[redacted]

A randomized, double-blind, dose-ranging, placebo controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with acute respiratory distress syndrome (ARDS) associated with at least severe COVID-19 (INTEGRIS-ARDS)

Protocol Number: PLN-74809-ARDS-204
Protocol Version: Amendment 2
Protocol Date: 23 October 2020

STATISTICAL ANALYSIS PLAN

Version 1.0

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STATISTICAL ANALYSIS PLAN
Version 1.0

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Note that the last signature date is the effective date of the plan.

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse events
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical, therapeutic, and chemical
COVID-19	Coronavirus disease
CS	Clinically significant
CTCAE	Common terminology criteria for adverse events
[redacted]	[redacted]
DSMB	Data safety and monitoring board
[redacted]	[redacted]
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EoT	End of treatment
ET	Early termination
EUA	Emergency use authorization (by the FDA)
FDA	Food and drug administration
FiO_2	Fraction of inspired oxygen
ICF	Informed consent form
ICU	Intensive care unit
MAP	Mean arterial pressure
MedDRA	Medical dictionary for regulatory activities
NCS	Not clinically significant
NE	Nasoenteric
NG	Nasogastric
[redacted]	[redacted]
PaO_2	Partial pressure of arterial oxygen
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
QD	Once daily

Abbreviation or Term	Definition/Explanation
[redacted]	[redacted]
RTSM	Randomization & trial supply management
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent severe adverse event
WHO	World health organization

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the Protocol # PLN-74809-ARDS-204, titled "A randomized, double-blind, dose-ranging, placebo controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with acute respiratory distress syndrome (ARDS) associated with at least severe COVID-19 (INTEGRIS-ARDS)." See the study protocol for full details.

This document details the statistical methods planned to perform the final analysis of the study.

Sections 2 and 3 represent descriptions of objectives, endpoints, and study as described in the protocol. Due to early termination of enrollment, some aspects have changed (e.g., only one cohort) and not all endpoints will be analyzed.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To assess the safety and tolerability of PLN-74809.

2.1.2 Secondary Objectives (analysis not described in this SAP)

- To evaluate the pharmacokinetics of PLN-74809 following multiple doses using sparse sampling.

2.1.3 Exploratory Objectives

- [redacted]

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint is the nature and proportion of treatment-emergent adverse events (TEAEs) between PLN-74809 and placebo groups.

2.2.2 Secondary Endpoints

2.2.2.1 Secondary Pharmacokinetic (PK) Endpoints

The secondary PK endpoints are the plasma PLN-74809 concentrations (total and unbound concentrations, as appropriate) at each sampling timepoint by dose and visit.

2.2.3 Exploratory Efficacy Endpoints

[redacted]

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a Phase 2a, multicenter, randomized, double-blind, dose-ranging, placebo-controlled, study to evaluate the safety, tolerability, and PK of treatment with PLN-74809 for at least 7 and up to 14 days in participants with ARDS associated with at least severe COVID-19. The study will include an up to 3-day screening period, a 7- to 14-day (or day of hospital discharge, whichever one is sooner) treatment period, and a 90-day follow-up period.

Approximately 36 participants will be enrolled sequentially into 3 cohorts. Within each cohort of 12 participants, 9 will be randomized to PLN-74809 and 3 will be randomized to placebo (3:1 ratio).

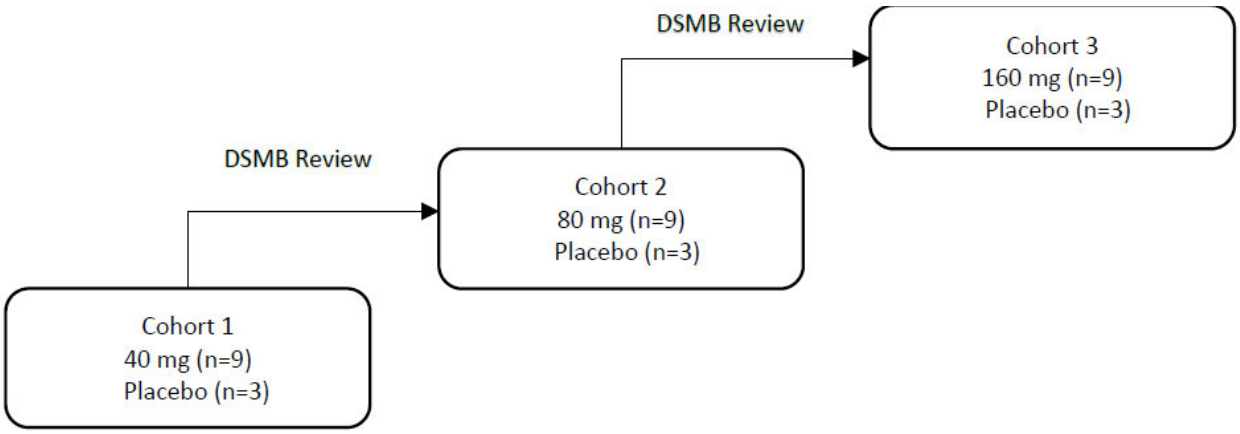
- In Part 1, approximately 12 participants will be randomized to 40 mg PLN-74809 or placebo QD (Cohort 1).
- In Part 2, approximately 12 participants will be randomized to 80 mg PLN-74809 or placebo QD (Cohort 2).
- In Part 3, approximately 12 participants will be randomized to 160 mg PLN-74809 or placebo QD (Cohort 3).

A data safety monitoring board (DSMB) will be established to assess participant safety at predetermined intervals during the study, and as needed. [redacted]

[redacted]

Commencement of Part 2 and Part 3 will occur only following favorable DSMB review of the previous study part. The 160 mg cohort will only be dosed following favorable DSMB review of the 80 mg cohort (see Figure 1: Study Schematic).

Figure 1: Study Schematic



Successful treatment of ARDS associated with COVID-19 will likely require co-administration of drugs with complementary mechanisms of action targeting different components of the disease, such as antiviral compounds to control viral replication (e.g., remdesivir) combined with drugs with the potential to address the pathophysiology of ARDS, in addition to respiratory support measures. Therefore, treatment with investigational COVID-19 therapies available under Emergency Use Authorization (EUA) by the FDA may be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director. Key considerations for allowing co-administration of PLN-74809 with investigational COVID-19 therapies under EUA will include the potential for drug interactions and adverse drug reactions. Treatment with off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 may also be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director.

Each participant will participate in the study for up to approximately 107 days, including screening, treatment, and post-treatment follow-up. The end of study is defined as the last visit of the last randomized participant.

See Appendix A for the Schedule of Assessments out to the 90-day follow-up.

3.2 Treatment

The following treatments will be administered for each part of the study:

- Part 1: 40 mg of PLN-74809 or matching placebo QD
- Part 2: 80 mg of PLN-74809 or matching placebo QD
- Part 3: 160 mg of PLN-74809 or matching placebo QD

[redacted]

[redacted]

3.2.1 Randomization scheme and treatment arm assignment

Within each part, participants will be randomized in a 3:1 manner to PLN-74809 or placebo. There will be no other stratification. A central randomization system, Medidata Rave Randomization & Trial Supply Management (RTSM)®, will be used for this study.

Participants who are randomized and never receive study drug will not be replaced.

3.2.2 Blinding

The PLN-74809 and placebo tablets will be identical in appearance and will be packaged identically to ensure that the participant, Investigator and clinical site staff are unaware of the treatment assignments, hence blinded.

After the last participant enrolled in each study part completes the end of treatment or early termination visit (whichever applies), selected Sponsor representatives with no direct interactions with clinical sites will subsequently be unblinded to allow for a more comprehensive review and assessment of the safety and PK data by the DSMB before proceeding to subsequent parts of the study.

In case a medical emergency requires knowledge of a participant's treatment assignment, the Principle Investigator and designated Sub-Investigator(s) at each site, as well as [redacted] Safety and Medical Monitors, will have rights to automatically obtain a participant's treatment assignment through Medidata Rave RTSM®, thereby breaking the blind.

3.2.3 Dosing schedule

All doses of study drug will be taken at the investigative site. [redacted]

3.2.4 Participant compliance

The Investigator may withdraw a participant from the study or discontinue study drug for any of the following reasons:

- Noncompliance with protocol procedures, including those relating to administration of study drug
- Occurrence of a serious adverse event (SAE) or intolerable adverse event (AE)
- Occurrence of a clinically significant change in a laboratory parameter

[redacted]

- Termination of the study by the Sponsor or Investigator
- The participant requests to be discontinued from the study

Participants who discontinue study drug (regardless of reason) will be asked to remain in the study to complete all remaining assessments until hospital discharge or Day 28, whichever is sooner, unless they withdraw consent or are lost to follow-up. If this is not feasible, the participant will be assessed for an early termination visit. All assessments that are required at the last study visit, as shown in Appendix A, should be completed for any participant who is withdrawn from the study or prematurely discontinues study drug and does not agree to complete all remaining assessments.

[redacted]

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

With the availability of COVID-19 vaccines beginning in the fourth quarter of 2020, as well as the increased and successful measures taken to contain the virus, a dramatic decrease in the number of patients with ARDS associated with severe and critical COVID-19 was observed. Given the current and predicted decline in potential study participants, the study was terminated by the Sponsor. No statistical hypotheses will be tested. Unless otherwise specified, continuous data will be summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage of participants within each category. All tabulations will be based on pooled data across centers.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

[redacted] will perform all efficacy and safety analyses described in this SAP. [redacted] will perform pharmacokinetic analysis. Pharmacodynamic analysis will be performed by [redacted].

Participant data will be listed, sorted by treatment arm, cohort, investigative center, and participant number. When applicable, listings will be additionally sorted by visit and assessment date/time.

4.1 Data Quality Assurance

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to [redacted] Biostatistics for final analysis.

Data may be pulled by [redacted] Biostatistics for DSMB analysis at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis data sets, tables, and listings are double programmed.

The SAS outputs will be compared and the programs will be updated until the outputs match.

4.2 Analysis Sets

The following analysis sets will be defined for this study:

Safety Set: The Safety Set will consist of all randomized participants who receive at least 1 dose of study drug.

PK Concentration Set: all randomized participants who receive at least 1 dose of study drug and have any measurable PLN-74809 concentration data.

4.3 Assessment Windows

All data will be included in the analysis based on the visit recorded in the database.

4.4 Handling of Dropouts or Missing Data

Missing data on demographic, baseline information and safety will be treated as missing; no method for imputation is planned.

Details of any missing data imputation will be specified in the analysis methods for each of the exploratory efficacy endpoints.

4.5 Multiple Comparisons

No hypotheses are being tested.

4.6 Data Derivations and Transformations

The following derivations will be used in this study:

Study day:

- Date of assessment – date of study drug administration + 1 for assessments done on or after date of study drug administration
- Date of assessment – date of study drug administration for assessments done before date of study drug administration

Baseline value: the last non-missing value prior to study drug administration.

Shift from baseline: current value – baseline value. Although generally reserved for quantitative variables, it is also applied to some numeric ordinals [redacted]

[redacted]

5. STUDY PARTICIPANTS

5.1 Disposition of Participants

A table of frequency counts and percentages of all participants in the Safety and PK Concentration sets will be provided. Participant disposition including study completion status and reasons for early termination (if applicable) will be tabulated by treatment arm and overall. A by participant listing will be provided.

5.2 Protocol Deviations

A listing of all protocol deviations will be provided.

5.3 Demographic Characteristics

Descriptive statistics will be used to summarize the demographic characteristics (age, sex, race, ethnicity, height, weight) for the participants in the Safety Set. A by participant listing will be provided.

5.4 Baseline Characteristics

Descriptive statistics will be used to summarize the baseline characteristics [redacted] for the participants in the Safety Set.

5.5 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. The number and percent of participants with each medical condition and surgical procedure will be presented for each SOC and PT for the Safety Set. A listing will also be provided.

5.6 Concomitant Medications/Therapies

5.6.1 Medications

Concomitant medications/therapies collected will be coded using the March 2021 B3 WHO-Drug Dictionary. A listing of medications will also be provided.

5.6.2 Non- drug therapy

Non- drug therapies (e.g., ice pack, intubation, tracheostomy, ECMO) will be coded using MedDRA (version 23.0). A listing of non-drug therapy will be provided.

6. EFFICACY ANALYSES

The PK analyses will be performed using the PK Concentration set. All other exploratory efficacy summaries will be conducted using the Safety Set.

6.1 Pharmacokinetic Endpoints and Analysis

Blood samples for determination of plasma levels of PLN-74809 will be obtained at the following timepoints:

- Day 1: 0.5 hours (±15 min), 3 hours (±60 min), and 10 hours (± 120 min) postdose
- Day 7: predose, 3 hours (±60 min), and 24 hours (±60 min) postdose
- Day 14: predose for participants on study drug

If the participant is no longer being treated with study drug, discontinues the study early, or is not treated with study drug on Day 14, a single plasma sample for PK should be taken at the Day 14/ end of treatment (EoT)/ early termination (ET) visit, if possible. Actual PK sample collection time and dosing time will be recorded. The PK sampling schema may be modified based on emerging data.

[redacted]

A listing of concentration values will be provided.

6.2 Exploratory Efficacy Endpoints and Analysis

6.2.1 Efficacy

The following will be summarized by treatment arm and applicable visit:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.2.2 Pharmacodynamics

Plasma and serum and will be analyzed for biomarkers (presence or actual concentration). These samples will be used to determine the levels of biomarkers in participants and the relationship between these markers.

The PD analysis will be performed by [redacted]. Available biomarkers [redacted] will be summarized by visit and treatment arm. A listing of available biomarker concentration will be provided.

7. SAFETY ANALYSIS

Safety assessments will include assessment of AEs, laboratory parameters, vital signs, and [redacted]. All safety summaries (or analyses if applicable) will be conducted using the Safety Set. No formal hypothesis testing will be performed to compare differences between treatment arms.

7.1 Extent of Exposure

The number of tablets received, the occurrence of dose interruption, the duration of interruption, and total amounts of PLN-74809 in mg will be tabulated.

7.2 Adverse Events

An AE is any event, side effect, or other untoward medical occurrence that occurs in conjunction with the use of a study drug in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

AEs will be coded using the MedDRA (version 23.0) and collected from the time the participant signs the informed consent form (ICF) until Day 28.

7.2.1 Treatment-Emergent Adverse Events

A TEAEs is defined as an AE that emerged or worsened in severity after the first administration of study drug.

7.2.2 Adverse Event Severity

Grading the severity of AEs will use the Common Terminology Criteria for Adverse Events (CTCAE) grading system, version 5.0 ([redacted]), as described below. The clinical significance of the AE is determined by the Investigator. The Investigator is encouraged to consult with the Medical Monitor.

For AEs or laboratory abnormalities not listed in the CTCAE grading system, please use the grading scale as described below.

Table 1: Adverse Event Severity Grading Terminology

CTCAE Grade	Common Terminology	Description[a]
Grade 1	Mild	asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL[b]

CTCAE Grade	Common Terminology	Description[a]
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[c]
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Death	Death related to AE

[a] A semi-colon indicates 'or' within the description of the grade.
[b] Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[c] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

7.2.3 Adverse Event Relationship to Study Drug

The Investigator will assess the relationship between study drug and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and on the eCRF. Alternative causes, such as medical history, concomitant therapy, or other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The relationship or association of the AE to a study drug (PLN-74809 or placebo) should be assessed using clinical judgment and the following considerations:

No: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

Yes: A temporal relationship exists between the AE onset and administration of the study drug that cannot be readily explained by the participant's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon re-challenge.

The relationship to study procedures (such as venipuncture) should be assessed using the following considerations:

No: Evidence exists that the AE has an etiology other than the study procedure.

Yes: The AE occurred as a result of protocol-mandated procedures

The relationships will be summarized using "Yes" or "No" for "Related to Investigational Product" and "Related to Trial Procedure".

7.2.4 Serious Adverse Events

A SAE is defined as an AE that meets at least one of the following serious criteria:

- Is life-threatening
- Results in death
- Requires inpatient hospitalization (i.e., admission, overnight stay) or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

An AE is considered life-threatening if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Important medical events that are not one of the preceding may be considered to be SAEs by the Investigator when, based upon appropriate medical judgement, they are considered to be clinically significant and may jeopardize the participant or when medical or surgical intervention may be required to prevent one of the outcomes listed above. (Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) occurring after study drug administration and by Day 28 of the study, regardless of relationship to study drug, will be included and classified by SOC and PT using MedDRA.

For TEAEs, the following will be summarized and presented for the Safety Set.

i. An overall summary of TEAEs, which includes:
    a. the number and percentage of participants experiencing a TEAE
    b. the number and percentage of participants experiencing a TEAE by strongest relationship to investigational product
    c. the number and percentage of participants experiencing a TEAE by strongest relationship to trial procedure
    d. the number and percentage of participants experiencing a TEAE by greatest severity
    e. the number and percentage of participants experiencing a TEAE with NCI CTCAE version 5.0 Grade 3 or higher
    f. the number and percentage of participants experiencing a treatment emergent serious adverse event (TESAE)
    g. the number and percentage of participants experiencing a TESAE by strongest relationship to investigational product
    h. the number and percentage of participants experiencing a TESAE by strongest relationship to trial procedure

i. the number and percentage of participants experiencing a TEAE leading to death

j. the number and percentage of participants experiencing a TEAE which leads to a premature withdrawal

ii. the number and percentage of participants experiencing a TEAE by SOC and PT

iii. the number and percentage of participants experiencing a TEAE by SOC, PT and the strongest relationship to investigational product

iv. the number and percentage of participants experiencing a TEAE by SOC, PT and the strongest relationship to trial procedure

v. the number and percentage of participants experiencing a TESAE by SOC, PT and the strongest relationship to trial procedure

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of participants, the total number of TEAE episodes will also be provided. If a participant has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of participants who have experienced the event by the total number of participants in the Safety Set. Thus, the incidence of TEAEs is shown in terms of the total number of participants and not in terms of the total number of episodes. If a participant has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship, will be counted in the summary tables.

A participant with more than one type of TEAE in a particular SOC or PT will be counted only once in the total of participants experiencing TEAEs in that particular SOC or PT.

All occurrences of all AEs and SAEs will be listed for each participant, grouped by treatment arm. The listing will contain the following information: treatment arm, verbatim term, SOC, PT, severity, related to investigational product, related to trial procedure, date and day of onset, date and day of resolution, action taken with regard to study drug, treatment given to treat the adverse event, the outcome, whether the event was an SAE, SAE criteria (if applicable), whether it led to study withdrawal, and whether it is a TEAE. Listings will be sorted by treatment arm, participant identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Clinical Laboratory Assessments

Clinical laboratory tests will be obtained at the time points presented in Appendix A. The incidence of treatment-emergent laboratory abnormalities will be summarized by severity and treatment group. Continuous clinical laboratory values will be summarized by presenting descriptive statistics of raw data and change from baseline values at each time point for each treatment arm.

Laboratory parameter results from unscheduled visits will be excluded from table summaries but will be included in data listings. When there are repeat measurements for a given visit, only the last measurement will be used in the table summaries.

Listings will include flags for values outside of the reference ranges, and clinical significance if a laboratory result is deemed abnormal, if available. The biomarker analysis is described separately

in Section 6.2.2.

7.4 Vital Signs

Descriptive summaries of the vital signs (both raw and change from baseline values) including weight, temperature, systolic and diastolic blood pressure, and heart rate will be prepared for each study treatment by visit.

Unscheduled visits will be excluded from the summaries but will be included in the data listings.

7.5 [redacted]

[redacted]

8. INTERIM ANALYSES

No interim analysis is planned.

9. DATA SAFETY MONITORING BOARD

A DSMB will be established to assess participant safety at predetermined intervals during the study, and as needed. The DSMB will formally assess and review all available safety and PK data and will issue recommendations pertaining to the conduct of the study and the dose escalation from Part 1 to Part 2 and from Part 2 to Part 3. Further details will be provided in the DSMB Charter. Due to the early termination of the study, the DSMB meetings did not occur.

[redacted]

10. SAMPLE SIZE AND POWER CALCULATIONS

[redacted].

11. REFERENCES

[redacted]

12. APPENDIX

12.1 Appendix A: Schedule of Events

	Screening	Treatment Period[a]						EoT/ET	Phone Call[b]	Phone Call[b]
	Day -3 to Day -1	Baseline Day 1	Day 3	Day 5	Day 7	Day 10[c]	Day 14	Day of Hospital Discharge	Day 28	Day 90
Informed consent	X									
Medical history	X									
Demographics (age, sex, race)	X									
SARS-CoV-2 infection by RT-PCR or COVID-19 tests authorized under EUA	X									
Serum pregnancy test (for women only)	X	X					X	X		
Check inclusion and exclusion criteria	X	X								
Complete physical examination (including height and weight)[d]	X									
Targeted physical examination[d]		X	X	X	X	X	X	X		
Randomization		X								
[redacted]	X	X	X	X	X	X	X	X		
Ventilator utilization[e]	←	—	—	—	—	—	—	→		
[redacted]	X	X	X		X		X	X		
[redacted]	←	—	—	—	—	—	—	—	—	→
Vital signs[g]	X	X	X	X	X	X	X	X		
[redacted]	X	X	X	X	X	X	X	X		
Confirm daily conduct of vital signs and safety labs[h]		←	—	—	—	—	→			
Hematology[g,h]	X	X	X	X	X	X	X	X		
Clinical chemistry[g,h]	X	X	X	X	X	X	X	X		
Coagulation (INR)[g,h]	X	X	X	X	X	X	X	X		
Pharmacokinetic sample plasma[i]		X			X		X	X		

	Screening	Treatment Period[a]						EoT/ET	Phone Call[b]	Phone Call[b]
	Day -3 to Day -1	Baseline Day 1	Day 3	Day 5	Day 7	Day 10[c]	Day 14	Day of Hospital Discharge	Day 28	Day 90
Plasma biomarker samples		X	X		X		X	X		
Serum biomarker samples		X	X		X		X	X		
Urinalysis (dipstick, followed up by micro if abnormal)	X	X	X	X	X	X	X	X		
Adverse events	←	—	—	—	—	—	—	—	→	
Concomitant medications	←	—	—	—	—	—	—	—	→	
Study drug administration [redacted]		←	—	—	—	—	—	→		
Hospital and ICU utilization[e]	←	—	—	—	—	—	—	—	—	→
Vital status								X	X	X

eCRF = electronic case report form; EUA = emergency use authorization; [redacted]; EoT = end of treatment; ET = early termination; ICU = intensive care unit; INR = international normalized ratio; [redacted] PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted]

[a] The treatment duration will be a minimum of 7 days and up to 14 days or day of hospital discharge, whichever one is sooner. Once participants are discharged from the hospital, they will no longer be administered study drug.

[b] Additional information will be obtained from medical records.

[c] If participant is no longer being treated with study drug and has been discharged from the hospital, the remaining assessments may be omitted, except for the Day 28 and 90 phone calls and/or medical records.

[d] Physical examinations may be performed if can be done safely. Otherwise nursing assessment or verbal review of systems may be performed.

[e] Ventilator utilization, [redacted] and ICU utilization to be assessed from medical records after day of hospital discharge.

[f] [redacted]

[g] [redacted]

[h] Vital signs and local laboratory assessments will be conducted per ICU standards and at least daily. Results from these safety laboratory assessments will be recorded on the days specified.

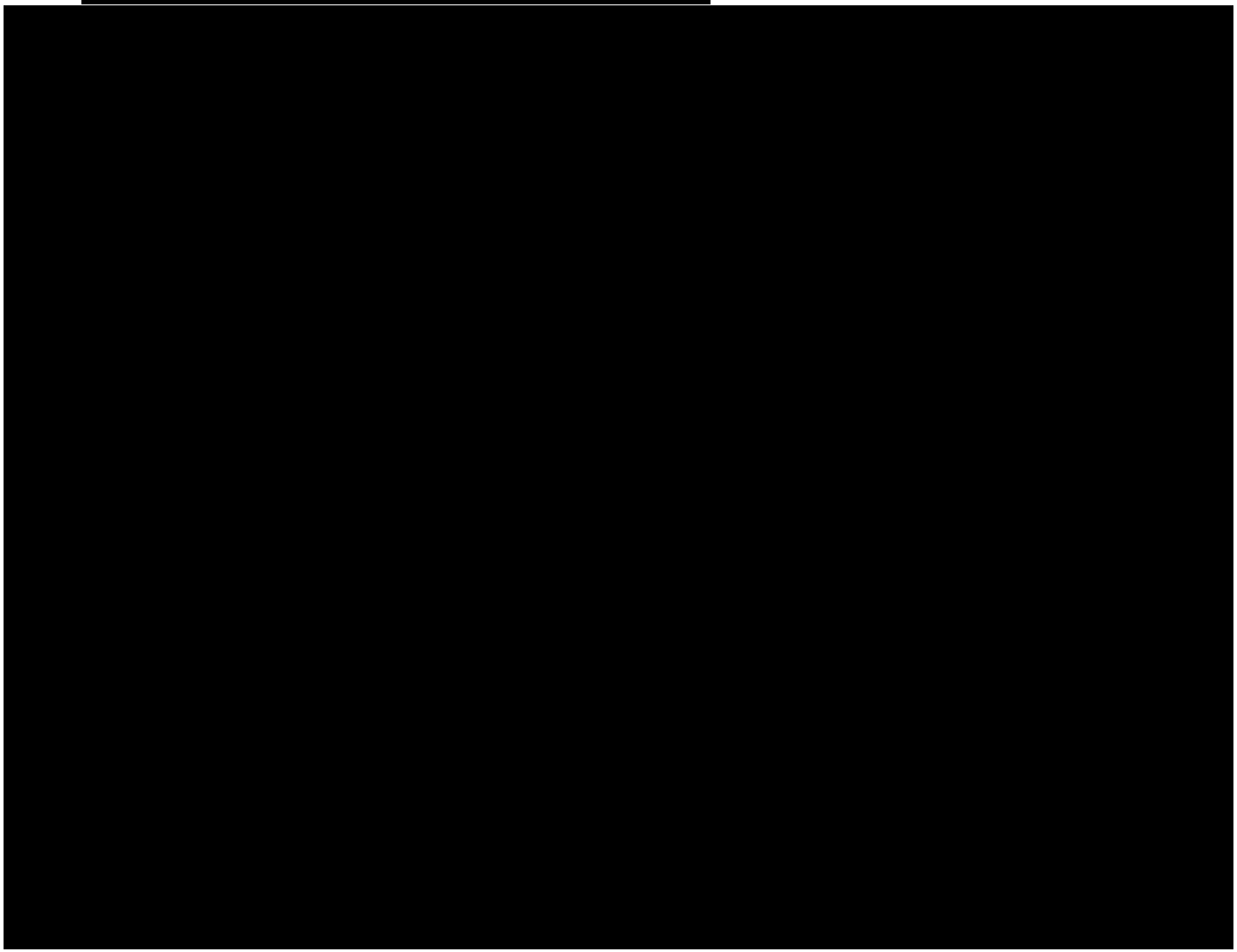
[i] Samples will be collected at the following timepoints:
Day 1: 0.5 hours (±15 min), 3 hours (±60 min), and 10 hours (± 120 min) postdose

Day 7: predose, 3 hours (±60 min), and 24 hours (±60 min) postdose
Day 14: predose for participants on study drug

If the participant is no longer being treated with study drug, discontinues the study early, or is not treated with study drug on Day 14, a single plasma sample for PK should be taken at the Day 14/EoT/ET Visit if possible. Actual PK sample collection time and dosing time will be recorded.

[j] For participants on hemodialysis, the study drug will be administered after the participant has completed the hemodialysis.

12.2 Appendix B: [redacted]



12.3 Appendix C: [redacted]

[redacted]