16.1.9 DOCUMENTATION OF STATISTICAL METHODS

This appendix includes

Document	Version, Date
Statistical Analysis Plan	1, 07 December 2021
Pharmacokinetics / Pharmacodynamics Data Statistical Analysis Plan	No version, 08 December 2021

Statistical Analysis Plan

Sironax

SIR365-US-101

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

Protocol Version 2.4: 08 Apr 2021

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Version	Date
Version 1	07 December 2021

Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
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LIST OF ABBREVIATIONS

Abbreviation	Full Notation
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
EAIR	Exposure Adjusted Incidence Rate
ECG	Electrocardiogram
eCRF	Electronic case report form
ICH	International Council for Harmonisation
ITT	Intent-to-treat
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PT	Preferred term
SAE	Serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of SIR365-US-101 (A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study to Assess Safety and Efficacy of SIR1-365 in Patients with Severe COVID-19). This document excludes detail on the analysis of pharmacokinetic (PK)/ pharmacodynamics (PD) endpoints, which will be detailed in a separate PK/PD analysis plan. The analyses excluded are the following:

- Serum Levels of Cytokines
- Serum Levels of Chemokines
- Biomarkers Indicative of Target Engagement
- Biomarkers Indicative of Kidney Injury
- Biomarkers Indicative of CV Endothelial Cell Damage
- Plasma Concentration of Study Drug

The purpose of this plan is to provide specific guidelines for the statistical analyses. Any deviations from this plan will be documented in the clinical study report (CSR).

2 STUDY DOCUMENTS

The following study documents are used for the preparation of the statistical analysis plan (SAP):

- Protocol, Version 2.4, 08 Apr 2021
- Annotated electronic case report form (eCRF), Version 2.0, 25 May 2021
- Data Management Plan, Version 1.0, 08 Sep 2020

3 STUDY OBJECTIVES

3.1 Primary Objective

- The primary objective of the study is to evaluate overall safety and tolerability of SIR1-365 in patients with severe COVID-19.

3.2 Secondary Objectives

Secondary objectives include:

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

4 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 treatment-emergent adverse events (TEAEs) during the treatment period (Baseline to Day 14). **Secondary Safety Measures:** • Proportion (%) of patients with any adverse events (AEs), serious adverse events (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 electrocardiogram (ECG) during the study (Baseline to Day 14 and Day 28) • Change in parameters for coagulopathy including D-dimer, fibrinogen, coagulation tests, and platelet count during the study (Baseline to Day 14 and Day 28) • Change in parameters of cardiac function including NT-proBNP (or BNP) and high-sensitivity cardiac troponin during 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.
Secondary	
Secondary Objectives: 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 PaO_2/FiO_2 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) • Change from Baseline to Days 7, 14, and 28 in the score of the World Health Organization (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 to Day 14 in plasma CRP levels • 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 serum cytokine levels including IL-6, TNF-α, IL-1β, IL-7, IL-8, IL-9, IL-10, total IL-18, G-CSF, and GM-CSF • Change from Baseline to Day 7 and Day 14 in serum chemokine levels including CXCL-1, CXCL-9, CXCL-10, IP-10, MCP-1 and MIP-1α

3) To assess the effects of SIR1-365 on biomarkers indicative of kidney injury in patients with severe COVID-19	Biomarker Assessment for Kidney Injury: • Change from Baseline to Day 7 and Day 14 in urine Neutrophil gelatinase-associated lipocalin (NGAL) level • Change from Baseline to Day 7 and Day 14 in urine Kidney injury molecule 1 (KIM-1) level
4) To assess the effects of SIR1-365 on biomarkers indicative of CV 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 in serum VWF antigen level • Change from Baseline to Day 7 and Day 14 in serum P-selectin level • Change from Baseline to Day 7 and Day 14 in serum soluble thrombomodulin level
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 plasma and/or PBMC phosphorylated RIP1 (pRIP1) level • Change from Baseline to Day 7 and Day 14 in plasma and/or PBMC phosphorylated Mixed Lineage Kinase Domain-Like protein (pMLKL) level 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 Good Laboratory Practice (GLP) guidance.

5 STUDY DESIGN AND PLAN

This is a multicenter, randomized, double-blinded, placebo-controlled study to evaluate safety and preliminary 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, 3 times per day (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, kidney injury and CV endothelial cell damage as well as SIR1-365 pharmacokinetics (PK).

Approximately 60 eligible patients will be randomly assigned at a 1:1 ratio to receive either SIRI-365 at 100 mg, TID or matching placebo for up to 14 consecutive days. For ethical and medical reasons, standard-of-care treatments for COVID-19 will be provided to all patients. Study treatments (either SIRI-365 or matching placebo) will be given as add-on therapy.

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. 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.

Table 5.1 Treatment 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.

Study procedures to assess safety, preliminary efficacy, biomarkers, and PK are shown in below table.

Table 5.2 Schedule of Assessments[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 CRP and ferritin [7]	X	X	X	X	X	X	X	X	X
Blood samples for coagulopathy and cardiac panels[8]		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
PaO_2/FiO_2 ratio	X	X		X				X	
WHO ordinal scale		X		X				X[13]	X
Blood sample for cytokine/ chemokine panels and CV biomarkers [9]		X		X				X	
Blood sample for PK analysis and pRIP1/pMLKL assay [10]		X		X				X	
Urine sample for NGAL and KM-1 assay [11]		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 the 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 3 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. CRP and ferritin tests will be done on Days 1, 3, 7, 10 and 14.
8. Coagulopathy panel including D-dimer, fibrinogen, PT, PTT and INR, and cardiac function panel including NT-proBNP (or BNP) and high-sensitivity cardiac troponin 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 cytokine/chemokine panels and CV biomarker assays to 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 2 for plasma pRIP1/pMLKL assay conducted at a central lab. PBMC preparation will be done at the sites with necessary equipment according to the laboratory manual for pRIP1/pMLKL assay.
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 NGAL and KIM-1 assay to 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*).

6 DETERMINATION OF SAMPLE SIZE

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.

7 RANDOMIZATION

Patients will be randomized to one of the 2 treatment groups: SIR1-365 100 mg or placebo at a 1:1 ratio. Randomization will be stratified according to age group (2 levels: < 60 or ≥ 60 years), Dexamethasone use (2 levels: Yes or No), and Remdesivir use (2 levels: Yes or No).

Randomization will be controlled by a web-based Randomization and Trial Supply Management (RTSM) system.

8 GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs.

Unless otherwise noted, all statistical testing will be 2-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated P-value is <0.05.

Continuous variables will be summarized by presenting the number of observations, mean, standard deviation, median, minimum, and maximum. Other summaries (eg, 95% confidence interval [CI]) may be used as appropriate.

Categorical variables will be summarized by presenting counts and percentages of patients in corresponding categories. All possible categories as defined in the CRF should be populated, even

if they have zero counts. Percentages for missing values are omitted and do not account for the percent calculation of other categories. Percentages are based on the total category count excluding the missing category if not otherwise mentioned. In certain tables (eg, AEs), the total number of patients in the analysis set is used as denominator. Footnotes in the table will specify the percent basis in those cases.

All summary tables will be presented by treatment group and a total column (except efficacy tables). Baseline summaries will also include a total summary column.

Individual patient data obtained from the eCRFs, external vendors (eg, laboratory data, ECG data), PK data, and any derived data will be presented by patient in data listings.

The analyses described in this plan are considered a priori, in that they have been defined before breaking the blind.

Any analyses performed after breaking the blind which are not specified in this analysis plan (or subsequent version prior to unblinding) will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS software Version 9.4 or higher. TLFs will be presented in rich text format (RTF). Additionally, collated portable document format (PDF) of all tables, listings and figures will be provided. Upon completion, all SAS programs and outputs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

8.1 Conventions

Derived data where it is known in advance the result will be an integer for example day, month, and year will be presented with zero decimal places.

The precision of original measurements will be maintained in summaries, when possible. Means, medians, and percentiles will be displayed to one more decimal place than the data, dispersion statistics (eg, standard deviation) will have 2 more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. The 95% CI will be presented to 2 decimal places and P-values will be presented to 4 decimal places. P-values less than 0.0001 will be presented as <0.0001. Percentages will be displayed with one decimal place.

In the case where a continuous variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

8.2 Standard Calculations

Variables requiring calculations will be derived using the following formulas:

- Baseline: A Baseline value, unless specified otherwise, is the last non-missing value recorded prior to the first dose of study drug.
- Study day: For a given date, study day will be calculated as the number of days from the day of first dosing of study drug, labeled day 1, therefore:

  Study day = date of event/measurement - date of first dose of study drug + 1, for events/measurements on or after first dose

  Study day = date of event/measurement - date of first dose of study drug, for events/measurements before first dose
- Durations (days): Durations, expressed in days, will be calculated as follows:

  Duration in days = (Stop date/time of event – Start date/time of event)/(3660x24)

  If the stop or start time is missing, only the date information will be used as follows:

  Duration in days = Stop date of event – Start date of event + 1
- Height: Height entries made in inches are converted to centimeters using the following formula:

  Height (cm) = Height (in) × 2.54
- Weight: Weight entries made in pounds are converted to kilograms using the following formula:

  Weight (kg) = Weight (lb)/2.2046
- Body Mass Index (BMI): BMI is calculated using height and weight and is calculated using the following formula:

  BMI (kg/m2) = Weight (kg) / [[Height (cm) / 100]^2]

8.3 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an AE start date or time is missing and it is unclear whether the AE is treatment emergent or not, the available information will be used to determine if an event is treatment emergent. If the classification of the event is inconclusive based on the available start/stop date information, a worst-case scenario will be taken, and AEs will be assumed to be treatment emergent.

All dates presented in the individual patient listings will be as recorded on the eCRF.

8.4 Early Discharge Assessments

If the patients are discharged from the hospital before Day 14, all the assessments planned for Day 14 should be carried out before discharge.

For all summaries and statistical analyses early discharge assessments will be analyzed and tabulated with Day 14/ EOT.

8.5 Unscheduled Visits

Only scheduled post-baseline laboratory, ECG, and vital signs values will be tabulated. Post-baseline repeat/unscheduled assessments will not be included in the summary statistics. However, these repeat/unscheduled post-baseline assessments will be listed in the relevant appendices to the CSR.

8.6 Laboratory Unit Conversion

Since more than one clinical laboratory will be used as a source for laboratory test results, an evaluation will be done to compare the units for each laboratory test and where units differ, the units will be converted to a standard unit and the conversion factors will be provided in analysis data model (ADaM) specifications.

9 ANALYSIS SETS

The following population will be used for safety analyses:

- Safety set
  All patients who are randomized and take at least 1 dose of study drug. Treatment assignment will be based on the treatment actually received.

The following populations will be used for efficacy analyses:

- Intention-to-Treat (ITT) set
  All patients who are randomized to study. Treatment assignment will be based on the randomized treatment.
- Modified Intention-to-Treat (mITT) set
  All patients who take at least one dose of study drug and have at least one follow-up efficacy or biomarker outcome evaluation. Treatment assignment will be based on the randomized treatment.
- Per Protocol (PP) set
  All patients who take at least one dose of study drug and do not have an important major protocol deviation. Treatment assignment will be based on the treatment actually received.

10 STUDY POPULATION

10.1 Patient Disposition

Patient disposition will be summarized as follows:

- The number of patients screened, the number of randomized patients, and number of patients in each analysis set will be summarized by treatment group and total.

- The number of patients randomized but not treated, completed the study drug, the reason for discontinuation of study drug, the number of patients completed the study, and the reason for discontinuation of study will be summarized by treatment group and total.

Additionally, the number of patients per site will be tabulated.

Patients excluded from the analysis sets and the reason for their exclusion will be listed in Appendix of the CSR.

The possible reasons for exclusion from the analysis sets are provided in the below table.

Table 10.1.1 Reason for Exclusion from Analysis Sets

Analysis Set	Reason for exclusion
ITT set	- Patient was not randomized to the study drug
Safety set	- Patient who did not take at least 1 dose of study drug
mITT set	- Patient who did not take at least 1 dose of study drug - Patient who did not have at least one follow-up outcome evaluation
PP set	- Patient who did not take at least 1 dose of study drug - Patient who had important major protocol deviation

Additionally, the number and percentage of patients remaining on the study at each visit will be summarized.

10.2 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.

Standard continuous variable summary for the age and categorical variable summaries for sex, ethnicity, race, inclusion criteria not met, and exclusion criteria met will be presented for total number of screen failure patients.

10.3 Protocol Deviations

Major protocol deviations that could potentially affect the safety or preliminary efficacy conclusions of the study will be identified before database lock and unblinding of individual patient treatment information. Details about protocol deviations can be found in the protocol deviation plan.

All protocol deviations, including the deviation designation (major or minor) and category will be presented in Appendix of the CSR.

10.4 Demographic and Baseline Characteristics

Standard continuous or categorical variable summaries will be presented by treatment group and total for the following variables based on the safety set.

- Age at informed consent (years)
- Age group (< 60 years, >= 60 years; sub categories: 60 – 69, 70 -79, >=80)
- Sex
- Ethnicity
- Race
- Height at screening (cm)
- Weight at screening (kg)
- Body mass index (BMI) at screening (kg/m^2)
- BMI group ($< 30\ kg/m^2$, $>= 30\ kg/m^2$)
- Female of childbearing potential
- Dexamethasone use at time of randomization
- Remdesivir use at time of randomization

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

10.5 Medical History

The verbatim term of the medical history (including smoking, drug, and alcohol use/abuse history) condition/event will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or above.

Separate listings of medical history and COVID-19 related medical history will be presented for the safety set.

10.6 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to Anatomical Therapeutic Chemical (ATC) class and preferred names using the WHODrug global dictionary (Version September, 2020) or above.

Prior medications are those medications that started and stopped before the initial dose of study drug. Concomitant medications are those medications that started after the initial dose of study drug or medications that started before the initial dose of study drug and continued during the treatment period.

Prior and concomitant medications will be summarized for each treatment by WHO ATC class and preferred term (PT). These summaries will present the number and percentage of patients

using each medication. Patients may have more than 1 medication per ATC class and PT. At each level of patient summarization, a patient is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending patient count in the total column by ATC level and PT. Additional summary will be provided for concomitant COVID-19 medications.

The safety set will be used to summarize medication data.

11 SAFETY ANALYSES

All safety analyses will be presented for the safety set.

11.1 Extent of Exposure

All patients are to receive 1 tablet, 3 times daily for 14 days. 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. Patients discharged from the hospital prior to Day 14 will not take any study drug after discharge.

The extent of exposure to study drug will be examined by assessing the total number of tablets received per patient. The total number of tablets taken per patient will be summarized using descriptive statistics by treatment group.

Additionally, the duration of treatment (days) will be calculated as follows:

- Treatment duration (days)=(Date of last administration–Date of first administration) + 1

The treatment duration per patient will be summarized using descriptive statistics by treatment group.

11.2 Adverse Events

Adverse events will be coded to System Organ Class (SOC) and PT using MedDRA (Version 23.0 or above). The coding process is described in the Data Management Plan. Severity of AEs will be graded based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

TEAEs are defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as such.

Elevated Alanine transaminase (ALT), Aspartate transaminase (AST), and creatinine levels in plasma are considered as AEs of potential interest. The list of preferred terms for AEs of potential interest are provided in Appendix 1.

TEAEs occurring during the 14-day treatment period will include those with onset in the first 14 days following first treatment date, irrespective of actual days of treatment.

Related AEs are those reported as "Definite," "Probable," or "Possible," and unrelated AEs are those reported as "Unlikely" or "Unrelated". AEs with a missing relationship are considered related to study drug.

Each AE summary will be displayed by treatment group and total. Summaries that are displayed by SOC and PT will be ordered by descending patient count in the total column by SOC and PT. Summaries of the following types will be presented:

- An overview of TEAEs
- Patient incidence of TEAEs and total number of unique TEAEs by MedDRA SOC and PT
- Patient incidence of TEAEs of potential interest and total number of unique TEAEs of potential interest by MedDRA SOC and PT
- Patient incidence of TEAEs and total number of unique TEAEs occurring with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC and PT
- Patient incidence of TEAEs occurring with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC, PT, and highest toxicity grade. At each level of patient summarization, a patient is classified according to the highest toxicity grade if the patient reported 1 or more events. Adverse events with missing toxicity grade will be considered severe for this summary.
- Patient incidence of TEAEs occurring with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC, PT, and closest relationship to study drug (Definitely Related/ Probably Related/ Possibly Related/ Unlikely Related/ Unrelated). At each level of patient summarization, a patient is classified according to the closest relationship if the patient reported 1 or more events. Adverse events with a missing relationship will be considered definitely related for this summary.
- Patient incidence of drug-related TEAEs occurring with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC and PT
- Patient incidence of drug-related TEAEs occurring with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC, PT, and highest toxicity grade
- Patient incidence of treatment-emergent SAEs occurring with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC and PT
- Patient incidence of TEAEs leading to study drug discontinuation with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC and PT
- Patient incidence of deaths with onset ≤ 7 days, onset ≤ 14 days and onset ≤ 28 days of first dose by MedDRA SOC and PT
- Listing of SAEs (presented in the Table section of the appendices)

- Listing of AEs resulting in study drug discontinuation (presented in the Table section of the appendices)
- Listing of AEs resulting in death (presented in the Table section of the appendices)

All AEs will be listed. An additional listing of all AEs of potential interest will also be created.

AEs will be analyzed descriptively including 2-sided 95% CI for between-group (SIRI-365 – placebo) incidence rates. Incidence rates among treatment groups will be compared using the Fisher exact test. AEs analyzed will include, but not necessarily limited to following:

- At least 1 AE with onset ≤ 7 days of first dose
- At least 1 AE with onset ≤ 14 days of first dose
- At least 1 AE with onset ≤ 28 days of first dose
- At least 1 TEAE with onset ≤ 7 days of first dose
- At least 1 TEAE with onset ≤ 14 days of first dose
- At least 1 TEAE with onset ≤ 28 days of first dose
- At least 1 Drug-Related TEAE
- At least 1 SAE
- At least 1 TEAE of Severe Intensity
- AE leading to study drug discontinuation
- Death

Additionally, the Exposure Adjusted Incidence Rate (EAIR) of AEs will be summarized by treatment group. The EAIR of AEs is calculated as the number of subjects with an event (preferred term), divided by the total exposure time of all subjects at risk of an initial occurrence of that event. For a subject who never experiences the event, the exposure time is calculated as the duration between the date/time of first study drug administration, to the date of last follow-up assessment (end of study participation). For subjects with at least one occurrence of an event, the exposure time is the duration between the date/time of first study drug administration, to the date/time of the first occurrence of that event.

This will be presented as the number of subjects reporting the event and calculated EAIR in person-weeks.

A similar summary will be provided of the EAIR of related AEs by preferred term.

11.3 Clinical Laboratory Evaluation

Laboratory parameters (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics at Baseline and at each post-baseline time point by treatment group.

Changes from Baseline will also be summarized. Refer to the list of laboratory tests to be performed in Appendix 2.

In addition, shift tables will be provided to assess changes in laboratory values from Baseline to the most extreme post-baseline value using clinically notable reference ranges to derive if a laboratory measurement as low, normal, or high compared to the reference ranges.

Selected laboratory parameters (refer to Appendix 3) will be graded according to NCI CTCAE v5.0[1]. The number and percentage of patients with CTCAE Grade ≥3 laboratory values will be summarized by treatment group.

The number and percentage of patients with clinically significant laboratory test findings will also be summarized by treatment group and visit. This will be done by laboratory category and laboratory parameter, as well as by overall.

Serology test and serum pregnancy test results at screening will be listed only.

11.4 Vital Signs

Vital sign data will be summarized by presenting summary statistics for observed and change from Baseline values, by visit and treatment group. Temperature will be collected in °C (Celsius) or °F (Fahrenheit) in eCRF, all values will be converted to °C for analysis.

The °F values will be converted using the formula given below.

$$°C = (°F - 32) * /9$$

Descriptive statistics for the following vital signs will be presented:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Respiration rate (breaths/min)
- Body temperature (°C)

The incidence rates of vital sign abnormalities (refer to Appendix 4: Criteria for Abnormal Values for Vital Signs) will be summarized by treatment group. A second summary table will also be produced, summarizing the incidence rates of vital sign abnormalities by treatment group and visit.

The incidence rates of clinically significant vital signs will be summarized by treatment group, as well as by treatment group and visit.

A data listing of vital signs will also be created.

11.5 Physical Examination

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.

Abnormal findings on physical examination prior to signing of informed consent will be included in medical history CRF whereas abnormal findings started after the signing of informed consent will be included in AE CRF.

Physical examination results will be included in data listings only.

11.6 12-Lead ECG

Values for the following 12-lead ECG parameters and change from Baseline values will be summarized through descriptive statistics by treatment group and visit.

- PR interval (sec)
- RR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- Corrected QT interval (msec)

Three ECGs with 1-3 min interval will be performed before 1st dose on Day 1 only, and for data recorded on continuous scale, the means of the 3 ECGs will be used as Baselines and overall interpretation will be presented as the most severe (worst case) of the respective readings for Baseline. A single ECG will be performed for all other time points.

All ECGs must be evaluated by the Investigator and assessed as normal or abnormal, including the clinical significance (Yes/No) of abnormal values. The number and percentage of patients with clinically significant abnormal interpretation of ECGs will also be summarized by treatment group and visit.

The maximum increase in corrected QT interval from Baseline will be summarized through descriptive statistics by treatment group.

11.7 Coagulopathy

Values for the following coagulopathy panel and change from Baseline values will be summarized through descriptive statistics by treatment group and visit.

Additionally for D-Dimer, the percentage change from Baseline values will also be summarized by treatment group and visit. The mean change and mean percentage change from Baseline up to Day 14, using the actual study day for Day14/EOT assessments, will be plotted per treatment group using line graphs. A non-parametric Wilcoxon Rank Sum test will be used to compare

the treatment groups with respect to the percentage change from baseline values at Day 7 and Day 14/EOT.

- D-dimer
- Fibrinogen
- Platelet count
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- International normalized ratio (INR)

A separate summary table will be produced, similar to what is described above, summarizing the results at Day 7 (assessments taking place on study day 7), Day 14 (assessments taking place on study day 14) and Day 28 (assessments taking place on study day 28). For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14. Day 28 missing observations will be imputed with the last available assessment that took place after study day 14. A summary table will be produced, summarizing these (imputed and reported) results. This data will also be presented using a boxplot.

11.7.1 Time to first time back to normal

Time to first time back to normal (in days) is the number of days between the date of first study drug administration and the first date that the result of a coagulopathy parameter returns back to within a normal range.

Time to first time back to normal will be analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% CI for SIR1-365 dose vs placebo.

The proportional hazard regression model will include a single term for treatment.

- Patients with a baseline value falling within the normal range will be censored on the first date of study drug administration.
- Death prior to returning back to normal will be handled as a competing risk event.
- Patients that do not return back to normal over the assessment period will be censored at the date of last assessment
- Patients with no post-baseline assessment value will be censored at Day 1.

The hazard ratio estimation of the event of interest (first time back to normal) will be derived from a cumulative incidence function. The Kaplan Meier estimate of median time to event will also be presented for each treatment group.

11.8 Cardiac Function Damage

Cardiac function damage panel including NT-proBNP (or BNP) and high sensitivity cardiac troponin will be summarized using descriptive statistics at Baseline and at each post-baseline time point by treatment group. Changes from Baseline will also be summarized.

A separate summary table will be produced, similar to what is described above, summarizing the results at Day 7 (assessments taking place on study day 7), Day 14 (assessments taking place on study day 14) and Day 28 (assessments taking place on study day 28). For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14. Day 28 missing observations will be imputed with the last available assessment that took place after study day 14. A summary table will be produced, summarizing these (imputed and reported) results.

11.9 Correlation Analysis for Safety Outcomes

Correlation of biomarker levels to safety outcomes will be assessed between the proportions of safety outcomes, i.e TEAE and SAE with Baseline levels of inflammatory biomarkers using logistic regression analysis as detailed below.

A logistic regression model will be fitted to the binomial presence (Yes/No) of adverse events per patient as a function of treatment, Baseline biomarker and the interaction between treatment and Baseline biomarker as fixed effects.

The regression coefficients, 95% CI and corresponding P-values will be reported and used to assess the association between the following Baseline biomarker parameters and the proportion of TEAE and SAE per treatment group:

- Baseline CRP
- Baseline Ferritin and lymphocyte counts

12 CLINICAL EFFICACY ANALYSES

The clinical efficacy analyses will be based on the ITT set, unless specified otherwise. The mITT set will be primary population for the biomarker analysis with exception of time to 50% reduction of CRP levels for which the ITT set will be primary.

12.1 Clinical Efficacy Variables

Clinical Efficacy Endpoints:

- Change from Baseline to Day 7 and Day 14 in PaO_2/FiO_2 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)

- 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)

Inflammatory Biomarker Measures:

- Change from Baseline to Day 7 and Day 14 in plasma CRP levels
- 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 serum cytokine levels including IL-6, TNF-α, IL-1β, IL-7, IL-8, IL-9, IL-10, total IL-18, G-CSF, and GM-CSF
- Change from Baseline to Day 7 and Day 14 in serum chemokine levels including CXCL-1, CXCL-9, CXCL-10, IP-10, MCP-1 and MIP-1α

Biomarker Assessment for Kidney Injury:

- Change from Baseline to Day 7 and Day 14 in urine NGAL level
- Change from Baseline to Day 7 and Day 14 in urine KIM-1 level

Biomarker Assessment for CV Endothelial Cell Damage:

- Change from Baseline to Day 7 and Day 14 in serum VWF antigen level
- Change from Baseline to Day 7 and Day 14 in serum P-selectin level
- Change from Baseline to Day 7 and Day 14 in serum soluble thrombomodulin level

Biomarker Assessment for Target Engagement:

- Change from Baseline to Day 7 and Day 14 in plasma and/or PBMC pRIP1 level
- Change from Baseline to Day 7 and Day 14 in plasma and/or PBMC pMLKL level

12.2 Adjustments for Covariates

Baseline measurement of the respective dependent variable will be used as a covariate in analysis of covariance (ANCOVA) models for selected efficacy variables.

12.3 Subgroup Analysis

Subgroup analyses will be performed on the CRP levels, PaO_2/FiO_2 ratio and WHO ordinal scale to summarize the treatment effects across countries based on mITT set by repeating the analysis as described for biomarker in Section 14.1.1 CRP Levels and preliminary efficacy

endpoints in Section 13.1.1 PaO_2/FiO_2 ratio and Section 13.1.4 WHO ordinal scale by country (USA, Mexico and Pakistan).

A subgroup analysis will also be performed on the duration of hospitalization after treatment, to summarize the treatment effect on those patients who completed study treatment, by repeating the analysis as described for hospitalization in Section 13.1.5 Days of Hospitalization for the subgroup of patients that completed treatment. Completed patients are defined as those patients that indicated 'Yes' to 'Was Study Treatment Completed?' on the End of Treatment CRF.

A subgroup analysis will also be done for the derived PaO_2/FiO_2 ratio to summarize the treatment effects across countries based on mITT set, by repeating the analysis as described for biomarker in Section 13.1.1.1 by country (USA, Mexico and Pakistan).

12.4 Handling of Dropouts or Missing Data

In the analysis of CRP levels if more than 10% of patients in either arm has missing Day 7 CRP values, a supportive analysis will be performed using a mixed model for repeated measures (MMRM). Details of this analysis is provided in Section 14.1 Inflammatory Biomarkers.

Additionally, in the analysis of the PaO_2/FiO_2 ratio if more than 10% of patients in either arm has missing Day 7 values, a supportive analysis will be performed using a mixed model for repeated measures (MMRM). Details of this analysis is provided in Section 13.1.1 PaO_2/FiO_2 ratio.

For any patients with missing results on study day 7, the Day 7 results for coagulopathy, cardiac function damage, the PaO_2/FiO_2 ratio, the WHO ordinal scale and CRP levels will be imputed with the last available assessment, prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that occurred after Day 7 and prior to Day 14. Where applicable, Day 28 missing observations will be imputed with the last available assessment that occurred after Day 14. More details are given in the relevant sections of this analysis plan.

12.5 Interim Analysis and Data Monitoring

No interim analysis is planned for this study. However, during the study, unblinded safety, biomarker, and clinical efficacy data will be reviewed by an independent data monitoring committee (IDMC) approximately when roughly 20 and 40 patients are enrolled.

13 METHODS OF EFFICACY ANALYSIS

13.1 Clinical Efficacy Analyses

Although the study is not powered for hypothesis testing of secondary endpoints, P-values will be generated to aid interpretation in addition to CIs about the estimates.

For all continuous measures, exploratory comparisons between treatment groups will be tested by comparing the mean change from Baseline values between treatment groups.

13.1.1 PaO_2/FiO_2 ratio

The PaO_2/FiO_2 ratio, change and percentage change from Baseline in PaO_2/FiO_2 ratio will be summarized by visit and treatment using both simple descriptive statistics and model-based estimates. A non-parametric Wilcoxon Rank Sum test will be used to compare the treatment groups with respect to the percentage change from baseline values at Day 7 and Day 14/EOT.

A separate summary table will be produced, similar to what is described above, summarizing the results at Day 7 (assessments taking place on study day 7) and Day 14 (assessments taking place on study day 14). For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14. A summary table will be produced, summarizing these (imputed and reported) results.

The change from Baseline at each visit will be compared between treatment groups using an ANCOVA model with fixed effects for treatment and the Baseline score as a continuous covariate. Comparison of the SIR1-365 dose and placebo will be constructed based on least-squares means (LSMean) from the model.

The mean change and mean percentage change from Baseline up to Day 14, using the actual study day for Day14/EOT assessments, will be plotted per treatment group using line graphs.

As a sensitivity analysis, to assess the impact of missing data, if more than 10% of patients in either arm has a missing Day 7 PaO_2/FiO_2 ratio, a MMRM analysis will be performed. The PaO_2/FiO_2 ratio will be analyzed by a MMRM with treatment group, Day (Days 2 to 14), and treatment group-by-Day interaction as fixed factors, and the Baseline score as a continuous covariate. Day will be used as the repeated measure using an unstructured covariance structure. For both treatment groups, at Day 7, the geometric LS mean in the PaO_2/FiO_2 ratio and corresponding 95% CI will be presented. The output will also include the estimated geometric LS mean ratio for SIR1-365 dose and placebo, the corresponding 95% CI and corresponding two-sided P-value for the ratio.

13.1.1.1 Derived PaO_2/FiO_2 ratio

The PaO_2/FiO_2 ratio will also be derived based on the Collected O_2Sat Level (%) and the Fraction of Inspired Oxygen (FiO_2) from the O_2 Saturation Readings CRF page, and the Fraction of Inspired Oxygen (FiO_2) from the PaO_2/FiO_2 ratio CRF page.

First, the estimated PaO_2 will be calculated based on the collected O_2Sat Level and the table below.

Table 13.1.1.1

SO_2 (%)	PaO_2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145
100	145

The derived PaO_2/FiO_2 ratio is calculated as follows:

Derived PaO_2/FiO_2 ratio = (Estimated PaO_2 / Collected FiO_2) x 100

If the FiO_2 is available from the PaO_2/FiO_2 ratio CRF page, then this will be used for the collected FiO_2 in the calculation above. Otherwise, the FiO_2 from the O_2 Saturation Readings CRF page will be used as the collected FiO_2 in the calculation.

For the analysis, the derived PaO_2/FiO_2 ratio will be used for imputation, if the collected PaO_2/FiO_2 ratio is missing. These collected and imputed values for the PaO_2/FiO_2 ratio, as well as the change and percentage change from Baseline, will be summarized by visit and treatment using both simple descriptive statistics and model-based estimates. A non-parametric Wilcoxon Rank Sum test will be used to compare the treatment groups with respect to the percentage change from baseline values at Day 7 and Day 14/EOT.

13.1.2 Time to improvement of oxygenation

Oxygen saturation will be measured daily via pulse oximetry.

Time to improvement of oxygenation (in days) 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.

The time to improvement will be analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% CI for SIR1-365 dose vs placebo.

The proportional hazard regression model will include a single term for treatment. Patients without a pulse oximetry >93% with an 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, whichever come later.

- Patients without a post-baseline oximetry measurement who did not receive supplemental oxygen will be censored at day 1.
- Death prior to an improvement will be handled as a competing risk event.

The hazard ratio estimation of the event of interest (improvement of oxygenation) will be derived from a cumulative incidence function.

Kaplan Meier curves of time to improvement of oxygenation will be plotted for each treatment group on the same graph.

13.1.3 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 treatment. An estimate of the difference in mean numbers of days between SIR1-365 dose and placebo will be provided along with a corresponding 95% CI based on an ANOVA model with treatment as fixed effect.

The continuous duration (in days) where a patient's oxygen requirement is 'Room Air' will be derived using the date and time information from the 'O_2 Saturation' and 'Changes in Patient O_2 Requirements' eCRFs to calculate the cumulative days (including fractional days) on 'room air' through the end of calendar Day 28 where Day 1 is the day of the first dose of SIR1-365/matching placebo (or date of randomization if not treated). In the event that days/time on only room air are available after the end of day 28 that time (beyond the interval of interest) will not be included in the oxygen-free days.

The above analysis will also be repeated Baseline to Day 14.

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

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.

When completing the WHO Ordinal Scale at Day 14/ EOT, if the patient has received physician orders to be discharged from the hospital, the score should be a 3 or less (*no longer hospitalized*).

Change and percentage 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.

A separate summary table will be produced, similar to what is described above, summarizing the results at Day 7 (assessments taking place on study day 7), Day 14 (assessments taking place on study day 14) and Day 28 (assessments taking place on study day 28). For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14. Day 28 missing observations will be imputed with the last available assessment that took place after study day 14. A summary table will be produced, summarizing these (imputed and reported) results.

Categorical summaries of patients having a clinical improvement during the study (Baseline to Day 28) will be generated presenting the number and percentage of patients with an improvement at any visit from Baseline to Day 28. Associated 95% CI for the proportion of improvement will be provided for each treatment group using the Clopper-Pearson method.

The distribution of outcomes on the ordinal scale will also be plotted using stacked bar charts representing the proportion of patients in each category (uninfected, ambulatory mild disease, hospitalized: moderate disease, hospitalized: severe disease and death), by treatment group over time. A second plot will be produced, similar to what is described above, summarizing the results at Day 7 (assessments taking place on study day 7), Day 14 (assessments taking place on study day 14) and Day 28 (assessments taking place on study day 28). For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14. Day 28 missing observations will be imputed with the last available assessment that took place after study day 14.

The mean absolute values and mean absolute change from Baseline up to Day 14, using the actual study day for Day14/EOT assessments, will be plotted per treatment group using line graphs.

13.1.4.1 Time to clinical improvement

Time to clinical improvement is defined as the number of days between the date of first study drug administration and the first date a patient achieves a 2-point reduction on the WHO ordinal scale.

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

The proportional hazard regression model will include a single term for treatment.

- Death prior to clinical improvement will be handled as a competing risk event.
- Patients that do not show any clinical improvement over the assessment period will be censored at the date of last assessment.
- Patients with no post-baseline assessment value will be censored at Day 1.

The hazard ratio estimation of the event of interest (clinical improvement) will be derived from a cumulative incidence function. The Kaplan Meier estimate of median time to event will also be presented for each treatment group.

Table 12.1.4 Categories for WHO Ordinal Scale

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

13.1.5 Days of hospitalization

Days of hospitalization after treatment will be determined using the 'Study Drug Administration' and 'Hospitalization Details' eCRFs. The date and time (in format 23:59) of 1st dose of study drug and discharge will be collected.

Duration of hospitalization after treatment up through 14 days will be calculated as

- Duration of hospitalization after treatment (days) = (Date and time of discharge – Date and time of 1st dose of study drug)/60/24

Missing discharge times will be assumed to be '23:59' in order to calculate the maximum duration of time hospitalized. In the event a patient is hospitalized more than 14 days, 14 days will be used for analysis.

For patients that died within the first 14 days while hospitalized, the duration of hospitalization will be imputed as 14 days in order not to underestimate the number of days of hospitalization. In the unlikely event a patient dies within 14 days but subsequent to discharge, the number of days hospitalized will be 14 minus the number of days from discharge to death.

For patients with multiple hospitalizations in the first 14 days, the sum of all intervals will be calculated for analysis.

Duration of hospitalization after treatment as a continuous variable will be summarized descriptively by treatment and analyzed using a 1-way ANOVA model with a single term for treatment.

A similar analysis will be done for the total duration of hospitalization:

- Total duration of hospitalization (days) = (Date and time of discharge – Date and time of admission)/60/24

Missing admission times will be assumed to be '00:00' and missing discharge times will be assumed to be '23:59' in order to calculate the maximum duration of time hospitalized.

13.1.6 Patients with 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). Other oxygen requirements recorded in the "Other, Specify' field of the eCRF

will be reviewed for any other criteria that may qualify. Any such cases will be identified prior to database lock and unblinding.

The number and percentage of patients with respiratory failure at any time from Baseline to Day 28 will be summarized by treatment. Associated 95% CI for the proportion of respiratory failure will be provided for each treatment group using Clopper-Pearson method. Patients without any post baseline oxygen requirement data recorded will be considered free of respiratory failure.

Changes in O_2 requirements which are considered to be respiratory failure will be flagged in the data listing.

13.1.7 All-cause mortality rate

All-cause mortality (from Baseline to Day 28) rate will be summarized by treatment group. Associated 95% CI for the proportion will be provided for each treatment group using Clopper-Pearson method.

13.2 Correlation Analysis for Preliminary Efficacy Outcomes

Correlation of biomarker levels to preliminary efficacy outcomes will be assessed between changes from Baseline in preliminary efficacy outcomes with Baseline levels of inflammatory biomarkers using Fisher's transformation of Pearson's or Spearman's correlation as detailed below.

The Fisher's transformation of Pearson correlation coefficient, 95% CI and corresponding P-value will be presented for the correlation between the following Baseline biomarker parameters and change from Baseline to Day 7 and Day 14 in PaO_2/FiO_2 ratio.

- Baseline CRP
- Baseline Ferritin and lymphocyte counts

The above analysis will be repeated based on assessments that took place on Study Day 7 and Study Day 14. For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14.

The Fisher's transformation of Spearman rank correlation will also be used to assess the correlation between the same Baseline biomarker profiles, as well as the PaO_2/FiO_2 ratio, and change from Baseline to Days 7, 14, and 28 in WHO ordinal scale.

This analysis will be repeated based on assessments that took place on Study Day 7, Study Day 14 and Study Day 28. For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day

7 and prior to study day 14. Day 28 missing observations will be imputed with the last available assessment that took place after study day 14.

13.3 Exploratory Analysis

As an exploratory analysis, to assess the effect of randomization stratification factors, an ANCOVA model with fixed effects for treatment, Dexamethasone use, and Remdesivir use and the Baseline score and age as continuous covariates will be fitted to the change from Baseline in PaO_2/FiO_2 ratio and CRP values.

The parameter estimates and corresponding P-values for each covariate, the LSMeans (standard error) for each treatment group, the LSMean difference between treatment groups, along with 95% CI of the treatment difference and P-value for treatment comparison will be presented.

The same statistical methods as described for preliminary efficacy endpoints in Section 13.1.1 PaO_2/FiO_2 ratio and biomarker in Section 14.1.1 CRP Levels will be followed for the analysis.

14 BIOMARKER ANALYSIS

Biomarkers will be analyzed using the mITT set, unless specified otherwise.

14.1 Inflammatory Biomarkers

Observed values of all inflammatory biomarkers will be graphically presented at each visit using box and whisker plots.

14.1.1 CRP Levels

Plasma CRP level will be measured on days 1, 3, 7, 10 and 14 at local laboratories.

Descriptive tabulation:

A descriptive summary tabulation will be provided displaying descriptive statistics of the CRP levels, changes and percentage changes from Baseline for each treatment group by visit. The mean change and mean percentage change from Baseline up to Day 14, using the actual study day for Day14/EOT assessments, will be plotted per treatment group using line graphs.

A separate summary table will be produced, similar to what is described above, summarizing the results at Day 7 (assessments taking place on study day 7) and Day 14 (assessments taking place on study day 14). For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14. A summary table will be produced, summarizing these (imputed and reported) results.

Inferential analysis:

Inferential analyses will be conducted to compare the difference in CRP levels between SIR-365 dose and placebo.

The CRP levels on Day 7 and Day 14 will be analyzed by an ANCOVA with treatment group as a fixed factor, and the respective Baseline score as a covariate in the model.

The CRP values will be log-transformed (natural log) for analysis. Comparison of the SIR1-365 dose 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.

For both treatment groups the number of observations, the geometric least square mean (LS mean) in plasma CRP levels and corresponding 95% CI will be presented. The output will also include the estimated geometric LS mean ratio for SIR1-365 dose and placebo, the corresponding 95% CI and corresponding two-sided P-value for the difference.

If the residuals are found to deviate substantially from normality a supportive analysis using the non-parametric Wilcoxon Rank Sum test will be performed.

A non-parametric Wilcoxon Rank Sum test will be used to compare the treatment groups with respect to the percentage change from baseline values at Day 7 and Day 14/EOT.

Sensitivity analysis:

As a sensitivity analysis, to assess the impact of missing data, if more than 10% of patients in either arm has missing Day 7 CRP values, a MMRM analysis will be performed. The plasma CRP levels will be analyzed by a MMRM with treatment group, Day (Days 2 to 14), and treatment group-by-Day interaction as fixed factors, and the Baseline score as a continuous covariate. Day will be used as the repeated measure using an unstructured covariance structure. For both treatment groups, at Day 7, the geometric LS mean in plasma CRP levels and corresponding 95% CI will be presented. The output will also include the estimated geometric LS mean ratio for SIR1-365 dose and placebo, the corresponding 95% CI and corresponding two-sided P-value for the ratio.

Additionally, the primary analysis for plasma CRP level on Day 7 and Day 14 will be repeated for PP set with no missing data imputation.

A separate summary table will be produced, similar to what is described above, summarizing the results at Day 7 (assessments taking place on study day 7) and Day 14 (assessments taking place on study day 14). For any patients with missing Day 7 results, the Day 7 results will be imputed using the last value reported prior to study day 7. Similarly, Day 14 missing observations will be imputed with the last available assessment that took place after study day 7 and prior to study day 14. A summary table will be produced on the PP set, summarizing these (imputed and reported) results.

Time to 50% reduction:

Time (days) to 50% reduction from Baseline in plasma CRP level during the treatment period will be analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% CI for SIR1-365 dose vs placebo.

The proportional hazard regression model will include treatment as a fixed effect.

- Patients without a 50% reduction will be censored at the date of their last CRP assessment.
- Patients with no post-baseline CRP value will be censored at Day 1.
- Death, prior to 50% reduction, will be handled as a competing risk event.

The hazard ratio estimation of the event of interest will be derived from a cumulative incidence function. The number and percentage of patients to reach 50% reduction from Baseline in plasma CRP level from Baseline to Day 14 will also be summarized. This analysis will be performed in the ITT set.

Kaplan Meier curves of time to 50% reduction from baseline in plasma CRP level will be plotted for each treatment group on the same graph.

14.1.2 Ferritin and white blood cell counts

Change and percentage change from Baseline in ferritin, lymphocyte, and neutrophil counts, as well as neutrophil to lymphocyte ratio as continuous variables will be summarized by visit and treatment. The mean change and mean percentage change from Baseline up to Day 14, using the actual study day for Day14/EOT assessments, will be plotted per treatment group using line graphs. A non-parametric Wilcoxon Rank Sum test will be used to compare the treatment groups with respect to the percentage change from baseline values at Day 7 and Day 14/EOT.

14.1.2.1 Time to first time back to normal

Time to first time back to normal (in days) is the number of days between the date of first study drug administration and the first date that the result of the parameter of interest returns back to within a normal range. Parameters used for this analysis will be ferritin, lymphocytes and neutrophils.

Time to first time back to normal will be analyzed using a Cox proportional hazards model to estimate the hazard ratio and corresponding 95% CI for SIR1-365 dose vs placebo.

The proportional hazard regression model will include a single term for treatment.

- Patients with a baseline value falling within the normal range will be censored on the first date of study drug administration.
- Death prior to returning back to normal will be handled as a competing risk event.
- Patients that do not return back to normal over the assessment period will be censored at the date of last assessment
- Patients with no post-baseline assessment value will be censored at Day 1.

The hazard ratio estimation of the event of interest (first time back to normal) will be derived from a cumulative incidence function. The Kaplan Meier estimate of median time to event will also be presented for each treatment group.

15 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

No changes to protocol-specified analysis.

16 REFERENCES

1. Common Terminology Criteria for Adverse Events (CTCAE). Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50
2. E3 Structure and Content of Clinical Study Reports. Available from: https://www.fda.gov/media/71271/download

17 APPENDICES

Appendix 1: AE of Potential Interest

The following preferred terms will be considered as AE of Potential Interest.

- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Blood creatinine increased

Appendix 2: Clinical Laboratory Tests to be Performed at Local Laboratory

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	Urea	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 3: CTCAE V5.0 for Clinical Laboratory Findings

Category	Lab Test	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry	Alanine Aminotransferase (U/L)	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Chemistry	Albumin (g/L)	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Chemistry	Alkaline Phosphatase (U/L)	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Chemistry	Aspartate Aminotransferase (U/L)	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Chemistry	Bicarbonate (mmol/L)	Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-
Chemistry	Bilirubin (umol/L)	Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal

			baseline was abnormal	baseline was abnormal	baseline was abnormal	
Chemistry	Calcium (mmol/L)	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
		Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences
Chemistry	Cholesterol (mmol/L)	Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Chemistry	Creatinine (umol/L)	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Coagulopathy	Fibrinogen (g/L)	Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL

Chemistry	Gamma Glutamyl Transferase (ukat/L)	GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Chemistry	Glucose (mmol/L)	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Hematology	Hemoglobin (g/L)	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80 g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
	Hemoglobin (g/L)	Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-
Chemistry	Lactate Dehydrogenase (U/L)	Blood lactate dehydrogenase increased	>ULN	-	-	-
Hematology	Leukocytes (10^9/L)	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10^9/L	<3000 - 2000/mm3; <3.0 - 2.0 x 10^9/L	<2000 - 1000/mm3; <2.0 - 1.0 x 10^9/L	<1000/mm3; <1.0 x 10^9/L
Hematology	Lymphocytes (10^9/L)	Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10^9/L	<800 - 500/mm3; <0.8 - 0.5 x 10^9/L	<500 - 200/mm3; <0.5 - 0.2 x 10^9/L	<200/mm3; <0.2 x 10^9/L
		Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3 <4 - 20 x 10^9/L	>20,000/mm3 >20 x 10^9/L	-

Hematology	Neutrophils (10^9/L)	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10^9/L	<1500 - 1000/mm3; <1.5 - 1.0 x 10^9/L	<1000 - 500/mm3; <1.0 - 0.5 x 10^9/L	<500/mm3; <0.5 x 10^9/L
Hematology	Platelets (10^9/L)	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10^9/L	<25,000/mm3; <25.0 x 10^9/L
Chemistry	Potassium (mmol/L)	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
		Hypokalemia	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Chemistry	Sodium (mmol/L)	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
		Hyponatremia	<LLN - 130 mmol/L	-	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences
Chemistry	Triglycerides (mmol/L)	Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences

Appendix 4: Criteria for Abnormal Values for Vital Signs

Vital Signs	Criterion Value
Heart Rate	< 54 beats/min > 120 beats/min
Respiration Rate	< 10 breaths/min > 17 breaths/min
Systolic Blood Pressure	< 90 mmHg > 140 mmHg
Diastolic Blood Pressure	< 60 mmHg > 90 mmHg
Body Temperature	< 35 °C > 38 °C

Appendix 5: List of Tables, Listings, and Figures

The following proposal for Sections 14 and 16.2 is completed according to ICH E3[2] guidelines. The heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

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PK/PD Data Statistical Analysis Plan

Study Number: SIR365-US-101

Study title: A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study to Assess Safety and Efficacy of SIR1-365 in Patients with Severe COVID-19 (Protocol Version 2.4 issued on April 8th, 2021)

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LIST OF ABBREVIATIONS

Abbreviation	Full Notation
BLQ	Below limit of quantification
CI	Confidence Interval
CV	Coefficient of Variation or Cardiovascular
eCRF	Electronic case report form
EOT	End of treatment or early discharge
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
SAP	Statistical analysis plan
SD	Standard deviation
TFL	Table, listing, figure
TID	Three times a day

1 INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of PK/PD data collected within the scope of SIR365-US-101 (A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Study to Assess Safety and Efficacy of SIR1-365 in Patients with Severe COVID-19). The purpose of this plan is to provide specific plans for the statistical analyses of PK/PD data.

2 STUDY DOCUMENTS

The following study documents are used for the preparation of the statistical analysis plan (SAP):

- Protocol, Version 2.4, Apr 8th, 2021
- Annotated electronic case report form (eCRF 2.0 April 26th, 2021)
- Data Management Plan, Version 1.0, Sep 8th, 2020

3 ANALYSIS OBJECTIVES

The objective of Study SIR365-US-101 is to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of SIR1-365 after oral administrations in patients with severe COVID-19.

To assess the PD effects of SIR1-365, the following biomarker measures will be carried out:

1). Biomarkers Indicative of Inflammation

- Change from Baseline to Day 7 and Day 14 in serum cytokine levels including INF-γ, IL-6, TNF-α, IL-1β, IL-7, IL-8, IL-9, IL-10, total IL-18, G-CSF, and GM-CSF
- Change from Baseline to Day 7 and Day 14 in serum chemokine levels including CXCL-1, CXCL-9, CXCL-10, MCP-1, MIP-1α, and MIP-1β

2). Biomarkers Indicative of CV Endothelial Cell Damage

- Change from Baseline to Day 7 and Day 14 in serum VWF antigen level
- Change from Baseline to Day 7 and Day 14 in serum P-selectin level
- Change from Baseline to Day 7 and Day 14 in serum soluble thrombomodulin level

3). Biomarkers Indicative of Kidney Injury

- Change from Baseline to Day 7 and Day 14 in urine NGAL level
- Change from Baseline to Day 7 and Day 14 in urine KIM-1 level

4). Biomarkers Indicative of Target Engagement

- Change from Baseline to Day 7 and Day 14 in plasma and/or PBMC pRIP1 level
- Change from Baseline to Day 7 and Day 14 in plasma and/or PBMC pMLKL level

4 STUDY DESIGN AND PLAN

This is 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, 3 times per day (TID) for up to 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 SIR1-365 PK.

Approximately 60 eligible patients will be randomly assigned at a 1:1 ratio to receive either SIRI-365 at 100 mg TID or matching placebo for up to 14 consecutive days. For ethical and medical reasons, standard-of-care treatments for COVID-19 will be provided to all patients. Thus, the study drugs (either SIRI-365 or matching placebo) will be given as add-on therapy.

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, no study drugs will be administered. A follow-up visit in person will be performed 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. Follow-up visit will be scheduled approximately on Day 28 (±3) or 14 days after discharge/end of treatment.

5 SAMPLE ANALYSIS

5.1. Measurement of Plasma Drug Levels (PK)

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

Day 7 and Day 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.

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

5.2. Measurement of Biomarker Levels (PD)

5.2.1. Measurement of Biomarkers Indicative of Inflammation

5.2.1.1. Cytokines

Serum cytokines including INF-γ, IL-6, TNF-α, IL-1β, IL-7, IL-8, IL-9, IL-10, total IL-18, G-CSF, GM-CSF will be measured at a central laboratory.

5.2.1.2. Chemokines

Serum chemokines including CXCL-1, CXCL-9, CXCL-10, MCP-1, MIP-1α and MIP-1β will be measured at a central laboratory.

5.2.2. Measurement of Biomarkers Indicative of Kidney Injury

Urine NGAL and KIM-1 levels will be measured at a central laboratory.

5.2.3. Measurement of Biomarkers Indicative of CV Endothelial Cell Damage

Serum VWF antigen, P-selectin and soluble thrombomodulin levels will be measured at a central laboratory.

5.2.4. Measurement of Biomarkers Indicative of Target Engagement

Levels of pRIP1 and pMLKL in plasma and PBMC will be measured at a central laboratory. PBMC preparation will be done at the sites with necessary equipment according to the laboratory manual for pRIP1/pMLKL assay.

6 STATISTICAL ANALYSIS

6.1. General Analysis Considerations

The statistical analyses will be reported using summary tables, listings, and figures (TFLs). Unless otherwise noted, all statistical testing will be 2-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated P value is <0.05.

Continuous variables will be summarized by presenting the number of observations, mean, standard deviation. Other summaries (e.g., 95% confidence interval [CI]) may be used as appropriate. Categorical variables will be summarized by presenting counts and percentages of patients in corresponding categories. Footnotes in the table will specify the percent basis in those cases.

All summary tables will be presented by treatment group. PK/PD data, and any derived data will be presented by patient in data listings.

The analyses described in this plan are considered a priori, in that they have been defined before unblinding.

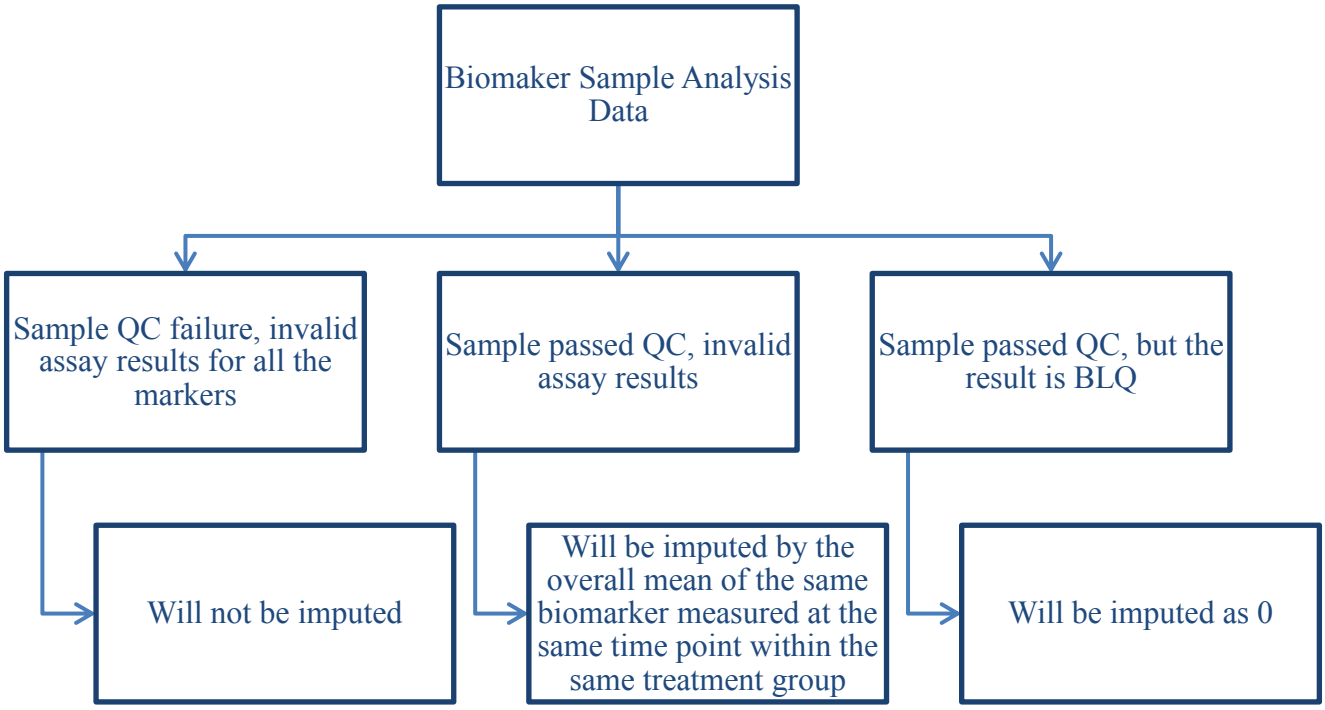
All analyses and tabulations will be performed using R (version 4.0.1 or higher) or SAS (Version 9.4 or higher).

All analyses will be conducted by a designated statistician. The programming code, results, analysis report will be independently reviewed by another statistician.

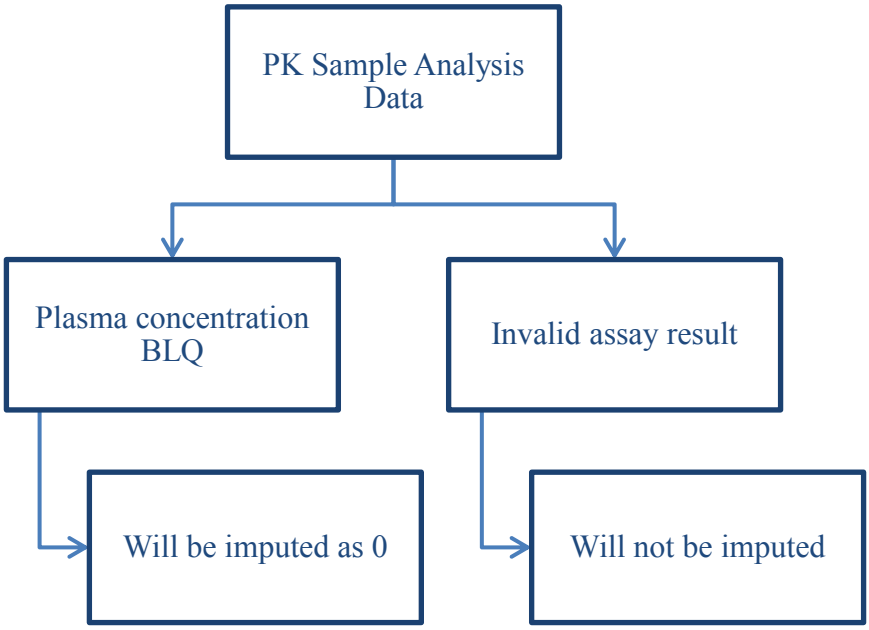
6.2. Analysis Set

All patients who receive study drug without major protocol deviation related to PK/PD analysis and have sufficient PK/PD data to obtain reliable estimates of the key PK/PD variables. Treatment assignment will be based on the treatment actually received.

If a sample yields invalid assay results for all the biomarkers, the data will not be imputed. If a sample has both valid and invalid assay results, the biomarkers with failed assay will be imputed by the overall mean of the same biomarker measured at the same time point within the same treatment group. If the assay passed QC but the result is BLQ, it will be imputed as 0. This process is shown by the flow chart below.



All plasma drug levels below the limit of quantitation (BLQ) values will be imputed as zero (0). If a sample yields invalid assay result, the data will not be imputed. The process is shown by the flow chart below.



For the analysis of both PK and PD biomarker data, if the sample was collected before or on Day 7, the time is labelled as Day 7; if the sample was collected after Day 7, the time is labelled as Day 14.

6.3. Statistical Analysis of PK Data

Summary statistics will be reported by treatment group for each sampling time point (D1 30 minutes predose, D1 2hr post dose, D7 30 mins predose, D7 2hr post dose, D14 30 mins predose, D14 2hr post dose). Summary statistics include N, mean, median, SD, Min, and max. The plasma drug concentration will be presented by line plots, which illustrate the mean +/- stderr for two groups.

6.4. Statistical Analysis of Biomarker Data

For each marker, raw signal value, change from baseline, and percentage change from baseline will be analyzed. Summary statistics (for raw signal measurements, change from baseline, and percentage change from baseline) will be reported for each marker at baseline, Day 7, and Day 14 by treatment group.

Line plots of change and percentage change from baseline will be presented for each marker. Each line illustrates the value of a PD marker (Y-axis) changes over time (X-axis) of a single subject. Each marker will be represented by one line plot, in which all the subjects are included, treatment groups will be labelled by different colors. In addition, mean +/- stderr line plots will be generated for the two treatment groups.

For pRIP1 and pMLKL, similar line plots will be presented for pre-dose and post-dose separately. Specifically, Day 1 pre-dose and Day 1 post-dose values will be used, respectively, as the baseline for the calculation of the change from baseline for pre-dose and post-dose plots.

One-sample t-test will be used to evaluate if the change from baseline (Day 7 and Day 14 respectively) is significant (i.e., if the change is different from zero). This will be performed for each treatment group separately. Two-sample t-test will be performed to evaluate if the change is different between the two treatment groups. Test will not be performed on percentage change.

Boxplots will be used to graphically represent the data in the 1-sample and 2-sample tests, the test p-value will be displayed in the boxplots.

Heatmap will be used to visualize the percent change of the all the markers (by marker types) for all the subjects.

7 APPENDIX: TFL SHELLS

This section describes the shells for tables, listings, and figures.

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Listing	
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7.3.2.	**PD Data**
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7.1. Table Shells

7.1.1. PK Data

Table 7.1.1.1. Summary Statistics for Plasma Drug Level Data

Visit	Parameter	Statistics (Control)	Statistics (Treatment)
D1 Predose			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
D1 Post-dose			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
D7 Predose			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
D7 Post-dose			

Visit	Parameter	Statistics (Control)	Statistics (Treatment)
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
D14 Predose			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
D14 Post-dose			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		

7.1.2. PD Data

7.1.2.1. Summary Statistics

Table 7.1.2.1.1. Summary Statistics for Biomarker PBMC pRIP1 (Predose)

Biomarker			**PBMC pRIP1 (Predose)**
Visit	**Parameter**	**Statistics (Control)**	**Statistics (Treatment)**
D1			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
D7			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
Change from Baseline to D7			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
% Change from Baseline to D7			
	n		

Biomarker			PBMC pRIP1 (Predose)
Visit	**Parameter**	**Statistics (Control)**	**Statistics (Treatment)**
	Mean		
	SD		
	Median		
	Min		
	Max		
D14			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
Change from Baseline to D14			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		
% Change from Baseline to D14			
	n		
	Mean		
	SD		
	Median		
	Min		
	Max		

7.1.2.2. T-test Results

Table 7.1.2.2.2. Changes on Biomarker Levels by Treatment Groups

Biomarker	Parameters	P value within Control	P value within Treatment	P value between Treatments
TNF-α				
	Change from Baseline to D7			
	Change from Baseline to D14			
INF-γ				
	Change from Baseline to D7			
	Change from Baseline to D14			
IL-1ß				
	Change from Baseline to D7			
	Change from Baseline to D14			
IL-6				
	Change from Baseline to D7			
	Change from Baseline to D14			
IL-7				
	Change from Baseline to D7			
	Change from Baseline to D14			
IL-8				
	Change from Baseline to D7			
	Change from Baseline to D14			
IL-9				
	Change from Baseline to D7			
	Change from Baseline to D14			
IL-10				
	Change from Baseline to D7			
	Change from Baseline to D14			
IL-18				

Biomarker	Parameters	P value within Control	P value within Treatment	P value between Treatments
	Change from Baseline to D7			
	Change from Baseline to D14			
G-CSF				
	Change from Baseline to D7			
	Change from Baseline to D14			
GM-CSF				
	Change from Baseline to D7			
	Change from Baseline to D14			
CXCL-1				
	Change from Baseline to D7			
	Change from Baseline to D14			
CXCL-9				
	Change from Baseline to D7			
	Change from Baseline to D14			
CXCL-10				
	Change from Baseline to D7			
	Change from Baseline to D14			
MCP-1				
	Change from Baseline to D7			
	Change from Baseline to D14			
MIP-1α				
	Change from Baseline to D7			
	Change from Baseline to D14			
MIP-1ß				
	Change from Baseline to D7			
	Change from Baseline to D14			
vWF				
	Change from Baseline to D7			

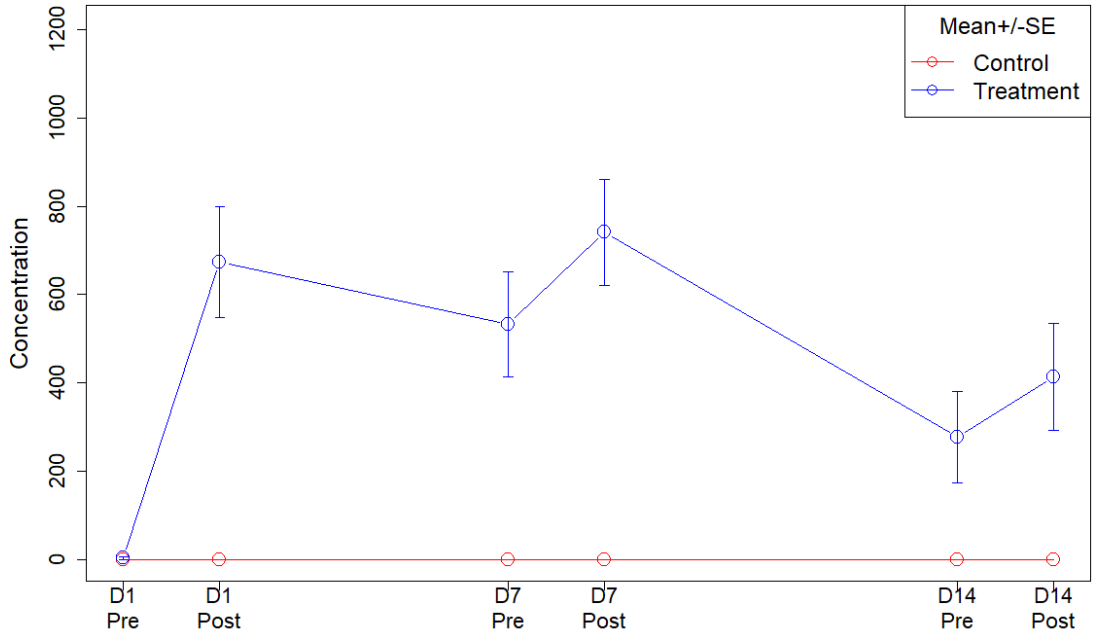
Biomarker	Parameters	P value within Control	P value within Treatment	P value between Treatments
	Change from Baseline to D14			
P-Selectin				
	Change from Baseline to D7			
	Change from Baseline to D14			
Thrombomodulin				
	Change from Baseline to D7			
	Change from Baseline to D14			
NGAL				
	Change from Baseline to D7			
	Change from Baseline to D14			
KIM-1				
	Change from Baseline to D7			
	Change from Baseline to D14			
PBMC pRIP1 (Predose)				
	Change from Baseline to D7			
	Change from Baseline to D14			
PBMC pRIP1 (Post-dose)				
	Change from Baseline to D7			
	Change from Baseline to D14			
PBMC pMLKL (Predose)				
	Change from Baseline to D7			
	Change from Baseline to D14			
PBMC pMLKL (Post-dose)				
	Change from Baseline to D7			
	Change from Baseline to D14			
plasma pRIP1 (Predose)				
	Change from Baseline to D7			
	Change from Baseline to D14			

Biomarker	Parameters	P value within Control	P value within Treatment	P value between Treatments
plasma pRIP1 (Post-dose)				
	Change from Baseline to D7			
	Change from Baseline to D14			
plasma pMLKL (Predose)				
	Change from Baseline to D7			
	Change from Baseline to D14			
plasma pMLKL (Post-dose)				
	Change from Baseline to D7			
	Change from Baseline to D14			

7.2. Figure Shells

7.2.1. PK Data

Figure 7.2.1.1. Mean Plasma Drug Levels Over Time by Treatment Group



7.2.2. PD Data

Figure 7.2.2.1.23. Individual Line Plot for PBMC pRIP1 (Predose)

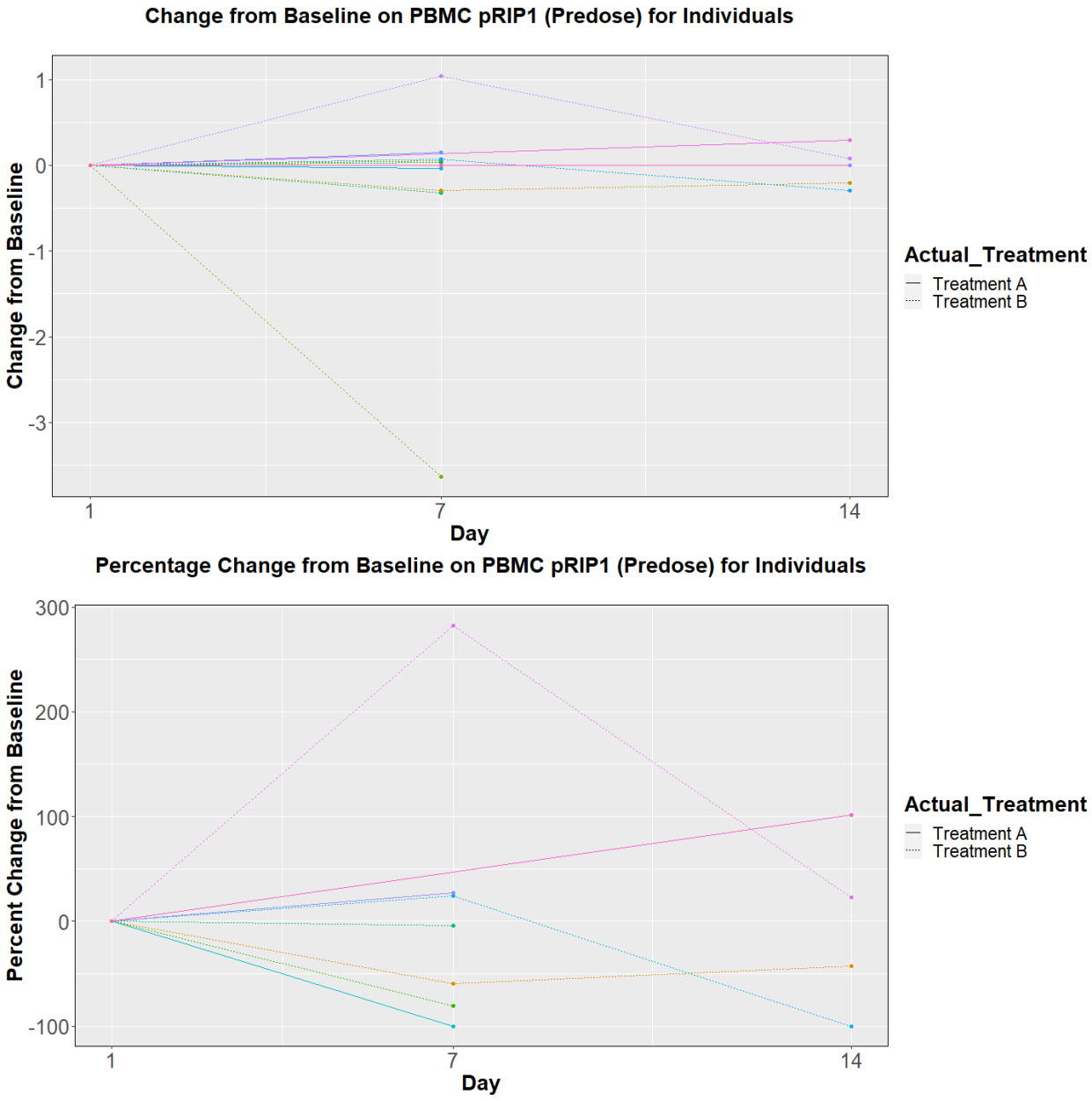


Figure 7.2.2.2.23. Mean PBMC pRIP1 Over Time by Treatment Group

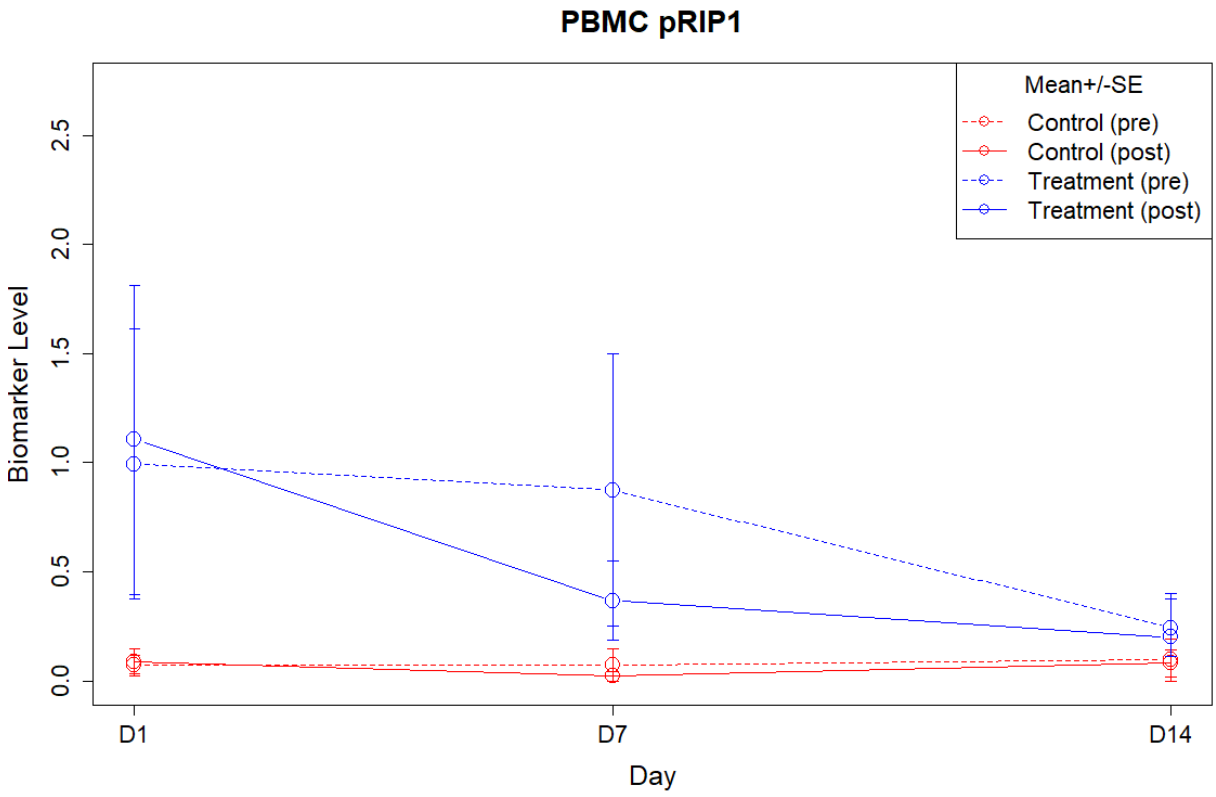


Figure 7.2.2.3.23. Mean Changes from Baseline Over Time on PBMC pRIP1 Levels by Treatment Group

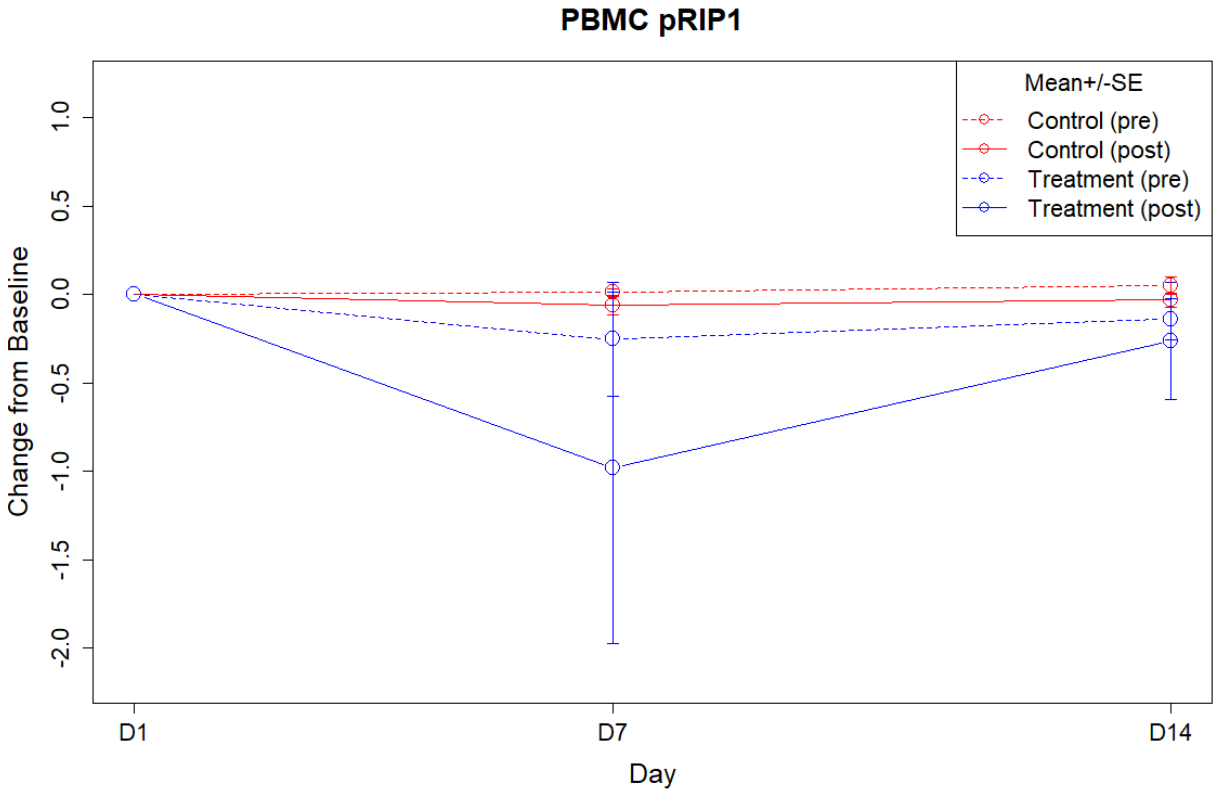


Figure 7.2.2.4.23. Mean Percentage Changes from Baseline Over Time on PBMC pRIP1 Levels by Treatment Group

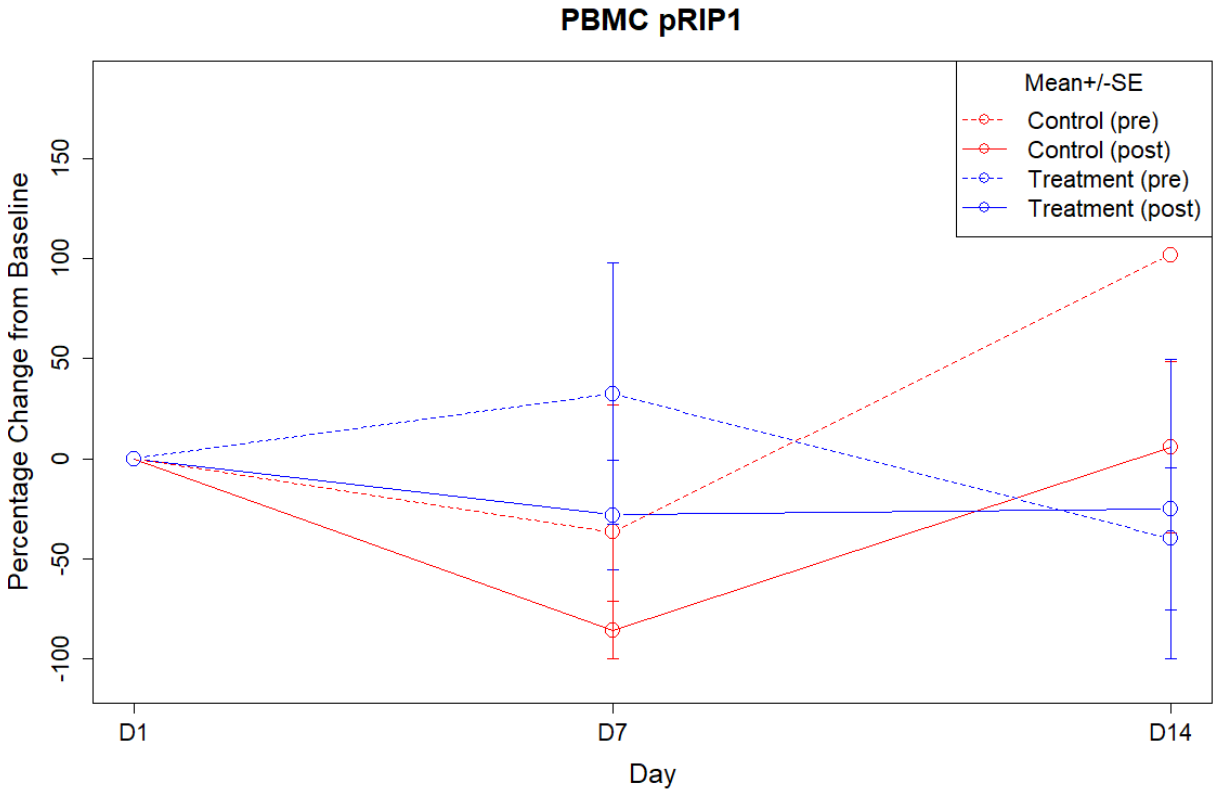
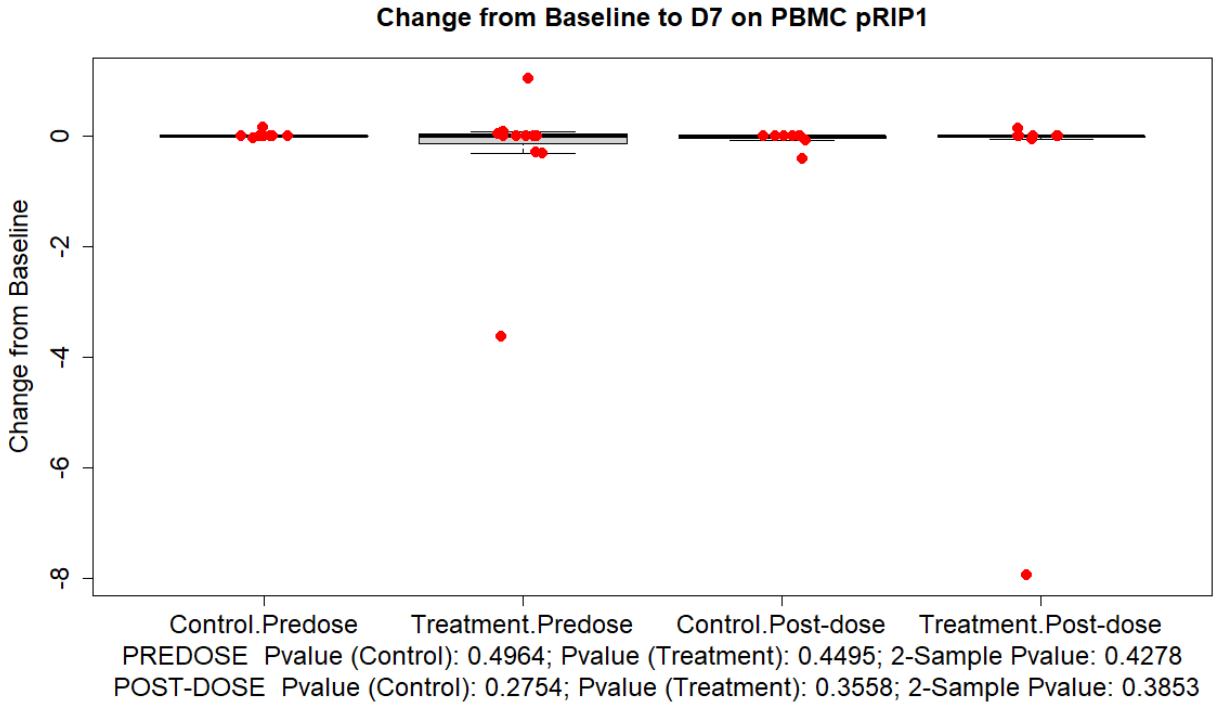


Figure 7.2.2.5.23. Boxplot of Changes from Baseline on PBMC pRIP1 by Treatment Group



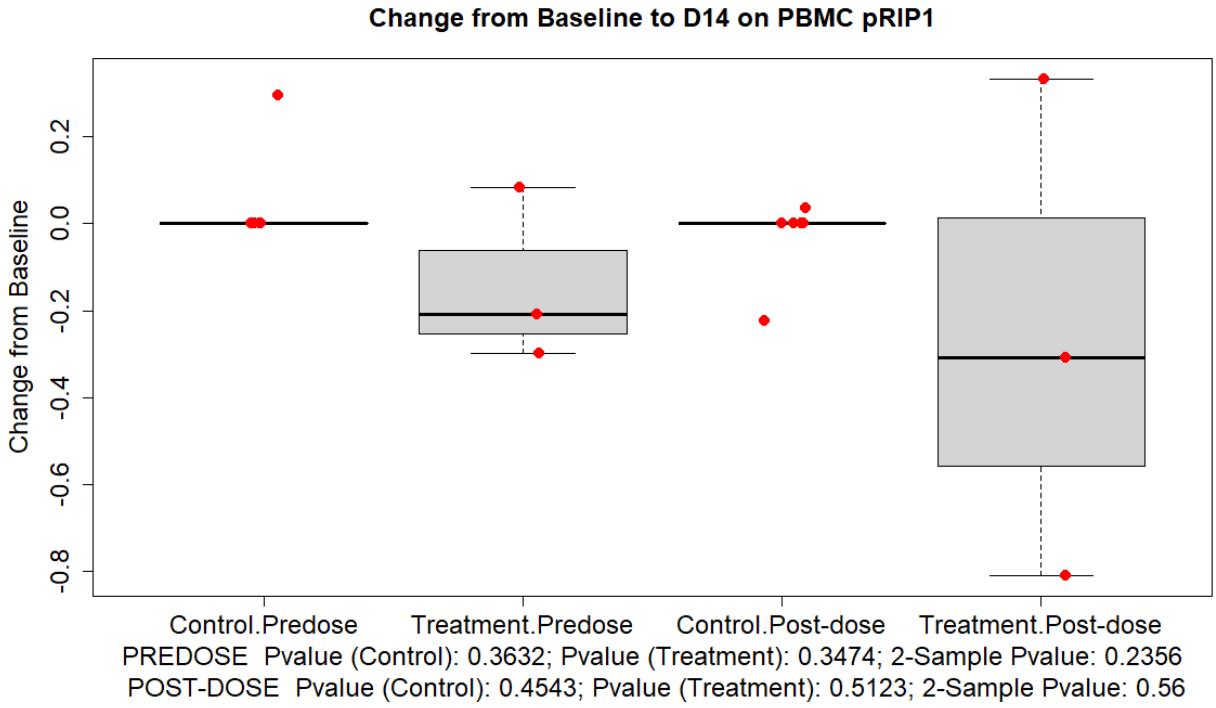
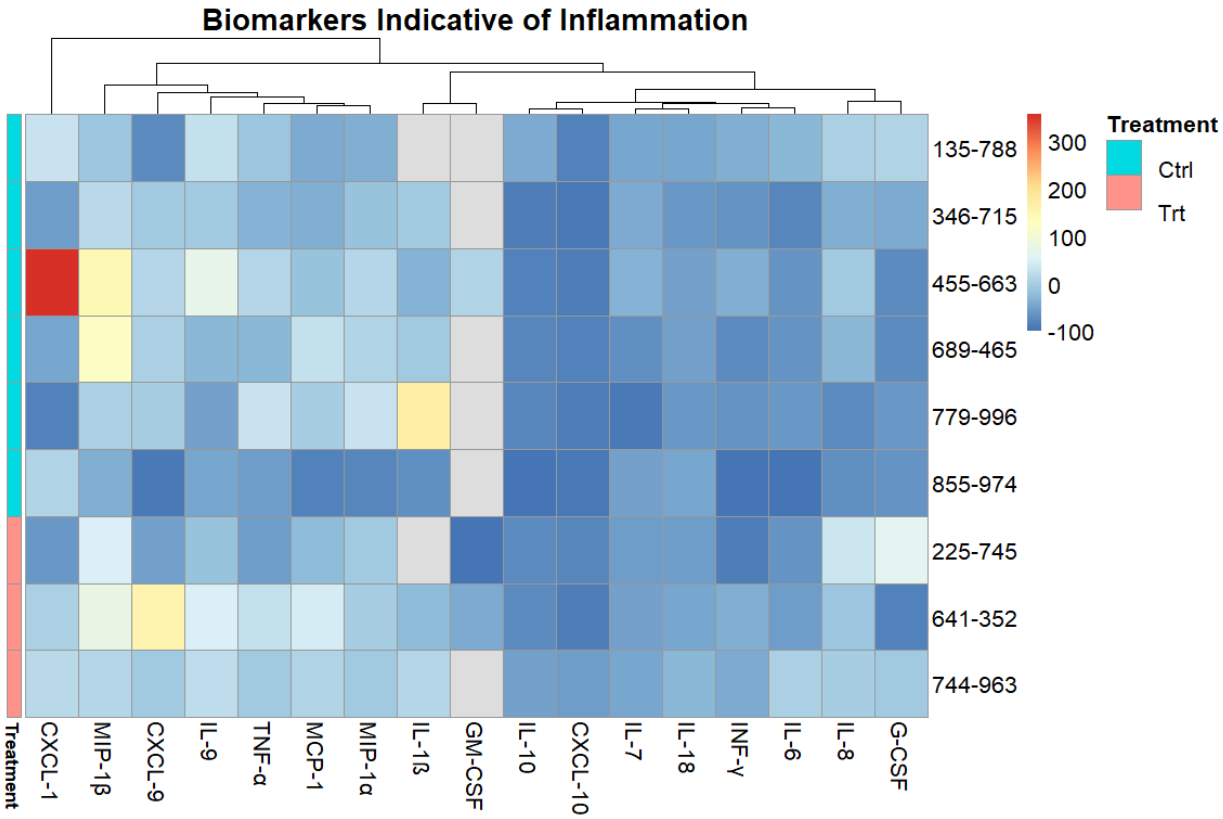


Figure 7.2.2.6.2. Heatmap of Percentage Change from Baseline to D14 on Biomarkers Indicative of Inflammation by Treatment Group



7.3. Listing Shells

Table 7.3.1. PK Data

Subject	Time Text	Concentration	Collection Date	Treatment

Table 7.3.2.1. Listing for Biomarkers Indicative of Inflammation

Sample ID	IL-6	TNF-α	IL-1β	IL-8	IL-10	INF-γ	IL-7	GM-CSF	IL-9	IL-18	G-CSF	CXCL-1	CXCL-9	CXCL-10	MCP-1	MIP-1α	MIP-1β	Treatment

Table 7.3.2.2. Listing for Biomarkers Indicative of CV Endothelial Cell Damage

Sample ID	Thrombomodulin	P-Selectin	vWF	Treatment

Table 7.3.2.3. Listing for Biomarkers Indicative of Kidney Injury

Sample ID	KIM-1	NGAL	Treatment

Table 7.3.2.4. Listing for Biomarkers Indicative of Target Engagement

Sample ID	Time Text	plasma pRIP1	plasma pMLKL	PBMC pRIP1	PBMC pMLKL	Treatment