Study Phase: Phase 1b study
Investigational Product, Dosage and Mode of Administration: SIR1-365 is a receptor-interacting protein kinase 1 (RIP1) inhibitor that is under development as a new investigational drug for the treatment of inflammatory diseases. SIR1-365 will be supplied as 10 mg, 25 mg, and 100 mg tablets. The study drug will be administered orally with water if patients can swallow or given as a disintegrated suspension via a nasogastric (NG) tube if patients cannot swallow.
Reference Therapies, Dosage and Mode of Administration: Placebo tablets matching SIR1-365 tablets
Objectives: <u>Primary Objective:</u> • To evaluate overall safety and tolerability of SIR1-365 in patients with severe COVID-19 <u>Secondary Objectives:</u> • To assess the clinical efficacy of SIR1-365 in patients with severe COVID-19 • To assess the effects of SIR1-365 on multiple inflammatory biomarker levels including C-reactive protein (CRP), ferritin, lymphocyte and neutrophil counts, cytokines, and chemokines [redacted] • To assess the effects of SIR1-365 on biomarkers indicative of kidney injury in patients with severe COVID-19

- To assess the effects of SIR1-365 on biomarkers indicative of cardiovascular endothelial cell damage in patients with severe COVID-19
- To measure plasma SIR1-365 and metabolite levels in patients with severe COVID-19

Introduction:

Study Rationale

There is evidence of a hyperinflammatory response in patients with COVID-19 coupled with an upregulation of pro-inflammatory biomarkers including cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-1β, IL-6, etc. and other inflammatory biomarkers such as CRP, and ferritin. The elevated plasma inflammatory biomarker levels are associated with disease severity and progression. Cytokine is produced in most types of inflammation especially in the acute phase and is important in the coordination and development of the inflammatory response. However, too much production of cytokine for too long becomes destructive. It has been hypothesized that anti-inflammatory drugs including anti-TNF-α and anti-IL-1 therapies should be evaluated in patients with COVID-19 upon hospital admission to prevent disease progression requiring intensive care support. Indeed, several studies have indicated clinical benefits of anti-TNF-α and anti-IL-1 agents in COVID-19 patients.

As a multiple functional serine/threonine protein kinase, RIP1 mediates the downstream effects of multiple cytokines. For example, RIP1 plays a key role in TNF-α induced systemic inflammatory response syndrome (SIRS) in mouse models. Mice harboring RIP1 kinase dead mutation were fully resistant to TNF-α-induced hypothermia and mortality, suggesting that RIP1 kinase inhibitors could

[redacted]

Dose Selection Rationale

In the mouse SIRS study, oral administration of SIR1-365 at [redacted] mg/kg resulted in about 50%, 75% and 100% survival rate, respectively. The plasma C_{max} levels for the 3 doses wer[redacted] respectively. Since in vitro cell function assays have shown that the potency of SIR1-365 is ab[redacted] higher in human cells than mouse cells, the approximate plasma levels of SIR1-365 to achieve similar effects in humans is estimated to[redacted]

Based on the PK data obtained from the completed multiple ascending dose (MAD) study in healthy adult subjects, the trough levels with 100 mg, three times a day (TID) [redacted] etween Day 1 and Day 10, respectively, which is between the estimated human exposure to achieve [redacted] survival rate. The peak levels with 100 mg TID ranged from 400 to 500 ng/ml, which is above the EC[redacted] r RIP1 inhibition. Therefore, the initial dose chosen for this study is 100 mg, TID (or 300 mg per day).

The AUC_{0-8} with 100 mg TID ranged fro[redacted] (or AUC_{0-24} aroun[redacted] Since the observed AUC_{0-24} with the no observable adverse effect level (NOAEL) dose[redacted] 28-day GLP studies in monkeys was[redacted] he dose of 100 mg TID should have a safety margin betwee[redacted] AUC basis.

Based on the safety, preliminary efficacy, biomarker, and PK results of 100 mg TID, additional dose level(s) may be evaluated.

Summary of Non-Clinical Safety Data

[redacted]

Summary of Clinical Data

A randomized, double-blinded, placebo-controlled SAD study and MAD study have demonstrated that a single oral administration of SIR1-365 at 10, 30, 100, 300 and 600 mg and multiple doses at 50 mg TID, 100 mg TID, 200 mg TID were safe and well tolerated by the study subjects. The reported AEs were mild to moderate events with no need of intervention and resolved in a few days. No subject discontinued from the study. PK data showed a good dose proportionality of plasma SIR1-365 concentrations at the 5 single dose and 3 multiple dose cohorts in healthy volunteers. Peak plasma exposure was achieved around 1-2 hours after dose, and the half-life ($T_{1/2}$) was around 6-7 hours depending on the doses.

A randomized, open-label, 2-way crossover study has demonstrated that food does not significantly affect the bioavailability of SRI1-365 after oral administration.

Comparable PK profiles have been seen after dosing with either tables or suspension, indicating that SIR1-365 tablets can be administered as a suspension via a gastric tube in those patients who cannot swallow the tablets.

A randomized, open-label, 2-way crossover study has shown that SIR1-365 can inhibit the activity of CYP450 isoform 2C19. Thus, medications that are mainly metabolized via CYP450 isoform 2C19 will be excluded in this study.

Study Design:

This will be a multicenter, randomized, double-blinded, placebo-controlled study to evaluate safety and efficacy of SIR1-365 in patients with severe COVID-19. The primary objective is to assess the overall safety and tolerability of SIR1-365 administered orally at 100 mg, TID for 14 days relative to the placebo group. The secondary objectives are to assess the effects of SIR1-365 on clinical efficacy endpoints, and the biomarkers indicative of inflammation, target engagement and kidney injury as well as plasma SIR1-365 levels.

Enrolled patients will receive either SIR1-365 at 100 mg TID or matching placebo in addition to standard-of-care treatment for up to 14 consecutive days either as tablets or as oral suspension via a NG tube if a patient cannot swallow.

Patients could be hospitalized and treated for up to 14 days. Patients will be assessed daily while hospitalized. If the patients are discharged from the hospital before Day 14, all the assessments planned for Day 14 should be carried out before discharge. If a patient is still hospitalized after Day 14, no study drug will be administered after the last dose on Day 14.

It is preferred that the follow-up visit is in person to obtain safety laboratory tests. However, infection control or other restrictions may limit the ability of the patients to return to the clinic. In this case, the follow-up visit may be conducted by phone and only safety data will be obtained. Study drugs will not be administered for early discharged patients.

Food and water will be allowed as needed.

To fit into the clinical practice of treating patients with severe COVID-19, screening visit and baseline visit can be combined in some patients. In that case, the number of dosing could be less than 3 times on that day. ECG, laboratory test and other test results obtained within 24 hours prior to consent can be used as baselines.

Safety will be assessed based on the findings of adverse events (AEs), vital signs, safety laboratory tests per local lab, 12-lead electrocardiography (ECG) per local ECG machine, and physical

[redacted]

Several clinical parameters including PaO2/FiO2 ratio or oxygen saturation (pulse oximetry), a WHO ordinal scale to assess clinical improvement, number of days without oxygen use, and length of hospital stay, all-cause mortality rate, etc. will be assessed.

[redacted]

For the determination of plasma SIR1-365 and metabolite levels, one blood sample will be collected from each patient within 30 min before and 2 hours (±5 min) after the 1st dose on Day 1, respectively. On Days 7 and 14, one blood sample will be collected within 30 min before and 2 hours (±5 min) after the 2nd dose, respectively. Each plasma sample will be divided into 4 parts: 2 for drug level analysis and 2 f[redacted]conducted by a central lab. Collected samples may also be used for the analysis of additional biomarkers and SIR1-365 metabolites in the future.

For those patients who complete the 14-day treatment period with SIR1-365, investigator will decide appropriate treatments for the period from Day 15 to Day 28. A follow-up visit will be scheduled for Day 28 (±3 days) or 14 (±3) days after the last dose for those who are discharged from the hospital before Day 14.

If an additional dosing cohort, or extended evaluation phase is added to the protocol to allow a more complete examination of the safety and efficacy of the compound, the protocol will be amended, and the new cohort(s) added prior to completion of the current study.

Safety Monitoring Plan:

Safety will be carefully monitored during the study based on a study specific safety monitoring plan that consists of the following main components:

Grade System of AEs and Findings

Severity of AEs, clinical findings and safety laboratory findings will be graded based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Independent Data Monitoring Committee

During the study, unblinded safety, biomarker, and clinical efficacy data will be reviewed by an independent data monitoring committee (IDMC). The IDMC includes a safety physician and two clinical physicians, and should be independent from the investigators, patients and the sponsor to ensure trial integrity. A study specific IDMC Charter will be developed prior to study initiation.

The IDMC is expected to meet when approximately 20 and 40 patients are enrolled and treated for about 7 days. Reports of suspected unexpected serious adverse reactions (SUSARs) and Serious Adverse Events (SAEs) will be forwarded to the IDMC Members on a weekly basis for review. The IDMC Chair may request additional patient information pertaining to these reports as necessary or request an ad hoc IDMC meeting to discuss any cases of concern based upon review of these events.

Pre-specified Treatment Discontinuation Rules

The presence of any of the following events may lead to treatment discontinuation based on the judgement of the site investigator with consultation with the medical monitor or IDMC:

- Patients started utilization of mechanical ventilation
- Patients experienced heart failure during the study
- Patients experienced respiratory failure during the study
- Patients experienced moderate to severe hepatic impairment during the study
- Patients experienced acute renal injury requiring dialysis during the study
- Any serious AE (SAE) assessed as related to study drug.

Pre-specified Study Halting/Stopping Rules

Enrollment in the study will be halting upon receiving reports of, until the IDMC is able to review the data and determine the safety of continuing with the study:

- Excess of two deaths in the treatment group which both the investigator and the IDMC agree are probably or definitely related to the investigational product.

or

- Excess of three deaths from any cause in the treatment group

In addition, any report of death or life-threatening SAE whose causal relationship to the study drug is judged to be probably or definitely related to investigational product by the treating investigator

must be reviewed by the IDMC within 7 calendar days after sponsor is notified. If this does not happen, or there is not sufficient information provided for the IDMC to fully review the case, enrollment will be halted until such time as the IDMC can review the case and determine the safety of proceeding with the study.

The study could be stopped if:

- New information or other evaluation regarding the safety of the study drug indicates a change in the known risk profile for the study drug, such that the risk is no longer acceptable for patients participating in the study. The IDMC or PI could recommend study termination, but the decision for study termination will be made by the Sponsor, the Institutional Review Board (IRB), or Regulatory Authority
- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor, the IRB, or Regulatory Authority decide to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. This procedure will be followed by the investigational site during termination or study suspension.

Planned Patient Number:

Due to the exploratory nature of this study, the sample size is not calculated based on statistical significance on any parameters. However, a sample size of 30 patients per group is considered to be sufficient to detect marked differences in the overall safety profile between treatments with a pre-specified safety monitoring plan. Furthermore, this sample size provides estimates of treatment differences in some clinical efficacy endpoints and the levels of some biomarkers such as CRP, for use in planning future studies. Therefore, approximately 30 patients will be enrolled for each group (total 60) in this study.

Patient Selection Criteria:

Inclusion Criteria:

Patients can be enrolled into this study if all of the following criteria are met at screening visit:

1. Hospitalized patient with clinical diagnosis of SARS-CoV-2 virus infection per World Health Organization criteria including positive nucleic acid test of any specimen (e.g., respiratory, blood, or other bodily fluid) within 2 weeks prior to screening.
2. Symptoms suggestive of severe systemic illness with COVID-19, which could include any of the following symptoms: fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath at rest, or respiratory distress.
3. Clinical signs indicative of severe systemic illness with COVID-19, which could include any of the following clinical signs: respiratory rate $\geq$ 30 per minutes, heart rate $\geq$ 125 per minute,

SpO2 ≤ 93% on room air, PaO2/FiO2 ratio < 300 mmHg, or lung infiltration >50% on chest X-ray imaging.

4. Patients with plasma CRP level >50 mg/L or 4x upper limit of normal range at screening.
5. Men or women ≥18 but ≤80 years of age at the time of signing the informed consent form.
6. Use of home oxygen is allowed
7. Patient is able to understand the purpose and risks of the study and provide signed and dated informed consent or have a legal representative provide consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).
8. Patient is able to swallow tablets or receive delivery of oral suspension via a nasogastric tube.
9. Patient agrees not to participate in another interventional study after signing the informed consent form and until the end of study (EoS) visit has been completed.

Exclusion Criteria:

Patients should be excluded from this study if any of the following criteria is met at screening visit:

1. Patient requires 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. However, periodically delivered at flow rates >20 L/min with fraction of delivered oxygen ≥ 0.5 is allowed), noninvasive positive pressure ventilation, extracorporeal membrane oxygenation (ECMO), or clinical diagnosis of respiratory failure.
2. Patient with shock defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressor.
3. Patient with multi-organ dysfunction or failure based on investigator's determination.
4. Patient is unlikely to survive beyond 2 days at the discretion of Investigator.
5. Patient has used chronic systemic corticosteroids (for example, >32 mg/day methylprednisolone or equivalent) within 2 weeks prior to screening. However, dexamethasone at a stable dose ≤6 mg/day or equivalent (such as 31.25 mg of Solu-Medrol) is allowed. One dose of dexamethasone at >6 mg but ≤12 mg or equivalent is allowed, provided baseline CRP level is measured 24 hours after the dexamethasone dosing at >6 mg but ≤12 mg.
6. Patient with moderate to severe hepatic impairment by Child-Pugh scoring system.

7. Patients with severe kidney injury requiring dialysis.
8. Patient with any of the following abnormal laboratory values: absolute neutrophil count (ANC) < 2,000 per mm^3, or platelets count <50,000 per mm^3, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 x upper limit of normal (ULN) detected within 24 hours at screening (per local lab).
9. Patient has uncontrolled or untreated symptomatic arrhythmias, myocardial infarction or congestive heart failure within the 6 weeks prior to screening.
10. Patient has received immunomodulatory drugs within 1 month prior to screening, including anti-cytokine therapies targeting TNF-α, IL-1, IL-6, interferon-beta, or Bruton Tyrosine Kinase (BTK). However, remdesivir, convalescent plasma therapy or hydroxychloroquine/chloroquine is allowed in this study.
11. Patient with a code status of do-not-resuscitate (DNR) or cardiopulmonary resuscitate (CPR) Select.
12. Patient with positive results for human immunodeficiency virus (HIV) or hepatitis B or C test.
13. Patient has known active tuberculosis (TB), history of uncontrolled TB, sepsis induced by systemic bacterial or fungal infections within 4 weeks prior to screening.
14. Patient is taking any medication that is mainly metabolized by CYP450 2C19 (a list of commonly used medications that are mainly metabolized by CYP450 2C19 can be found in Appendix 6). The investigator could provide an alternative medication that is not mainly metabolized by CYP450 2C19.
15. Female patient who is pregnant or lactating or has a positive serum pregnancy test within 72 hours prior to screening and/or randomization, has been pregnant within 6 months before screening or breastfeeding within 3 months before screening or who is planning to become pregnant within the total study period. Woman of Childbearing Potential (WOCBP) must agree to use a highly effective method of contraception consistently and correctly as described in Appendix 5.
16. Patient has a known or suspected hypersensitivity to SIR1-365 or any components of SIR1-365 tablets.
17. Patient has received any investigational drug within 30 days or 5 half-lives, whichever is longer, prior to screening.
18. Patient has any other condition, which makes the patient unsuitable for study participation.

Duration of Study:

The study will include 3 periods: screening period (up to 7 days), treatment period (up to 14 days), and a follow-up visit (approximately on Day 28 (±3 days) or 14 (±3) days after the last dose for those who are discharged from the hospital before Day 14).

Outcome Measures:

Primary Outcome Measure:

- Proportion (%) of patients with any TEAEs during the treatment period (Baseline to Day 14)

Secondary Outcome Measures:

Safety Endpoints:

- Proportion (%) of patients with any AEs, SAEs and drug-related AEs during the study (Baseline to Day 14 and Day 28)
- Proportion (%) of patients with clinically significant abnormality in clinical laboratory tests and ECG during the study (Baseline to Day 14 and Day 28)
- Change in parameters for coagulopathy including [redacted] ng the study (Baseline to Day 14 and Day 28)
- Change in parameters of cardiac function including [redacted] ng the study period (Baseline to Day 14 and Day 28)

Changes in safety outcomes in patient populations with different Baseline levels of inflammatory biomarkers to assess the correlation of biomarker profile to safety outcomes.

Clinical Efficacy Endpoints:

- Change from Baseline to Day 7 and Day 14 in PaO2/FiO2 ratio
- Time to improvement of oxygenation defined as oxygen saturation (pulse oximetry) >93% and increased ≥1% from Baseline breathing only room air in the 48 hours preceding the measurement during the study (Baseline to Day 28)
- Number of days without oxygen use during the study (Baseline to Day 28)
- Change from Baseline to Days 7, 14 and 28 in the score of the WHO ordinal scale
- Proportion (%) of patients with clinical improvement defined as a reduction of 2 points in the WHO ordinal scale during the study (Baseline to Day 28).
- Number of days hospitalized during the study (Baseline to Day 28)
- Proportion (%) of patients free of respiratory failure during the study (Baseline to Day 28)

- All-cause mortality rate during the study (Baseline to Day 28)

Changes in clinical efficacy endpoints in patient populations with different Baseline levels of inflammatory biomarkers to assess the correlation of biomarker profile to clinical efficacy outcomes

Inflammatory Biomarker Measures:

- Change from Baseline to Day 7 and to Day 14 in plasma CRP level
- Time and number of the patients to reach 50% reduction from Baseline in plasma CRP level during the treatment period (Baseline to Day 14)
- Change from Baseline to Day 7 and Day 14 in inflammatory biomarker levels including ferritin, lymphocytes and neutrophil to lymphocyte ratio.
- Change from Baseline to Day 7 and Day 14 in serun
- Change from baseline to Day 7 and Day 14 in serun

Biomarker Assessment for Kidney Injury

- Change from Baseline to Day 7 and Day 14
- Change from Baseline to Day 7 and Day 14

Biomarker Assessment for CV Endothelial Cell Damage

- Change from Baseline to Day 7 and Day 14 in
- Change from Baseline to Day 7 and Day 14
- Change from Baseline to Day 7 and Day 14

Biomarker Assessment for Target Engagement

- Change from Baseline to Day 7 and Day 14
- Change from Baseline to Day 7 and Day 14

Additional biomarkers may be assessed as appropriated. Details about sample collection and biomarker analysis will be provided in laboratory manual.

Measurement of Plasma Drug and metabolite Levels

Blood samples will be collected at defined timepoints. The harvested plasma will be split into two approximately equal aliquots, labeled and stored for PK analysis. Plasma parent drug and metabolite levels will be measured by validated bioanalytical method following GLP guidance.

Additional analysis may be performed as appropriated. Details about sample collection and analysis will be provided in laboratory manual. Data will not be shared with any 3rd party.

Statistical Analysis

A 2-sided alpha-level of 0.05 will be used for construction of confidence intervals. No adjustment for multiple endpoints will be employed. Although the study is not powered for hypothesis testing of secondary endpoints, p-values will be generated to aid interpretation in addition to confidence intervals about the estimates.

Clinical Efficacy Parameters

Change from Baseline in the PaO_2/FiO_2 ratio as a continuous variable will be summarized by visit and treatment using both simple descriptive statistics and model-based estimates obtained from an analysis of covariance model with terms for treatment as a class variable and the baseline score as a continuous covariate.

Time to improvement in oxygenation will be analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% confidence interval for SIR1-365 dose vs placebo.

Number of days without oxygen use in the first 28 days will be summarized descriptively and an estimate of the difference mean numbers of days will be provided along with a corresponding 95% confidence interval based on a 1-way ANOVA model with a single term for treatment.

Descriptive summaries of WHO ordinal scale, number of days hospitalized, patients with respiratory failure and all-cause mortality will be provided.

Safety Parameters

Safety parameters will be summarized using descriptive statistics for patients who receive study drug (SIR1-365 or placebo).

TEAEs are defined as AEs that commence or worsen after the first dose of study medication during the study. TEAEs will be analyzed descriptively including 2-sided 95% CI for between-group (SIR1-365 – placebo) incidence rates. TEAEs analyzed will include, but not necessarily limited to, the following:

- At least 1 TEAE
- At least 1 Related TEAE
- At least 1 SAE
- At least 1 TEAE of severe intensity
- Individual TEAE Preferred terms
- Individual TEAE Preferred terms considered related to study medication

TEAEs occurring during the 14-day treatment period will include those with onset in the first 14

days, irrespective of actual days of treatment, where study day 1 is the date of the first dose of study medication. All TEAEs with onset ≤ 28 days will be summarized similarly.

Biomarker Levels

The difference between treatments in Day 7 [redacted] l be analyzed using an ANCOVA model with terms for treatment as a class variable and the baseline value as a continuous covariate [redacted] ill be log-transformed (natural log) for analysis. Comparison of the SIR1-365 group vs placebo will be constructed based on least-squares means from the model. The results will be back transformed for presentation including 95% CI constructed for both within and between treatment estimates. Timepoints other than Day 7 will be analyzed similarly.

Time (days) to 50% reduction from baseline [redacted] uring the study will be analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% confidence interval for SIR1-365 dose vs placebo.

All biomarker level data will be summarized using descriptive statistics by treatment

Plasma Drug and Metabolite Levels

Plasma drug and metabolite level data will be summarized using descriptive statistics by treatment.

This study will be conducted in accordance with the guidelines for Good Clinical Practice (GCP) and GLP. Study drugs will be manufactured in accordance with the guidelines for Good Manufacturing Practice (GMP).

2. Introduction

2.1. Overview of COVID-19

Beginning in December 2019, a novel coronavirus, designated SARS-CoV-2, has caused an international outbreak of illness termed Coronavirus Disease 2019 (COVID-19). The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death.

So far, there are no specific therapeutic agents for coronavirus infections, although the corticosteroid dexamethasone and antiviral remdesivir have been recommended for patients with severe COVID-19.

There is evidence of hyperinflammatory response in patients with COVID-19 coupled with an upregulation of pro-inflammatory biomarkers including cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-1β, IL-6, etc. and other inflammatory biomarkers such as C-reactive protein (CRP) and ferritin. The elevated plasma inflammatory biomarker levels are associated with disease severity and progression. Cytokine is produced in most types of inflammation especially in the acute phase and is important in the coordination and development of the inflammatory response. However, prolonged excess production of cytokine becomes destructive. It has been hypothesized that anti-inflammatory drugs including anti-TNF-α and anti-IL-1 therapies should be evaluated in patients with COVID-19 upon hospital admission to prevent disease progression to the requirement for intensive care support. Indeed, several studies have indicated clinical benefits of anti-TNF-α and anti-IL-1 agents in COVID-19 patients.

2.2. Overview of RIP1 and SIR1-365

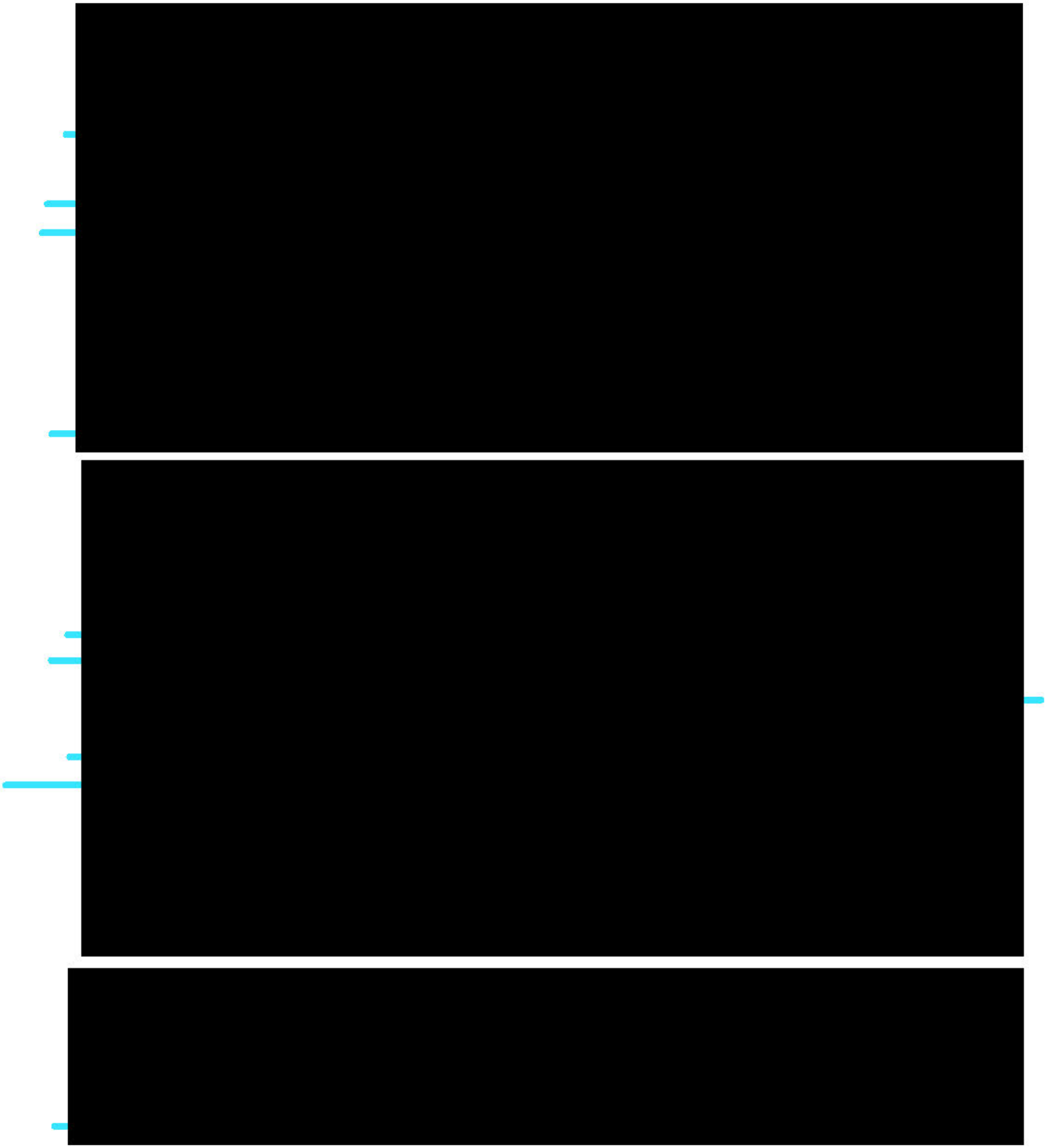
Receptor-interacting protein 1 (RIP1) is a serine/threonine protein kinase, which was initially identified as a death domain-containing protein that interacts with the death domain of death receptor Fas. RIP1 is comprised of a kinase domain at its N terminus, a death domine at its C terminus and a RHIM (RIP homotypic interaction motif) at the middle region of the protein. The death domain and RHIM domain are both protein interaction domains. RIP1 is recruited to either Fas or to TNFR1 complex via its death domain, whereas it interacts with RIP3 via the RHIM domain.

RIP1 mediates the downstream effects of multiple biological activities including: 1) RIP1 mediates TNFα induced NFκB activation pathway in a kinase-independent manner. 2) RIP1 mediates caspase8-FADD dependent apoptosis pathway in a kinase-dependent manner. 3) RIP1 mediates RIP3-MLKL dependent necroptosis pathway in a kinase-dependent manner. 4) RIP1 suppresses caspase-8 dependent apoptosis in a kinase-independent manner. 5) RIP1 suppresses ZBP1-RIP3-MLKL dependent necroptosis in a kinase-independent manner. 6) RIP1 mediates cytokine production and secretion in myeloid cells in a kinase-dependent but cell death-independent manner. 7) RIP1 mediates RIP3-kinase-dead-mutant-induced apoptosis in a kinase-independent manner.[1,2,3]

Therefore, RIP1 inhibitors may be advantageous over selective inhibitors for a specific cytokine to reduce inflammatory response.

Genetic removal of RIP1 in a mouse model led to perinatal death, caused by the loss of RIP1's ability to suppress capase8-dependent apoptosis and ZBP1-RIP3-MLKL dependent necroptosis. Both suppressing abilities require RIP1's function as a scaffold protein instead of its kinase activity. [4,5] Nevertheless, mice containing RIP1 kinase dead knock-in mutants showed no defect in development and growth, indicating RIP1's kinase activity is not essential for embryonic development or for animal growth. [6] Moreover, RIP1 kinase dead knock-in mice were resistant to various animal disease models, such as TNFα-induced systemic inflammatory response syndrome (SIRS), chronic intestine inflammation, autoimmune skin disorder, and multiple sclerosis. [7,8]

RIP1 protein contains a unique allosteric pocket located in its kinase domain, which allows the development of highly selective type III kinase inhibitors. Using several different RIP1 kinase inhibitors in various animal models has demonstrated that blocking RIP1's kinase activity could prevent TNFα induced systemic inflammatory response syndrome, alleviate the progression of Alzheimer's disease, amyotrophic lateral sclerosis, male reproductive aging, chemotherapy-associated kidney injury, ischemia reperfusion injury to organs such as heart, brain, retina, and kidney, as well as colitis and multiple sclerosis. [7,8,9,10]



[redacted]

2.4. Summary of Clinical Data

The following studies have been completed in Australia:

- A randomized, double-blinded, placebo-controlled SAD study and MAD study were conducted in Australia to evaluate the safety, tolerability and PK of SIR1-365 in healthy adult volunteers. The results demonstrated that a single oral administration of SIR1-365 at 10, 30, 100, 300 and 600 mg and multiple doses at 50 mg TID, 100 mg TID, 200 mg TID were safe and well tolerated by the study subjects. The reported AEs were mild to moderate events with no need of intervention and resolved in a few days. No subject discontinued from the study. PK data showed a good dose proportionality of plasma SIR1-365 concentrations at the 5 single dose and 3 multiple dose cohorts in healthy volunteers. Peak plasma exposure was achieved around 1-2 hours after dose, and the half-life ($T_{1/2}$) was around 6-7 hours depending on the doses.
- A randomized, open-label, single-dose, 2-way crossover study was conducted to assess the effect of food on bioavailability of SIR1-365 tablet after a single oral dose at 100 mg. The results of this study demonstrated that food does not significantly affect the bioavailability of SRI1-365 after oral administration. Thus, SIR1-365 oral tablets can be administered before or after meal.
- An open-label study was conducted to assess the PK profile of SIR1-365 given as an oral disintegrated suspension. The results of this study demonstrated that the plasma SIR1-365 concentrations-time curves and PK parameters were comparable when SIR1-365 was administered at a single oral dose of 100 mg either as a disintegrated suspension in the suspension PK study or as a solid tablet in the SAD study. Thus, SIR1-365 tablets can be administered as a disintegrated suspension via a gastric tube in those patients who cannot swallow the tablets.

- An open-label study was conducted to assess possible inhibitory effects of SIR1-365 on the activities of CYP450 isoforms 2C19 in healthy volunteers using sensitive index substrate omeprazole. The results of this study demonstrated that SIR1-365 can inhibit the activity of CYP450 isoform 2C19. Thus, medications that are mainly metabolized via CYP450 isoform 2C19 should be excluded in patient studies.

2.5. Benefit/Risk Assessment

RIP1 inhibitors may be beneficial for treatment of severe COVID-19. However, no RIP1 inhibitors have been assessed in large clinical studies for any indication.

The SAD and MAD studies showed that a single oral administration of SIR1-365 at 10, 30, 100, 300, and 600 mg and repeated oral administration of SIR1-365 at 50, 100 and 200 mg, TID for 10 days were safe and well tolerated. The reported AEs were mild to moderate events that resolved in few days without treatment. No deaths, discontinuations, or SAEs were reported.

A safety monitoring plan has been developed to carefully monitor safety during the current study. An independent data monitoring committee (IDMC) will review unblinded safety, efficacy, pharmacodynamic (PD) and PK data every month based on a study specific IDMC Charter developed prior to study initiation. At any time, the IDMC may recommend stop patient treatment and/or terminate study based on pre-specified treatment discontinuation and study stopping rules.

Furthermore, investigators will be instructed to use local clinical laboratory for safety assessments in a timely manner.

Therefore, benefit/risk assessment did not indicate any significant concern at this stage.

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of SIR1-365 can be found in the current IB of SIR1-365.

3. Trial Design

3.1. Overall Design

This will be a multicenter, randomized, double-blinded, placebo-controlled study to evaluate safety and efficacy of SIR1-365 in hospitalized patients with severe COVID-19. The primary objective is to assess the overall safety and tolerability of SIR1-365 administered orally at 100 mg, three times per day (TID) for up to 14 consecutive days relative to the placebo group. The secondary objectives are to assess the effects of SIR1-365 on clinical efficacy endpoints, and the biomarkers indicative of inflammation, target engagement and kidney injury as well as SIR1-365 PK.

Approximately 60 eligible patients will be randomly assigned at a 1:1 ratio to receive either SIR1-365 at 100 mg, TID or matching placebo for up to 14 consecutive days. Patients could be hospitalized for up to 14 days. Patients will be assessed daily while hospitalized. If the patients are discharged from the hospital before Day 14, all the assessments planned for Day 14 should be carried out before discharge. If a patient is still hospitalized after Day 14, no study drug will be administered after the last dose on Day 14.

It is preferred that the follow-up visit is in person to obtain safety laboratory tests. However, infection control or other restrictions may limit the ability of the patients to return to the clinic. In this case, the follow-up visit may be conducted by phone and only safety data will be obtained. Study drugs will not be administered for early discharged patients.

All randomized patients will receive standard supportive medical care for treatment of COVID-19 throughout the study. Follow-up visit will be scheduled approximately on Day 28 (±3) or 14 (±3) days after the last dose for those who are discharged from the hospital before Day 14.

SIR1-365 will be administered orally either as intact tablets with water if patient can swallow or as disintegrated suspension form to be delivered via a nasogastric (NG) tube if patient cannot swallow. Food and water will be allowed as needed.

To fit into the clinical practice of treating patients with severe COVID-19, screening visit and baseline visit can be combined in some patients. In that case, the number of dosing could be less than 3 times on that day. ECG, laboratory test and other test results obtained within 24 hours prior to consent can be used as baselines.

Safety will be assessed based on the findings of adverse events (AEs), vital signs, safety laboratory tests per local lab, 12-lead electrocardiography (ECG) per local ECG machine, and physical [redacted]

Clinical efficacy will be assessed by measuring [redacted] PaO2/FiO2 ratio, time to improvement of oxygenation, number of days without oxygen use, a WHO ordinal scale to assess clinical improvement, length of hospital stay, percentage of patients free of respiratory failure, and all-cause mortality.

[redacted]

Correlation of biomarker levels to efficacy and safety outcomes will be assessed by analyzing the changes in efficacy and safety outcomes in patient populations with different Baseline levels of inflammatory biomarkers.

[redacted]

For the measurement of trough and peak plasma SIR1-365 and metabolite levels, one blood sample will be collected from each patient within 30 min before and 2 hours (±5 min) after the 1st dose on Day 1, respectively. On Days 7 and 14, one blood sample will be collected within 30 min before and 2 hours (±5 min) after the 2nd dose, respectively. The harvested plasma sample will be split into 4 approximately equal aliquots: 2 for drug level analysis an[redacted]o be conducted by a central lab. Collected samples may also be used for the analysis of additional biomarkers and SIR1-365 metabolites in the future.

The overall duration of the study will be up to 35 days, including up to 7 days for screening, up to 14 days for treatment, and a follow-up visit on approximately Day 28 (±3 days) or 14 (±3) days after the last dose for those who are discharged from the hospital before Day 14.

For those patients who complete the 14-day treatment period with SIR1-365, the investigator will decide appropriate treatments for the period from Day 15 to Day 28.

If an additional dosing cohort, or extended evaluation phase is added to the protocol to allow a more complete examination of the safety and efficacy of the compound, the protocol will be amended, and the new cohort(s) added prior to completion of the current study.

3.2. Scientific Rationale for Trial Design

The randomized, double-blind, placebo-controlled design is considered the most convincing research design. Randomization eliminates the influence of unknown or immeasurable confounding variables and blinding eliminates confounding by cointerventions, thus minimizing bias and incorrect estimate of treatment effect. The main reason to have a placebo group is to be sure that any observed effects are actually caused by the test drug but not some other factors.

For ethical and medical reasons, standard of care treatments for COVID-19 will be provided to all patients. Study treatments (either SIR1-365 or matching placebo) will be given as add-on therapy.

3.3. Justification for Dose Selection

In the mouse SIRS study, oral administration of SIR1-365 at [redacted] resulted in about 50%, 75% and 100% survive rate, respectively. The mean plasma C_{max} levels for the 3 doses were [redacted] espectively. Since in vitro cell function assays have shown that the potency of SIR1-365 is abou[redacted]gher in human cells than mouse cells, the approximate plasma levels of SIR1-365 to achieve similar effects in human could be aroun[redacted] ng/ml.

Based on the PK data obtained from the completed MAD study in healthy adult subjects, the trough levels with 100 mg, TID we[redacted]ween day 1 and day 10, respectively, which is between the estimated human exposure t[redacted]survival rate. The peak levels with 100 mg TID ranged fro[redacted]which is above the EC[redacted] [redacted]P1 inhibition. Therefore, the initial dose chosen for this study is 100 mg, TID (or 300 mg per day).

The AUC_{0-8} with 100 mg TID ranged fro[redacted]or AUC_{0-24} aroun[redacted] [redacted]g/mL). Since the observed AUC_{0-24} with NOAEL dos[redacted]8-day GLP studies in monkeys wa[redacted]e dose of 100 mg TID should have a safety margin betwee[redacted] [redacted]n an AUC basis.

Based on the safety, preliminary efficacy, biomarker and PK results of 100 mg TID dose, additional dose(s) may be added for further evaluation.

4. Objectives and Outcome Measures

Objectives	Outcome Measures
Primary	
Primary Objective: To assess the overall safety and tolerability of SIR1-365 in patients with severe COVID-19	**Primary Safety Measure** • Proportion (%) of patients with any TEAEs during the treatment period (Baseline to Day 14) **Secondary Safety Measures** • Proportion (%) of patients with any AEs, SAEs and drug-related AEs during the study (Baseline to Day 14 and Day 28) • Proportion (%) of patients with clinically significant abnormality in clinical laboratory tests and ECG during the study (Baseline to Day 14 and Day 28) • [redacted] • [redacted] Changes in safety outcomes in patient populations with different Baseline levels of inflammatory biomarkers to assess the correlation of biomarker profile to safety outcomes.
Secondary	
1. To assess the clinical efficacy of SIR1-365 in patients with severe COVID-19	<u>Clinical Efficacy Endpoints</u> • Change from Baseline to Day 7 and Day 14 in PaO2/FiO2 ratio • Time to improvement of oxygenation defined as oxygen saturation (pulse oximetry) >93% and increased by ≥1% from Baseline breathing only room air in the 48 hours preceding the measurement during the study (Baseline to Day 28) • Number of days without oxygen use during the study (Baseline to Day 28)

Objectives	Outcome Measures
	• Change from Baseline to Days 7, 14 and 28 in the score of the WHO ordinal scale • Proportion (%) of patients with clinical improvement defined as a reduction of 2 points in the WHO ordinal scale during the study (Baseline to Day 28). • Number of days hospitalized during the study (Baseline to Day 28) • Proportion (%) of patients free of respiratory failure during the study (Baseline to Day 28) • All-cause mortality rate during the study (Baseline to Day 28) Changes in clinical efficacy endpoints in patient populations with different Baseline levels of inflammatory biomarkers to assess the correlation of biomarker profile to clinical efficacy outcomes
2. To assess the effects of SIR1-365 on multiple inflammatory biomarker levels including CRP, ferritin, lymphocyte and neutrophil counts, cytokines and chemokines	<u>Inflammatory Biomarker Measures</u> • Change from Baseline to Day 7 and Day 14 i[redacted] levels • Time and number of the patients to reach 50% reduction from Baseline i[redacted]uring the treatment period (Baseline to Day 14) • Change from Baseline to Day 7 and Day 14 in inflammatory biomarke[redacted]ymphocytes and neutrophil to lymphocyte ratio. • [redacted] • [redacted]
3. To assess the effects of SIR1-365 on biomarkers indicative of kidney injury	<u>Biomarker Assessment for Kidney Injury</u> • Change from Baseline to Day 7 and Day 14 i[redacted]

Objectives	Outcome Measures
in patients with severe COVID-19	• Change from Baseline to Day 7 and Day 14 [redacted]
4. To assess the effects of SIR1-365 on biomarkers indicative of vascular endothelial cell damage in patients with severe COVID-19	Biomarker Assessment for CV Endothelial Cell Damage • Change from Baseline to Day 7 and Day 14 i[redacted] • Change from Baseline to Day 7 and Day 14 [redacted] • Change from Baseline to Day 7 and Day 14 i[redacted]
5. To assess the effects of SIR1-365 on biomarkers indicative of target engagement in patients with severe COVID-19	Biomarker Assessment for Target Engagement • Change from Baseline to Day 7 and Day 14 in[redacted] • Change from Baseline to Day 7 and Day 14 in[redacted] Additional biomarkers may be assessed as appropriated. Details about sample collection and biomarker analysis will be provided in laboratory manual.
6. To measure plasma SIR1-365 levels in patients with severe COVID-19	Measurement of Plasma SIR1-365 and metabolite Levels One blood sample will be collected from each patient within 30 min before and 2 hours (±5 min) after the 1st dose on Day 1, respectively. On Days 7 and 14, one blood sample will be collected within 30 min before and 2 hours (±5 min) after the 2nd dose, respectively. Plasma SIR1-365 and metabolite levels will be measured by validated bioanalytical method following GLP guidance.

5. Selection of Patients

Eligibility is determined at the time of screening. Approval of protocol deviations related to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

The target population for this study is patients with severe COVID-19, per FDA guideline. [15]

5.1. Inclusion Criteria

Patients can be enrolled into this study if all of the following criteria are met at screening visit:

1. Hospitalized patient with clinical diagnosis of SARS-CoV-2 virus infection per World Health Organization criteria including positive nucleic acid test of any specimen (e.g., respiratory, blood, or other bodily fluid) within 2 weeks prior to screening.
2. Symptoms suggestive of severe systemic illness with COVID-19, which could include any of the following symptoms: fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath at rest, or respiratory distress.
3. Clinical signs indicative of severe systemic illness with COVID-19, which could include any of the following clinical signs: respiratory rate $\geq$ 30 per minutes, heart rate $\geq$ 125 per minute, SpO2 $\leq$ 93% on room air, PaO2/FiO2 ratio < 300 mmHg, or lung infiltration >50% on chest X-ray imaging.
4. Patients with plasma CRP level >50 mg/L or 4x upper limit of normal range at screening.
5. Men or women $\geq$18 but $\leq$80 years of age at the time of signing the informed consent form.
6. Use of home oxygen is allowed
7. Patient is able to understand the purpose and risks of the study and provide signed and dated informed consent or have a legal representative provide consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).
8. Patient is able to swallow tablets or receive delivery of oral suspension via a nasogastric tube.
9. Patient agrees not to participate in another interventional study after signing the informed consent form and until the end of study (EoS) visit has been completed.

5.2. Exclusion Criteria

Patients should be excluded from this study if any of the following criteria is met at screening visit:

1. Patient requires 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. However, periodically delivered at flow rates >20 L/min with fraction of delivered oxygen ≥ 0.5 is allowed), noninvasive positive pressure ventilation, extracorporeal membrane oxygenation (ECMO), or clinical diagnosis of respiratory failure.

2. Patient with shock defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressor.
3. Patient with multi-organ dysfunction or failure.
4. Patient is unlikely to survive beyond 2 days at the discretion of Investigator.
5. Patient has used chronic systemic corticosteroids (for example, >32 mg/day methylprednisolone or equivalent) within 2 weeks prior to screening. However, dexamethasone at a stable dose ≤6 mg/day or equivalent (such as 31.25 mg of Solu-Medrol) is allowed. One dose of dexamethasone at >6 mg but ≤12 mg or equivalent is allowed, provided baseline CRP level is measured 24 hours after the dexamethasone dosing at >6 mg but ≤12 mg.
6. Patient with moderate to severe hepatic impairment by Child-Pugh scoring system.
7. Patients with severe kidney injury requiring dialysis.
8. Patient with any of the following abnormal laboratory values: absolute neutrophil count (ANC) < 2,000 per mm3, or platelets count <50,000 per mm3, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 x upper limit of normal (ULN) detected within 24 hours at screening (per local lab).
9. Patient has uncontrolled or untreated symptomatic arrhythmias, myocardial infarction or congestive heart failure within the 6 weeks prior to screening.
10. Patient has received immunosuppressant or immunomodulatory drugs within 1 month prior to screening, including anti-cytokine therapies targeting TNF-α, IL-1, IL-6, interferon-beta, or Bruton Tyrosine Kinase (BTK) within 30 days prior to screening. However, remdesivir, convalescent plasma therapy or hydroxychloroquine/chloroquine is allowed in this study.
11. Patient with a code status of do-not-resuscitate (DNR) or cardiopulmonary resuscitate (CPR) Select.
12. Patient with positive results for human immunodeficiency virus (HIV) or hepatitis B or C test.
13. Patient has known active tuberculosis (TB), history of uncontrolled TB, sepsis induced by systemic bacterial or fungal infections within 4 weeks prior to screening.
14. Patient is taking any medication that is mainly metabolized by CYP450 2C19 (a list of commonly used medications that are mainly metabolized by CYP450 2C19 can be found in

Appendix 6). The investigator could provide an alternative medication that is not mainly metabolized by CYP450 2C19.

15. Female patient who is pregnant or lactating or has a positive serum pregnancy test within 72 hours prior to screening and/or randomization, has been pregnant within 6 months before screening or breastfeeding within 3 months before screening or who is planning to become pregnant within the total study period. Woman of Childbearing Potential (WOCBP) must agree to use a highly effective method of contraception consistently and correctly as described in Appendix 5.
16. Patient has a known or suspected hypersensitivity to SIR1-365 or any components of SIR1-365 tablets.
17. Patient has received any investigational drug within 30 days or 5 half-lives, whichever is longer, prior to screening.
18. Patient has any other condition, which makes the patient unsuitable for study participation.

5.3. Lifestyle Restrictions

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. Data for screening failures will be included in the study database.

Individuals who do not meet the criteria for participation in this study (screening failures) may not be rescreened.

6. Treatments

Study treatments include SIR1-365 100-mg tablets and matching placebo tablets.

6.1. Treatments Administered

Study Drug Name:	SIR1-365	Placebo
Dosage formulation:	Tablets	Matching tablets
Unit dose strength/Dosage level:	100 mg tablets	NA
Route of Administration	Oral/gastric tube	Oral/gastric tube
Dosing Instructions:	Take 1 tablet three times daily	

Food and water will be allowed as needed.

The first dose of study treatment will be administered in the hospital on Day 1 after all eligibility criteria are met and randomization procedures are completed. The time of first dose establishes time zero for subsequent doses. The exact time of study treatment administration as well as the dosage (number of tablets taken) will be recorded for all doses given while in the hospital.

If hospitalized, patients are to take study treatment according to the dosing schedule (once every 8 hours ± 1 hour from Day 1 up to Day 14). If any dose of study treatment is missed, defined as no medication intake 1 hour after the scheduled dosing time, the event should be recorded in electronic Case Report Form (eCRF) and the patient should resume dosing at the next scheduled dosing time.

If the disease worsens, the patients may require mechanical ventilation and be unable to swallow study medication. In such cases, the medication will be given as an oral suspension via nasogastric tube. The suspension will be prepared immediately before dosing by dispersing one 100-mg tablet of SRI1-365 in a container with about 20 mL of water and stirring the mixture approximately 3-5 times in about 5 minutes. The oral suspension will be administered within 1-2 minutes after the preparation. The container will then be rinsed twice with about 20 ml of water each, which will be administered to the patient as well. The details for the preparation and administration of oral disintegrated suspension will be included in Pharmacy Manual.

6.2. Method of Treatment Assignment

All patients will be centrally randomized using an interactive response technology (IRT). Before the trial is initiated, the login information and directions for using the system will be provided to each site.

6.3. Blinding and Unblinding

This is a double-blinded clinical trial. The placebo tablets will match the appearance of SIR1-365 tablets, and each patient will take one tablet, TID.

If a patient becomes seriously ill during the study, the blind will be broken for that patient only if knowledge of the administered study treatment will affect treatment options available to the patient. As soon as possible, the Investigator should first contact the medical monitor to discuss the medical

emergency and the reason for revealing the actual treatment received by that patient. The treatment assignment will be unblinded through the interactive response technology.

If the blind is broken, the date, time, staff involved, and reason must be recorded in the eCRF and any associated reports.

If a patient is unblinded for any reason, the study treatment will be discontinued. The patient will be followed through Day 28 or until early termination from the study.

During the study, unblinded safety, biomarker and clinical efficacy data will be reviewed by an IDMC.

6.4. Dose Modification

Dose modification is not allowed in this study. At any time, the IDMC may recommend treatment discontinuation if there is a clinically significant safety signal.

6.5. Preparation/Handling/Storage/Accountability

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment.

Instructions for suspension preparation and administration will be provided in the Pharmacy Manual.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions (controlled room temperature (15-25 ℃) with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study treatment will be reconciled and retained or destroyed according to applicable regulations. Further guidance and information for preparation, handling, storage and disposition of unused study drugs can be found in the Pharmacy Manual.

6.6. Treatment Compliance

The Investigator and study personnel should promote compliance by dispensing the study treatment as planned and record the dosing information in the eCRF. The investigational site staff will perform pill counts after dosing or at early termination if a patient discontinues early from the treatment phase; and record the information in the eCRF. Reasons for departure from the expected dosing regimen must also be recorded.

6.7. Concomitant Therapy

6.7.1. Permitted Medications

The following medications are permitted in this study:

1) Standard of care for the treatment of COVID-19 that are consistent with the NIH or WHO treatment guidelines.
2) Remdesivir, convalescent plasma therapy or hydroxychloroquine/chloroquine at approved doses
3) Dexamethasone at a stable dose ≤6 mg/day or other corticosteroids with the total daily dose equivalencies
4) Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient has received within 30 days prior to enrollment or receives during the study period. However, patients cannot receive COVID vaccine during the study and within 30 days after the completion of this study.

The use of permitted medications will be documented in the patient's source documentation and the eCRF to include the following information:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency, and route of administration
- Any changes in concomitant medications

The medical monitor should be contacted if there are any questions regarding concomitant or prior medication therapy.

6.7.2. Prohibited Medications

The following medications are prohibited in this study:

1) Chromic systemic use of corticosteroids within 2 weeks prior to screening at the following daily doses:
   - Methylprednisolone >32 mg/day
   - Prednisone >40 mg/day
   - Hydrocortisone >160 mg/day

2) Use of immunosuppressant or immunomodulatory drugs within 1 month prior to screening, which include but not are limited to the following drugs:

Category	Medication
Interferon Alfa and Interferon Beta	Interferon Alfa, Interferon Beta

Interleukin-1 Inhibitor	Anakinra
Interleukin-6 Inhibitors	Sarilumab, Siltuximab, Tocilizumab
Bruton's Tyrosine Kinase Inhibitors:	Acalabrutinib, Ibrutinib, Zanubrutinib
Janus Kinase Inhibitor:	Baricitinib (Baricitinib at ≤4 mg/day for less than 7 days prior to screening is allowed. However, this medication should be discontinued after enrollment), Ruxolitinib, Tofacitinib

3) Any medications that are mainly metabolized by CYP450 2C19 will be excluded at screening and should not be used during the study for the treatment of AEs (See Appendix 6).

6.8. Treatment after the End of the Study

At the EOS, the Investigator should advise patients to return to their primary care physician. Any reported AEs should be followed up.

7. Discontinuation of Treatment and Study

7.1. Discontinuation of Treatment

Study treatment for an individual patient will be up to 14 days (whether or not medication is taken) or until a treatment discontinuation criterion is met. Reasons for discontinuation of treatment include the following:

- Adverse Events
- Pregnancy
- Death
- Noncompliance resulting in protocol deviation
- Withdrawal of consent
- Investigator decision
- Other (specify)

A patient may withdraw from the study at any time at his/her own request, at the discretion of the investigator for safety, behavioral, or administrative reasons. If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent

Upon occurrence of a serious or intolerable AE where study treatment discontinuation is considered, the Investigator should confirm with the medical monitor. If a patient is discontinued because of an AE, the event will be followed until it is resolved, based on the medical judgement of the Investigator.

Pre-specified Treatment Discontinuation Roles

- The presence of any of the following events may lead to treatment discontinuation based on the judgement of the site investigator with consultation with the medical monitor or IDMC: Patients started utilization of mechanical ventilation
- Patients experienced heart failure during the study
- Patients experienced respiratory failure during the study
- Patients experienced moderate to severe hepatic impairment during the study
- Patients experienced acute renal injury requiring dialysis during the study
- Any serious AE (SAE) assessed as related to study drug.

7.2. Pause/Discontinuation of Study

Enrollment in the study will be halting upon receiving reports of, until the IDMC is able to review the data and determine the safety of continuing with the study:

- Excess of two deaths in the treatment group which both the investigator and the IDMC agree are probably or definitely related to the investigational product.

or

- Excess of three deaths from any cause in the treatment group

In addition, any report of death or life-threatening SAE whose causal relationship to the study drug is judged to be probably or definitely related to investigational product by the treating investigator must be reviewed by the IDMC within 7 calendar days after sponsor is notified. If this does not happen, or there is not sufficient information provided for the IDMC to fully review the case, enrollment will be halted until such time as the IDMC can review the case and determine the safety of proceeding with the study.

The study could be stopped if:

- New information or other evaluation regarding the safety of the study drug indicates a change in the known risk profile for the study drug, such that the risk is no longer acceptable for patients participating in the study. The IDMC could recommend study termination based on pre-specified study stopping rules. However, the decision for study termination will be made by the Sponsor, the IRB, or Regulatory Authority
- The study is terminated by the Sponsor for administrative reasons.

If the Sponsor, the IRB, or Regulatory Authority decide to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. This procedure will be followed by the investigational site during termination or study suspension.

7.2.1. Follow-up for Patients Who Discontinued from Treatment/Study

If the patients are discharged from the hospital before Day 14, it is preferred that the follow-up visit is in person to obtain safety laboratory tests and blood samples for biomarker analysis as well as clinical outcome data. However, infection control or other restrictions may limit the ability of the patients to return to the clinic. In this case, the follow-up visit may be conducted by phone and only safety data will be obtained

Patients who complete the 14-day treatment should be instructed to have the scheduled follow-up visit on Day 28. If a patient determines he/she no longer wishes to participate in follow-up visit, all the procedures associated with Day 28/Early Discontinuation/End of Study (EOS) visit should be completed at the time of discontinuation.

In both cases, follow-up for AEs should occur as per the discretion of the investigator. It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

Refer to the schedule of assessments (SoA) for data to be collected at the time of study discontinuation, follow-up, and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to complete scheduled visit procedures and is unable to be contacted by the study site.

The following actions must be taken if a patient is unable to complete a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 2 documented telephone calls and, if necessary, a registered letter to the patient's last known mailing address). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. Study Assessments and Procedures

Study procedures to assess safety, efficacy, biomarker and PK are shown in the SoA. Adherence to the trial requirements, including those specified in the SoA is essential for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria within 2 weeks of clinically diagnosis of SARS-CoV-2 virus infection. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients could be hospitalized for up to 14 days. Patients will be assessed daily while hospitalized. If the patients are discharged from the hospital before Day 14, all the assessments planned for Day 14 should be carried out before discharge. If a patient is still hospitalized after Day 14, no study drug will be administered after the last dose on Day 14.

It is preferred that the follow-up visit is in person to obtain safety laboratory tests. However, infection control or other restrictions may limit the ability of the patients to return to the clinic. In this case, the follow-up visit may be conducted by phone and only safety data will be obtained. Study drug will not be administered for early discharged patients.

To fit into the clinical practice of treating patients with severe COVID-19, screening visit and baseline visit can be combined in some patients. In that case, the number of dosing could be less than 3 times on that day. ECG, laboratory test and other test results obtained within 24 hours prior to consent can be used as baselines.

For those patients who complete the 14-day treatment period, the investigator will decide appropriate treatments for the period from Day 15 to Day 28.

A follow-up visit will be scheduled approximately on Day 28 (±3) or 14 (±3) days after the last dose for those who are discharged from the hospital before Day 14.

Procedures conducted as part of the patient's routine clinical management and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening purposes, provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the Schedule of Assessments (SoA). Repeat or unscheduled tests or procedures may be performed for safety reasons or for technical issues.

Protocol waivers or exemptions are not granted under any circumstances. Major protocol deviations defined as events related to safety and/or integrity of study data must be discussed with the medical monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Schedule of Assessments (SoA) [12]

	Screening	Treatment in Hospital							Follow-up visit/EOS
Days	**-7 to -1**	**1** [1]	**2-6**	**7**	**8-9**	**10**	**11-13**	**14 (±2) /EOT** [2]	**28 (±3)** [3]
Informed consent	X								
Medical history	X								
Demographics	X								
Physical examinations	X [4]							X	
Vital signs [5]	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X [6]		X		X		X	X
Blood samples for routine lab tests including [redacted]	X	X	X	X	X	X	X	X	X
[redacted]		X	X	X		X		X	X
Urine sample for urinalysis	X	X	X	X		X		X	X
Serum serology and pregnancy tests for screening	X								
Inclusion and exclusion	X								
Randomization		X							
Treatment		X	X	X	X	X	X	X	
Oxygen use and saturation (pulse oximetry)	X	X	X	X	X	X	X	X	X
PaO2/FiO2 ratio	X	X		X				X	
WHO ordinal scale		X		X				X [13]	X
[redacted]		X		X				X	
Blood sample for PK analysis and [redacted]		X		X				X	
Urine sample [redacted]		X		X				X	
AE and ConMed	X	X	X	X	X	X	X	X	X

1. Enrollment and baseline. Screening and baseline visits can be combined. ECG, laboratory test and other test results taken within 24 hours prior to consent will be used as baselines.
2. End of Treatment (EOT) or early discharge.
3. End of Study (EOS) or early discontinuation.
4. For enrolled patients, physical examination obtained at screening will be the baseline. Weight and height will be measured at screening.
5. Vital signs will be taken before the 1st dose on Day 1 as baseline, and within 3 hours before the 2nd dose on other days
6. Three ECGs with 1 - 3 min interval before the 1st dose on Day 1 only, and the means of the three ECGs will be used as baselines. ECGs will be done within 3 hours before the 2nd dose on other days. Local ECG machine will be used in this study.
7. Routine laboratory tests before the 2nd dose will be done daily at local labs [redacted] will be done on days 1, 3, 7, 10 and 14.
8. Coagulopathy panel [redacted] cardiac function panel including [redacted] will be done on Days 1, 3, 7, 10 and 14 at local labs with samples collected before the 2nd dose.
9. One blood sample collected before the 1st dose on Day 1 and before the 2nd dose on Days 7 and 14 for [redacted] be conducted at a central lab
10. One blood sample will be collected from each patient within 30 min before and 2 hours (±5 min) after the 1st dose on Day 1, respectively. On Days 7 and 14, one blood sample will be collected within 30 min before and 2 hours (±5 min) after the 2nd dose, respectively. Each plasma sample will be divided into 4 parts, 2 for PK analysis and [redacted] conducted at a central lab. [redacted] be done at the sites with necessary equipment according to the laboratory manual for [redacted]
11. About 10 mL of urine sample will be collected before dosing on Day 1, and in the morning on Days 7 and 14 for [redacted] o be conducted at a central lab
12. If the patients are discharged from the hospital before Day 14, all the assessments planned for Day 14 should be carried out before discharge. Study drugs will not be administered in early discharged patients. It is preferred that the follow-up visit is in person to obtain safety laboratory tests. However, infection control or other restrictions may limit the ability of the patients to return to the clinic. In this case, the follow-up visit may be conducted by phone and only safety data will be obtained. If a patient is still hospitalized after Day 14, no study drug will be administered after the last dose on Day 14.
13. When completing the WHO Ordinal Scale at Day 14 / EOT, if the subject has received physician orders to be discharged from the hospital, the score should be a 3 or less *(no longer hospitalized)*.

8.1. Clinical Efficacy Assessments

Clinical efficacy of SIR1-365 in hospitalized patients with severe COVID-19 will be assessed by monitoring the changes from baseline on the following parameters between the treatment groups. All the assessment will be performed and administered per the SoA. The results will be documented in the eCRF.

For eligible and enrolled patients, the values of their last efficacy assessments obtained on Day 1 before dose will be used as baseline value.

Correlation of biomarker profile to efficacy outcomes will be determined by analyzing the changes on efficacy outcomes in patient populations with different baseline levels of biomarkers. Details of this analysis will be included in the Statistical Analysis Plan (SAP).

8.1.1. PaO_2/FiO_2 ratio

PaO_2/FiO_2 ratio will be evaluated by blood gas analyzer at screening for eligibility determination, within 30 minutes before dosing on Day 1 as baseline, and within 30 minutes after 2nd dose on Day 7 and Day 14. Change from baseline to Day 7 and to Day 14 on PaO2/FiO2 ratio will be one of the secondary efficacy measures in this study.

8.1.2. Time to improvement of oxygenation

Oxygen saturation will be measured daily via pulse oximetry. Time (days) to improvement of oxygenation is defined as oxygen saturation (pulse oximetry) >93% and increased by ≥1% from baseline breathing only room air in the 48 hours preceding the measurement during the study (Baseline to Day 28).

8.1.3. Days without Oxygen Use

Oxygen use data will be recorded in the eCRF.

8.1.4. WHO Ordinal Scale

The WHO ordinal scale is a 10-level ordered categorical scale developed by a special committee at WHO to measure illness severity over time. The scale will be used to assess patients' clinical status during the study. A 2-point reduction on the score of WHO ordinal scale is considered as clinical improvement.

This endpoint will be collected 4 times during the study: Baseline, Days 7, 14, and 28.

The scale can be found in Appendix 2.

8.1.5. Days of Hospitalization

Hospitalization admission and discharge date and time will be recorded in the eCRF.

8.1.6. Free of Respiratory Failure

Respiratory failure is defined as need for mechanical ventilation, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ⩾ 0.5). Related information will be recorded in the eCRF.

8.1.7. All-cause Mortality Rate

All-cause mortality and related information will be recorded in the eCRF.

8.2. Safety Assessments

Safety assessments will include the summaries of AEs, vital signs, laboratory tests, 12-lead ECG, and physical examination findings at various time points during the study.

Planned time points for all safety assessments are provided in the SoA (Table 1). For the eligible and enrolled patients, the values of their safety assessments obtained before dosing will be used as baseline values.

The independent IDMC will review unblinded safety, efficacy and biomarker information during the trial. The data to be reviewed by the IDMC will be described in study specific IDMC Charter that will be finalized before the study is initiated.

The safety database and clinical database will be reconciled, and SAE/TEAE line listings will be completed at the end of the study prior to database lock.

Correlation of biomarker profile to safety outcomes will be determined by analyzing the changes on safety outcomes in patient populations with different baseline levels of biomarkers. Details of this analysis will be included in the SAP.

8.2.1. Safety Monitoring Plan:

Safety will be carefully monitored during the study based on a study specific safety monitoring plan that consists of the following main components:

Grade System of AEs and Findings

Severity of AEs, clinical findings and safety laboratory findings will be graded based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Independent Data Monitoring Committee

During the study, unblinded safety, biomarker, and clinical efficacy data will be reviewed by an independent data monitoring committee (IDMC). The IDMC includes a safety physician and two clinical physicians, and should be independent from the investigators, patients and the sponsor to ensure trial integrity. A study specific IDMC Charter will be developed prior to study initiation.

The IDMC is expected to meet when approximately 20 and 40 patients are enrolled. Reports of suspected unexpected serious adverse reactions (SUSARs) and Serious Adverse Events (SAEs) will

be forwarded to the DMC Members on a weekly basis for review. The DMC Chair may request additional patient information pertaining to these reports as necessary or request an ad hoc DMC meeting to discuss any cases of concern based upon review of these events.

Pre-specified Treatment Discontinuation Rules

See Section 7.1

Pre-specified Study Halting/Stopping Rules

See Section 7.2

8.2.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

An AE will be reported by the patient (or, when appropriate, by a physician, caregiver).

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for treating and following up any AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue the study (see Appendix 4). Medications that are mainly metabolized by CYP2C19 (see Appendix 6) should not be used for the treatment of AEs.

AEs will be coded based on the current version of Medical Dictionary for Regulatory Activities (MedDRA) and concomitant medications will be coded based on the current version of The WHO Drug Dictionary (WhoDrug).

8.2.2.1. Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time when ICF is signed until the end of the patient's participation in the study.

All SAEs will be recorded and reported within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data within 24 hours of it being available. The SAE should be entered to EDC as defined in Appendix 4.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.2.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.2.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AEs of potential interests, will be followed until resolution, stabilization, until the event is otherwise explained or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.2.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAE) from the sponsor will file it along with the IB and will notify the IRB, if appropriate according to local requirements.

8.2.2.5. Pregnancy

Details of all pregnancies in female patients will be collected after the start of study treatment and until Day 28/EOS/Early DC visit using a Pregnancy Information Form (provided in the Study Manual).

If a pregnancy is reported, the Investigator should inform the medical monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study treatment must be promptly reported to the medical monitor. The pregnancy should be reported immediately, using a Pregnancy Information Form, via email or Designated Fax number located in Appendix 5.

If the patient agrees to have her primary care physician informed, the Investigator should document such a decision and notify the patient's primary care physician that she was participating in a clinical study at the time that she became pregnant and the Investigator should provide the details of the treatment that the patient received.

All pregnancies will be followed until final outcome, using the Pregnancy Information Form, and indicating that it is a follow-up report. The outcome, including any premature termination, must be reported.

8.2.2.6. Treatment-Emergent Adverse Events of Potential Interest

No specific AEs have been reported in the complete SAD study in healthy subjects.

Since liver and kidney impairments may be associated with new drugs tested in human for the first time, elevated ALT, AST and creatinine levels in plasma are considered as AEs of potential interest. Therefore, those TEAEs, if reported in this study, will be analyzed as TEAEs of potential interest. Details of this analysis will be included in the SAP.

8.2.2.7. Treatment of Overdose

Taking study medication greater than protocol defined dose is considered an overdose. In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for AEs/SAEs and evaluation of liver function.
3. Provide appropriate medical care, as clinically indicated.
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF as an AE.

8.2.3. Vital Signs

Vital sign assessments include blood pressure, heart rate, respiratory rate, and temperature.

Blood pressure will be measured using an automated cuff on the arm that is not used for blood sample collection and not switched between arms unless necessary.

Respiratory rate will be documented in breaths per minute.

8.2.4. Clinical Safety Laboratory Tests

Refer to Appendix 3 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are

those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

All protocol-required laboratory tests will be conducted at local laboratory in this study. All local laboratories will be certified and provide normal or reference ranges in accordance with US Title 42 Code of Federal Regulations (CFR) Part 493.

Clinical safety tests will be done under fasted conditions (fasted for about 10 hours overnight). Urine microscopy will be performed without positive urinalysis results for other items.

Approximately 15 mL of blood for routine laboratory tests including CRP and ferritin, 10 mL for coagulopathy and cardiac function panels, and 8 mL for serology tests for screening will be collected. Approximately 10 mL urine will be collected for urinalysis. The blood and urine samples will be prepared using procedures outlined in the laboratory manual.

If serum βHCG is the standard pregnancy test, this value can be used to determine eligibility.

Coagulopathy Panel includes the following tests:

[redacted]

Cardiac Function Damage Panel includes the following tests:

- [redacted]

8.2.5. 12-Lead ECGs

Triplicate ECG tests with 1-3 min interval in between will be obtained on Day 1 before the 1st dose, and the mean of the 3 ECG tests will be used as the baseline. A single ECG is required before the 2nd dose on other days. All ECGs will be performed after the patient has been resting in a supine position for at least 5 minutes.

Outputs from the local ECG machine will be used in this study. All ECGs must be evaluated by the Investigator. Clinically significant abnormal ECGs may be repeated at the discretion of the Investigator.

8.2.6. Physical Examinations

A complete physical examination will include but not limited to the evaluation of the following organs or body systems: skin; head, eyes, ears, nose, and throat; thyroid, respiratory, cardiovascular, and central nervous systems, abdomen (liver and spleen), lymph nodes, and extremities.

Weight and height will be measured at Screening only.

8.3. Biomarker Measures

Blood samples to be collected will be used for the measurements of a set of biomarkers including [redacted] appropriate. Data will not be shared with any 3rd party.

Details about sample handling and analysis for biomarkers will be provided in laboratory manual.

8.3.1. Inflammatory Biomarkers

8.3.1.1. [redacted]

As a proinflammatory biomarker [redacted] significantly elevated in COVID-19 patients and is associated with disease severity and progression. Thus [redacted] a reliable indicator of hyperinflammatory state.

[redacted] will be measured daily at local laboratories with validated methods. Change from baseline to Day 7, time (days) and number of the patients to reach 50% reduction from Baseline in [redacted] during the treatment period (Baseline to Day 14), and changes in daily plasma [redacted] during the treatment period (Baseline to Days 1-14) will be analyzed.

8.3.1.2. [redacted] White Blood Cell Count

[redacted] hite blood cell count including differential will be measured at local laboratories. Neutrophil to lymphocyte ratio will be calculated.

8.3.1.3. [redacted]

[redacted]

8.3.1.4. Chemokines

[redacted]

8.3.2. Biomarkers Indicative of Target Engagement

[redacted]will be measured at a central laboratory with validated methods. [redacted]ill be done at the sites with necessary equipment according to the laboratory manua[redacted]

8.3.3. Biomarkers for Kidney Injury

[redacted]ill be measured at a central laboratory with validated methods.

8.3.4. Biomarkers for CV Endothelial Cell Damage

[redacted] will be measured at a central laboratory with validated methods.

8.4. PK Analysis

Approximately 60 patients enrolled in the study will have peak and trough blood samples obtained within 30 min before and 2 hours (±5 min) after the 1st dose on Day 1, respectively. On Days 7 and 14, one blood sample will be collected within 30 min before and 2 hours (±5 min) after the 2nd dose, respectively.

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Plasma drug concentrations of SIR1-365 and metabolites will be summarized using descriptive statistics. Additional details for plasma concentration assessment will be included in a separate PK analysis plan. The PK analysis plan will supersede the protocol.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

8.5. Pharmacogenomics

Pharmacogenomics are not being evaluated in this study.

8.6. Health Economics

Health economics/medical resource utilization and health economics parameters are not being evaluated in this study.

9. Study Procedures and Assessments

Study procedures and assessments are summarized across study visits in the SoA and described below.

9.1. Screening

The Screening visit should occur ≤ 2 weeks of COVID-19 diagnosis and of randomization and can be combined with baseline visit:

- Informed consent
- Medical history including smoking, drug, and alcohol use/abuse history
- Demographic
- Physical examination (weight and height at screening only)
- Vital signs including blood pressure, heart rate, respiratory rate, and temperature
- 12-lead ECG test with local ECG machine
- Routine clinical laboratory tests includin[redacted]e at local laboratory
- Urinalysis
- Serology tests for screening (pregnancy test for females only)
- Inclusion and exclusion criteria verification
- Oxygen use and saturation (pulse oximetry)
- PaO_2/FiO_2 ratio
- AE/SAE assessment and record prior and concomitant medications/current procedures

9.2. Treatment Day 1/Baseline

- Randomization
- Vital signs
- Three 12-lead ECG tests with 1-3 min interval in between on Day 1 pre-dose only. The mean of the three ECGs will used as baseline
- Routine clinical laboratory tests includin[redacted]e at local laboratory
- Coagulopathy and cardiac function panels done at local laboratory
- Urinalysis
- Study drug administration
- Oxygen use and saturation (pulse oximetry)
- PaO_2/FiO_2 ratio

- WHO ordinal scale
- Blood sample for serum cytokine and chemokine panels and CV biomarkers
- Blood sample collected before the 1st dose for plasma drug level analysis and [redacted] assay
- Urine sample fo[redacted]
- AE/SAE assessment and concomitant medications/current procedures

9.3. Treatment Days 2-6

- Vital signs
- Routine clinical laboratory tests includir[redacted]e at local laboratory on Days 1 and 3
- Coagulopathy and cardiac function panels done at local laboratory on Days 1 and 3
- Urinalysis
- Study drug administration
- Oxygen use and saturation (pulse oximetry)
- AE/SAE assessment and concomitant medications/current procedures

9.4. Treatment Day 7

- Vital signs
- 12-lead ECG
- Routine clinical laboratory tests includin[redacted]e at local laboratory
- Coagulopathy and cardiac function panels done at local laboratory
- Urinalysis
- Study drug administration
- Oxygen use and saturation (pulse oximetry)
- PaO_2/FiO_2 ratio
- WHO ordinal scale
- Blood sample for[redacted]CV biomarkers
- Blood sample collected before the 2nd dose for plasma drug level analysis and [redacted]
- Urine sample fo[redacted]

- AE/SAE assessment and concomitant medications/current procedures

9.5. Treatment Days 8-9

- Vital signs
- Routine clinical laboratory tests done at local laboratory
- Study drug administration
- Oxygen use and saturation (pulse oximetry)
- AE/SAE assessment and concomitant medications/current procedures

9.6. Treatment Day 10

- Vital signs
- 12-lead ECG
- Routine clinical laboratory tests includin[redacted]ne at local laboratory
- Coagulopathy and cardiac function panels done at local laboratory
- Urinalysis
- Study drug administration
- Oxygen use and saturation (pulse oximetry)
- AE/SAE assessment and concomitant medications/current procedures

9.7. Treatment Days 11-13

Same assessments as for Days 8-9

9.8. Treatment Day 14/End of Treatment (EOT)/Early Discharge

- Physical examinations
- Vital signs
- 12-lead ECG
- Routine clinical laboratory tests including[redacted]ne at local laboratory
- Coagulopathy and cardiac function panels done at local laboratory
- Urinalysis
- Study drug administration
- Oxygen use and saturation (pulse oximetry)
- PaO_2/FiO_2 ratio

- WHO ordinal scale
- Blood sample for serur[redacted]
- Blood sample collected before the 2nd dose for plasma drug level analysis and [redacted]
- Urine sample for[redacted]
- AE/SAE assessment and concomitant medications/current procedures

9.9. Follow-up Visit on Day 28/End of Study (EOS)

- Vital signs
- 12-lead ECG
- Routine clinical laboratory tests including[redacted]one at local laboratory
- Coagulopathy and cardiac function panels done at local laboratory
- Urinalysis
- Oxygen use and saturation (pulse oximetry)
- WHO ordinal scale
- AE/SAE assessment and concomitant medications/current procedures

If the patients are discharged from the hospital before Day 14, all the assessments planned for Day 14 should be carried out before discharge. If a patient is still hospitalized after Day 14, no study drug will be administered after the last dose on Day 14.

It is preferred that the follow-up visit is in person to obtain safety laboratory tests. However, infection control or other restrictions may limit the ability of the patients to return to the clinic. In this case, the follow-up visit may be conducted by phone and only safety data will be obtained. Study drugs will not be administered for early discharged patients.

10. Statistical Analysis

10.1. Sample Size Determination

Due to the exploratory nature of this study, the sample size is not calculated based on statistical significance on any parameters. However, a sample size of 30 patients per group is considered to be sufficient to detect marked differences in the overall safety profile between treatments with a pre-specified safety monitoring plan. Furthermore, this sample size provides estimates of treatment differences in some clinical efficacy endpoints and the levels of some biomarkers such as CRP, for

use in planning future studies. Therefore, approximately 30 patients will be enrolled for each group (total 60) in this study.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Safety set	All patients who are randomized and take at least 1 dose of study drug (SIR1-365 or placebo). Patients will be analyzed according to the treatments received.
Intention-to-Treat (ITT) set	All patients who are randomized to the study
Modified Intention-to-Treat (mITT) set	All patients who take at least one dose of study drug and have at least one follow-up outcome evaluation
Per protocol (PP) set	All patients who take at least one dose of study drug and do not have the important major protocol deviation
PK/ PD set	All patients who receive study drug without major protocol deviation and have sufficient PK/PD data to obtain reliable estimates of the key PK/PD variables

In this study, major protocol deviation categories include the follows:

- ICF not signed
- Violation of key inclusion or exclusion criteria
- Wrong study drug treatment
- Use of prohibited medication(s)
- Major GCP violation such as SAE reporting requirement

In regard to establishing a PP set, the decision as to whether a deviation from the above list of major protocol deviations warrants exclusion of the patient from the analysis set will be determined and documented prior to unblinding.

10.3. Statistical Analyses

A detailed SAP will be developed and finalized before database lock.

A 2-sided alpha-level of 0.05 will be used for construction of confidence intervals. No adjustment for multiple endpoints will be employed. Although the study is not powered for hypothesis testing,

p-values will be generated to aid interpretation in addition to confidence intervals about the estimates.

The safety population will be the primary population for safety analysis. Analyses will be performed on observed data.

For clinical efficacy endpoints, the primary analysis will be in the ITT population. Rules for addressing missing data will be detailed in the statistical analysis plan. Sensitivity analyzes for the clinical efficacy endpoints may be performed in the mITT and/or PP populations.

The mITT population will be primary population for the biomarker analysis with exception of time to 50% reduction of CRP levels for which the ITT population will be primary. Sensitivity analyses incorporating imputation for missing biomarker values may be performed.

In general, baseline for each parameter is the last non-missing value collected prior to the first dose of study medication including pre-dose measurements made on the date of the first dose of study medication.

All data analyses will be conducted using SAS® (SAS Institute, Inc, Cary, North Carolina) software. In general, for descriptive summaries, continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. All data will be presented in data listings.

10.3.1. Clinical Efficacy Analysis

Efficacy will be assessed based on the change in the following measures:

PaO_2/FiO_2 ratio

Change from Baseline in the PaO_2/FiO_2 ratio as a continuous variable will be summarized by visit and treatment using both simple descriptive statistics and model-based estimates obtained from an analysis of covariance model with terms for treatment as a class variable and the baseline score as a continuous covariate. Comparison of the SIR1-365 group vs placebo will be constructed based on least-squares means from the model.

Time to improvement of oxygenation

Time to improvement of oxygenation (in days) defined as oxygen saturation (pulse oximetry) increased by ≥1% from baseline breathing only room air in the 48 hours preceding the measurement will analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% CI for SIR1-365 dose vs placebo. Patients without a pulse oximetry increase ≥1% from baseline will be censored at the date of their last pulse oximetry measurement (meeting the preceding 48 hours room air only requirement) or the last date that supplemental oxygen was received. Patients without a post-baseline oximetry measurement who did not receive supplemental oxygen will be censored at day 1.

WHO ordinal scale

Change from Baseline to Days 7, 14 and 28 in the scores of WHO ordinal scale as a continuous variable will be summarized by visit and treatment. Categorical summaries of patients having a 2 points reduction in the scores of WHO ordinal scale will be generated by number and percentage.

Number of days without oxygen use

Number of days without oxygen use during the study (Baseline to Day 28) will be summarized as a continuous variable by visit and treatment. An estimate of the difference mean numbers of days will be provided along with a corresponding 95% CI based on a 1-way ANOVA model with a single term for treatment. The definition of a "day", such as calendar day versus a 24 hours period, will be defined in the SAP.

Days of hospitalization

Days of hospitalization as a continuous variable will be summarized by visit and treatment. The definition of a "day", such as calendar day versus a 24 hours period, will be defined in the SAP.

Patients free of respiratory failure

The number and percentage of patients free of respiratory failure will be summarized by visit and treatment.

All-cause mortality rate

All-cause mortality rate will be summarized by visit and treatment.

Correlation of biomarker profiles to clinical outcome

The clinical outcomes will be compared in patient groups with inflammatory biomarker levels at baseline and post-baseline timepoints to assess correlation of biomarker profiles to clinical outcomes. Details of this analysis will be included in the SAP.

10.3.2. Safety Analysis

TEAEs

TEAEs are defined as AEs that commence or worsen after the first dose of study medication during the study. TEAEs will be analyzed descriptively including 2-sided 95% CI for between-group (SIR1-365 – placebo) incidence rates. TEAEs analyzed will include, but not necessarily limited to, the following:

- At least 1 TEAE
- At least 1 Related TEAE
- At least 1 SAE
- At least 1 TEAE of severe intensity
- Individual TEAE Preferred terms

- Individual TEAE Preferred terms considered related to study medication

TEAEs occurring during the 14-day treatment period will include those with onset in the first 14 days, irrespective of actual days of treatment, where study day 1 is the date of the first dose of study medication. All TEAEs with onset ≤ 28 days will be summarized similarly.

Laboratory Analyses

Laboratory data including coagulopathy panel and cardiac function panel will be summarized using summary statistics of raw data and change from Baseline values (pre-dose Day 1 values/last non-missing pre-dose value), by presenting shift tables using clinically notable ranges (Baseline to most extreme postbaseline value), and by flagging notable values in data listings. The number and percentage of patients with clinically meaningful laboratory test findings will also be summarized by treatment group and visit.

Vital Sign Measurements

Vital sign data (SBP and DBP, heart rate, respiratory rate, and oral temperature) will be summarized by presenting summary statistics for change from baseline values. The incidence rates of clinically significant vital sign abnormalities will be summarized.

12-Lead Electrocardiograms

Values for 12-lead ECG parameters (RR, PR, QRS, QT, and corrected QT interval) and change from Baseline values will be summarized through descriptive statistics by treatment group and visit. The number and percentage of patients with clinically significant ECG findings will also be summarized by treatment group and visit. The maximum increase in corrected QT interval from Baseline will be summarized.

Physical Examinations

Clinically meaningful findings on physical examinations for each patient will be listed.

Correlation of biomarker profiles to safety outcome

The safety outcomes will be compared in patient groups with inflammatory biomarker levels at baseline and post-baseline timepoints to assess correlation of biomarker profiles to safety outcomes. Details of this analysis will be included in the SAP.

10.3.3. Biomarker Analysis

Inflammatory Biomarkers

[redacted]

The difference between treatments in Day 7 and Day 14 in plasma [redacted] ll be analyzed using an ANCOVA model with terms for treatment as a class variable and the baseline score as a continuous covariate. [redacted] will be log-transformed (natural log) for analysis. Comparison of the

SIR1-365 group vs placebo will be constructed based on least-squares means from the model. The results will be back transformed for presentation including 95% CI constructed for both within and between treatment estimates. If the residuals are found to deviate substantially from normality a supportive analysis using the non-parametric Wilcoxon Rank Sum test may be performed. Additional supportive analysis using multiple imputation and/or MMRM may be considered if more than 10% of patients in either arm has missing Day [redacted] Timepoints other than Day 7 will be analyzed similarly.

Time (days) to 50% reduction from baseline in plasma [redacted] uring the treatment period will be analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% confidence interval for SIR1-365 dose vs placebo. Patients without a 50% or reduction will be censored at the date of their last CRP assessment or at Day 1 in the event no post-baselin [redacted] value is available.

[redacted] ***d white blood cell counts***

Change from Baseline [redacted] phocyte, and neutrophil counts, as well as neutrophil to lymphocyte ratio as continuous variables will be summarized by visit and treatment.

[redacted]

[redacted] a continuous variable will be summarized by visit and treatment.

[redacted]

Change from Baseline in in serum levels o [redacted] [redacted] a continuous variable will be summarized by visit and treatment.

Biomarkers Indicative of Kidney Injury

Change from Baseline on urin [redacted] s a continuous variable will be summarized by visit and treatment.

Biomarkers Indicative o [redacted]

Change from Baseline o [redacted] as a continuous variable will be summarized by visit and treatment.

Biomarkers Indicative of [redacted]

Change from Baseline on plasma and/ [redacted] uous variable will be summarized by visit and treatment.

10.3.4. PK Analysis

Plasma peak and trough levels of SIR1-365 and metabolites will be described in a PK analysis plan to be finalized before database lock. The PK analysis report may be presented separately from the main clinical study report (CSR).

10.3.5. Interim Analysis

No interim analyses are planned for this study.

11. Direct Access to Source Data/Documents

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

12. Quality Control and Quality Assurance

All patient data relating to the study will be recorded in an eCRF database and transmitted to the sponsor or designee electronically. The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF when requested to do so at the conclusion of the trial.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region product or at least 2 years have elapsed since the formal discontinuation of clinical development of

the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

13. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAE or other significant safety findings as required by IRB procedures
- Overall conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

14. Data Handling and Protection

Patients will be assigned a unique identifier by the contract research organization (CRO). Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.

The patient must be informed that his/her medical records may be examined by the Sponsor, by the Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality.

All records will be kept in a secure storage area with limited access.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the study.

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the CSR is prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s)

15. Financing and Insurance

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

16. Publication Policy

The results of this study may be published or presented at scientific meetings only with approval from the Sponsor. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to

the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

Data are the property of and cannot be published without prior authorization from the Sponsor.

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14) SIR1-365 Investigator Brochure

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Appendix 1: Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
β-HCG	β-Human Chorionic Gonadotropin
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
C_{max}	Maximum Concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPR	Cardiopulmonary resuscitate
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation or Cardiovascular
CXCL-1	Chemokine Ligand-1
CYP	Cytochrome P450
DNR	Do-not-resuscitate
EC	Ethics Committee
EC_{50}	The half maximal effective concentration
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Definition
G-CSF	Granulocyte Colony-Stimulating Factor
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GMP	Good Manufacturing Practice
HED	Human Equivalent Dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	The half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IL-1β	Interleukin-1β
INR	International normalized ratio
IP-10	Interferon induced Protein
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-to-Treat
IV	Intravenous
[redacted]	
LOCF	Last observation carried forward
MABEL	Minimal Anticipated Biological Effect Level
MAD	Multiple Ascending Dose
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MIP-1α	Macrophage inflammatory protein-1α
mITT	Modified ITT
MTD	Maximum Tolerate Dose
NA	Not applicable
NCI	National Cancer Institute
NG	Nasogastric
[redacted]	
NOAEL	No observable adverse effect level

Abbreviation	Definition
[redacted]	
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics or protocol discrepancy
[redacted]	
RIP1	Receptor-interacting protein kinase 1
PK	Pharmacokinetics
[redacted]	
PT	Prothrombin time
PTT	Partial thromboplastin time
SAD	Single Ascending Dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SIRS	Systemic inflammatory response syndrome
SoA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reactions
$T_{½}$	Terminal half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TID	Three times a day
TNF-α	Tumor Necrosis Factor-α
ULN	Upper limit of normal
USA	United States of America
WHO	World Health Organization
WhoDrug	The WHO Drug Dictionary
WOCBP	Women of childbearing potential

Appendix 2: WHO Ordinal Scale

The WHO ordinal scale is a 10-level ordered categorical scale developed by a special committee at WHO to measure illness severity over time. The scale could be a measure of patients' clinical status at a particular time point after enrollment. A 2-point reduction on the score is considered as clinical improvement

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory Mild Disease	Asymptomatic; viral RNA detected	1
	Symptomatic; Independent	2
	Symptomatic; Assistance needed	3
Hospitalized: Moderate disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe disease	Hospitalized; Oxygen by NIV or High flow	6
	Intubation & mechanical ventilation, pO_2/FIO_2 ≥150 or SpO_2/FIO_2≥200	7
	Mechanical ventilation pO_2/FIO_2<150 (SpO_2/FIO_2 <200) **or** vasopressors	8
	Mechanical ventilation pO_2/FIO_2<150 **and** vasopressors, dialysis, or ECMO	9
Death	Dead	10

Appendix 3: Clinical Laboratory Tests To be Performed at Local Laboratory

- The tests detailed in the table below will be performed at local laboratories. Investigators must document their review of each laboratory safety report.
- All other protocol-required tests will be analyzed by a central laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in the protocol.

Routine Clinical Laboratory Tests

Hematology	Clinical Chemistry		Urinalysis
Hemoglobin (Hgb)	Glucose	C-Reactive Protein (CRP)	pH
Hematocrit (Hct)	Albumin	Ferritin	Specific gravity
Red blood cell count	Total protein	Lactic dehydrogenase (LDH)	Protein
White blood cell count with differential	Bicarbonate	Urate	Glucose
Platelet count	Phosphate	Blood urea nitrogen	Ketones
	Sodium	Creatinine	Bilirubin
	Potassium	Total bilirubin (TBL)	Blood
	Chloride	Alkaline phosphatase (ALP)	Nitrites
	Calcium	Aspartate transaminase (AST)	Leukocytes
	Total cholesterol (TC)	Alanine transaminase (ALT)	Urobilinogen
	Low-density lipoprotein cholesterol (LDL-C)	Gamma-glutamyl transferase (GGT)	Microscopic analysis
	Triglyceride (TG)		

Other Clinical Laboratory Tests

Serology Tests for Screening	Coagulopathy Panel	Cardiac Function Panel
Human immunodeficiency virus (HIV)	D-dimer	High-sensitivity cardiac troponin
Hepatitis B surface antigen (HBsAg)	Fibrinogen	NT-proBNP or BNP
Hepatitis C virus (HCV)	Prothrombin time (PT)	
Pregnancy test	Partial thromboplastin time (PTT)	
	International normalized ratio (INR)	

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event (AE):

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal or clinically relevant laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events Meeting the AE Definition
• Any clinically significant abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the Investigator (ie, not related to expected progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition (eg, noted caroTID arteriography or echocardiographic findings unknown prior to enrollment). • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of a Serious Adverse Event (SAE):

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death.
b. Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires in patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization can be AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but does not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect.

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AEs and SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all patient identifiers, with the exception of the patient number, will be blinded on the copies of the medical records before submission to sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study based on the criteria of CTCAE.

Assessment of Causality

- The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:
- Unrelated: This relationship suggests that there is no association between the study drug and the reported event.
- Unlikely related: This relationship suggests that there is unlikely association between the study drug and the reported event.

- Possible related: This relationship is based on evidence suggesting a causal relationship between the study drug and the AE, ie, there is a reasonable possibility that the drug caused the event. The event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.
- Probable related: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely.
- Definite related: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to CRO. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to CRO.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide CRO with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF/ SAE form.
- The Investigator will submit any updated SAE data to CRO within 24 hours of receipt of the information.

Reporting of SAE to the CRO

SAE Reporting to CRO
• Investigators are instructed to report, within 24hours of awareness, all SAEs and report of pregnancy by entering the event to EDC. • If notification cannot be made via EDC due to technical delivery problems, initial notification may be made by a telephone call to the SAE Hotline. Contact information is available on the SAE Report Form, pregnancy form, and site file. • A telephone call to the SAE Hotline does not substitute for the site's responsibility to submit a written SAE Report Form. SAEs reported via the telephone call to the SAE Hotline must be followed with the SAE report the same day.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

1. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel: review of patient's medical records, medical examination, or medical history interview.
2. Premenarchal
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[a] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[a] • oral • injectable
Highly Effective Methods That Are User Independent

• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.)*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.

Female patients of reproductive potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table above.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative serum pregnancy test. If serum βHCG is the standard of care, then this value can be used to determine eligibility.

Collection of Pregnancy Information

Female patients who become pregnant

- Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the medical monitor and sponsor within 24 hours of learning of a patient's pregnancy.
- Patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on patient and neonate, which will be forwarded to the medical monitor and sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy that is considered reasonably related to the study drug by the Investigator will be reported to CRO and the sponsor as described in

Appendix 4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating:

- will discontinue study drug and be withdrawn from the study immediately.
- an early termination safety visit should be conducted with all procedures performed.

Appendix 6: Medications that are Mainly Metabolized by CYP450 2C19

Brivaracetam	Ospemifene
Carisoprodol	Phenobarbitone
Chloramphenicol	Phenytoin
Citalopram*	Pomalidomide
Cyclophosphamide	Primidone
Diazepam	Proguanil
Flibanserin	Propranolol
Hexobarbital	r-mephobarbital
Moclobemib	r-warfarin
Nelfinavir	s-mephenytoin
Nilutamide	Teniposide
	Voriconazole

*Citalopram ≤20 mg/day is allowed, because citalopram at ≤20 mg/day is the maximum recommended dose in patients taking a CYP2C19 inhibitor based on the FDA approved label.