STATISTICAL ANALYSIS PLAN
PHASE 2
(Part 1)

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Multi-center Study of an Inhaled Pan-Janus Kinase Inhibitor, TD-0903, to Treat Symptomatic Acute Lung Injury Associated with COVID-19
Short Study Title:	TD-0903 for ALI Associated with COVID-19
Sponsor Study Number:	TD-0903-0188
Test Product:	TD-0903
Sponsor:	Theravance Biopharma Ireland Limited
Legal Registered Address:	Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland

Regulatory Agency Identifier Number(s)

EudraCT No.	2020-001807-18
US IND:	149220

This study will be conducted in compliance with Good Clinical Practice.

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TD-0903-0188
SAP (Part 1)
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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse event
AUC	Area under the curve
BMI	Body mass index
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical study report
DLRC	Dose Level Review Committee
Intent-to-Treat	Intent-to-Treat
HLH	Hemophagocytic lymphohistocytosis
HR	ITT
LOD	Lower limit of quantitation/limit of detection
MedDRA	Medical Dictionary For Regulatory Activities Terminology
ND	Not Detected
PT	Preferred Term
SaO2/FiO2 ratio	Ratio of peripheral oxygen saturation to the fraction of inspired oxygen
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

SAP VERSION HISTORY

1. INTRODUCTION

This statistical analysis plan (SAP) provides a detailed description of the statistical analyses (Part 1) of the efficacy and safety data specified in the protocol of study TD-0903-0188.

This is a Phase 2 (2-part), randomized, double-blind, placebo-controlled, parallel-group, multi-center study of an inhaled pan-Janus kinase inhibitor, TD-0903, to treat symptomatic acute lung injury associated with Coronavirus Disease 2019 (COVID-19).

The SAPs for [redacted] will be prepared separately.

Specifications of tables, figures, and data listings are contained in a separate document.

1.1. Objectives and Endpoints

1.1.1. Objective(s) and Endpoint(s)

Based on a subject population hospitalized with confirmed COVID-19 and requiring supplemental oxygen, the objectives are to:

- Evaluate the safety and tolerability of inhaled TD-0903 in subjects with COVID-19
- Assess the plasma PK of TD-0903 in subjects with COVID19
- Characterize the effect of TD-0903 on reducing the acute lung injury (as measured by ratio of peripheral oxygen saturation to the fraction of inspired oxygen [SaO2/FiO2 ratio]) associated with COVID-19

Endpoints are described in Table 3.

Table 3: Summary of Endpoints

Through Day 7	Through Day 28 or Entire Study Duration
• Change from baseline in vital signs and clinical laboratory results • Incidence and severity of treatment -emergent adverse events	• Change from baseline in vital signs and clinical laboratory results • Incidence and severity of treatment-emergent adverse events
• Change from baseline in SaO2/FiO2 ratio • Area under the curve (AUC) in SaO2/FiO2 ratio from Day 1 to Day 7 • Proportion of subjects with a SaO2/FiO2 ratio > 315 on Days 5 and 7 • Proportion of subjects with an oxygen saturation > 93% on room air by study day up to Day 7 • Change from baseline in the modified Borg Dyspnea Score on Day 7 • Modified HScores on Day 7	• Proportion of subjects discharged on Days 7, 14, 21 and 28 • Time to hospital discharge • 28-day all-cause mortality rate • Proportion of subjects in each category of the clinical status scale, as measured with an 8-point ordinal scale on Days 7, 14, 21 and 28 • Proportion of subjects alive and respiratory failure-free on Day 28

Note: SaO2/FiO2, ratio of peripheral oxygen saturation to the fraction of inspired oxygen

1.1.2. Secondary Objective(s) and Endpoint(s)

Not applicable.

1.1.3. Exploratory Objective(s) and Endpoint(s)

[redacted]

1.2. Study Design

This is a two-part study; this SAP applies only to Part 1.

Part 1 is a randomized, double-blind, placebo-controlled, multiple ascending dose study in hospitalized subjects with confirmed symptomatic COVID-19 who require supplemental oxygen.

Baseline assessments (Day 1) will include medical and medication history, vital signs (blood pressure, heart rate, respiratory rate [BP, HR, RR], and body temperature), a physical examination (including height and weight, and hepato- or splenomegaly at a minimum), and measures of oxygenation (pulse oximetry, FiO2). Female subjects of childbearing potential will undergo a serum pregnancy test. Blood samples will be collected from all subjects for hematology (complete blood count [CBC] with differential at a minimum), and serum chemistry (renal function, liver function tests, and triglycerides at a minimum). The investigator will also evaluate the subject's clinical status and review inclusion/exclusion criteria. Subjects who meet all inclusion criteria except the viral testing results can be enrolled if, in the opinion of the investigator they have clinical evidence of COVID-19.

Eligible subjects will be randomized and dosed for up to 7 days or until discharge from the hospital, whichever is earlier. [redacted]

study for TD-0903) has completed dosing and the Dose Level Review Committee (DLRC) has recommended escalation. [redacted]

At the end of dosing for all subjects in each cohort, the DLRC will review unblinded data through Day 7, and results from the same dose level cohort in Study TD--0903-0183 to inform progression to the next dose level and/or to initiate Part 2 of the study.

Subject follow-up after the dosing period will be via chart review for 21 days (until Day 28).

Part 1 will assess safety, tolerability, and PK of TD-0903. Serial blood samples will be collected from all subjects for PK assessments. Oxygenation data will be collected for all subjects, and the SaO2/FiO2 ratio will be measured to guide dose selection for Part 2.

Oxygenation will be assessed via SaO2/FiO2 ratio. Use of a ventilatory support, presence in the ICU, clinical status (including mortality), and date of discharge will be recorded for all subjects as appropriate.

Clinical status will be assessed using an 8-point scale for all subjects daily up to Day 28.

Subject safety will be assessed throughout the study using standard measures, including adverse event (AE) monitoring, physical examinations (including height and weight, and hepato- or splenomegaly at a minimum), vital signs (at a minimum, temperature, BP, HR, and respiratory rate [RR]), clinical laboratory tests (at a minimum, CBC with differential, renal function [creatinine, blood urea nitrogen], and liver function tests [aspartate aminotransferase {AST}, alanine aminotransferase {ALT}, alkaline phosphatase {Alk Phos}, and total bilirubin {TBili}]), and concomitant medication usage.

1.3. Treatment Assignment

Study drug comprises the following:

- Cohort 1: TD-0930 [redacted] loading dose vs placebo on Day 1; [redacted] vs placebo on Days
- Cohort 2: TD-0903 [redacted] loading dose vs placebo on Day 1; [redacted] vs placebo on Days 2 through 7
- Cohort 3: TD-0903 [redacted] vs Placebo on Days 1 through 7 (i.e., no loading dose)
- Schedule of Assessments

The schedule of assessments is presented in Table 4.

Table 4: Schedule of Study Procedures (Part 1)

Procedure	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14 Chart Review	Day 21 Chart Review	Hospital Discharge	Day 28
Informed Consent[a]	X	X										
Review Inclusion/Exclusion Criteria		X										
Medication and Medical History[b]		X										
Vital Signs		X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[d]	X[d]	X[d]	X[d]
Physical Examination[e]		X						X				
Height and Weight		X[f]										
Serum Pregnancy Test		X										
Pulse Oximetry[g]		X	X	X	X	X	X	X	X	X	X	X
Modified Borg Dyspnea Score[h]		X	X	X	X	X	X	X				
Hematology (CBC with Diff)[i]		X	Record results of any lab evaluations performed for clinical purposes.					X	Record results of any lab evaluations performed for clinical purposes.			
Serum Chemistry[j]		X						X				
Plasma PK samples[k]		X	X	X				X				
Serum and plasma for biomarkers, and antibodies, and for storage for future analysis (if feasible)[l]		X						X				
Swab for SARS-CoV-2 viral PCR[m]		X						X				
Clinical Status		X	X	X	X	X	X	X	X	X	X	X[n]
Randomization		X										
Study Drug Dosing		X	X	X	X	X	X	X				
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[n]
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X[n]

Abbreviations: Alk Phos, alkaline phosphatase, ALT, alanine aminotransferase; AST, aspartate aminotransferase, BP, blood pressure; CBC, complete blood count; COVID-19. Coronavirus Disease 2019; FiO2, fraction of inspired oxygen; HR, heart rate; PCR, polymerase chain reaction; PK, pharmacokinetic; RR, respiratory rate; SARS-CoV-2; Severe Acute Respiratory Syndrome-associated Coronavirus-2; TBili, total bilirubin

[a] Informed consent may be obtained on either Day 0 or Day 1, up to 1 week prior to study enrollment in subjects undergoing testing for COVID-19, but with milder symptoms that, in the investigator's opinion, may worsen.

[b] Including known immunosuppression and source of immunosuppression i.e., disease or medication)

[c] Includes BP, HR, RR, and body temperature. Measured before dosing (first daily dose if study drug given twice daily).

[d] Morning vital signs

[e] Including hepato-or splenomegaly at a minimum

[f] If not available from subject's chart

[g] Oxygen saturation via pulse oximeter is considered equivalent to arterial oxygen saturation (SaO2) for this study. Record FiO2 at each assessment.

[h] Collected while subject is at rest.

[i] At a minimum. Day 1 samples must be collected within 24 hours before dosing, inclusive of those collected prior to informed consent; Day 7 samples must be collected predose. Laboratory testing as per local hospital protocols will be followed.

[j] Including renal function, liver function tests (AST, ALT, Alk Phos, TBili), triglycerides, ferritin, and fibrinogen. Day 1 samples must be collected within 24 hours before dosing, inclusive of those collected prior to informed consent; Day 7 samples must be collected predose. Laboratory testing as per local hospital protocols will be followed.

[k] Serial blood samples for plasma PK analyses will be collected pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours (i.e., the following day) after the dose on Day 1 and Day 7. If the dose on Day 1 occurs in the evening (after 1 pm / 13:00), Day 1 serial PK will be collected on Day 2 and the 24-hour sample will be collected on Day 3.

[l] Blood samples for biomarkers and antibodies (if feasible) will be collected predose on Day 1, and at 3 hours ± 2 hours postdose on Day 7.

[m] Swab can be oropharyngeal and/or nasal (anterior nares or nasopharyngeal) consistent with site standard of care.

[n] For subjects discharged prior to Day 14, 21, or 28 and known to be alive at discharge, this information will be collected via telephone on these days (± 3 days). Other assessments for this day will not be performed for these subjects.

1.4. Sample Size Determination

[redacted]

2. ANALYSIS SETS

The analysis sets are defined below and the treatment assignments that will be used for each type of analysis are shown in Table 5.

Table 5: Analysis Sets

Analysis Set	Definition	Treatment Assignment
Safety	All subjects who receive at least one dose of study drug. This analysis set will be used for all safety analyses.	Treatment received
Intent-to-Treat (ITT)	All subjects who are randomized into the study. This analysis set will be used for pharmacodynamic and exploratory analyses.	Randomized treatment

3. STATISTICAL ANALYSES

3.1. General Considerations

[redacted]

3.1.1. Visit Windows

Analyses will be based on nominal CRF visits.

3.2. Study Subjects

3.2.1. Enrollment

Number and percentage of subjects enrolled in the study will be summarized by treatment group and total for each investigator by frequency distributions, sorted by highest enroller first. The ITT analysis set will be used for this summary.

A listing of subject eligibility (inclusion or exclusion criteria exceptions) will be provided.

3.2.2. Subject Disposition and Completion Status

Subjects' study status will be displayed in a table, including the following categories:

- Randomized
- Randomized and treated
- Completed the study
- Discontinued the study drug
- Discontinued from the study, including reason.

Reasons for not completing the study will be presented based on eCRF categories (adverse events, lost to follow-up, physician decision, pregnancy, protocol violation, study termination by sponsor, withdraw by subject, other).

For all categories, the percentages will be calculated using the number of randomized patients as the denominator.

A listing of subjects' disposition and completion status will be provided. The listing of subject disposition will include analysis set flags (ITT, Safety (Yes/No)), date the informed consent form was signed, dates of first and last dose of study drug, primary reason for discontinuation of study treatment, study completion status, and date of last contact.

3.2.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics (age, sex, race, ethnicity, height, weight, BMI) will be summarized in total and by treatment group. Age will be analyzed with descriptive statistics. Sex, race and ethnicity will be analyzed using frequency distributions.

A listing of subjects' demographic and baseline characteristics will be provided.

3.2.4. Protocol Deviations

The following protocol deviations are defined as major:

[redacted]

[redacted]

A summary of protocol deviations by site and treatment group based on the ITT analysis set will be provided.

In addition, a summary of protocol deviations by treatment group based on the ITT analysis set will be provided.

A subject listing with all protocol deviations identified prior to database lock will be provided. In addition, a subject listing with newly identified nonmajor protocol deviations identified during site closeout visits following database lock will be provided as applicable. Moreover, a listing of all major analysis protocol deviations will be provided. All subject listings will be based on the ITT analysis set.

Subjects with major analysis protocol deviations will be identified before unblinding.

3.2.5. Medical History

Medical history is defined as conditions with onset dates prior to the first dosing of study medication and will be coded using the Medical Dictionary for Regulatory Activities [MedDRA] version 23.1 or newer.

The number and percentage of subjects with medical history in each system organ class (SOC) and preferred term (PT) will be summarized by treatment group using the Safety analysis set.

To the extent possible, medical history on Day 1 will include evaluation for past and present conditions, or any other disease disorders, including known immunosuppression and source of immunosuppression (i.e., disease or medication).

A listing of subjects' clinical characteristics, medical history of comorbidity as well as concurrent use of antiviral therapy at baseline using the Safety analysis set will be provided.

3.2.6. Prior/Concomitant Medications

Prior medications include all medications taken prior to the first dose of investigational product, regardless of medication end data. Concomitant medications prescribed and over-the-counter, encompass all non-study medicinal products that the subject was taking prior to Day 1 that are ongoing at the visit, in addition to all medications that have a start date on or after the first dose of investigational product of the treatment period.

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) for this study with Theravance review and approval of the mappings. The 3Q2020 C3 or later version of the WHODD will be used.

A listing of subjects' prior and concomitant medications will be provided.

3.3. Pharmacodynamic Endpoint Analysis

The PD endpoint is the SaO2/FiO2 ratio, calculated as SaO2 divided by FiO2. The raw values and change from baseline in SaO2/FiO2 will be summarized using an 8-point descriptive summary on ITT analysis set.

A listing of subjects' SaO2/FiO2 measurements will be provided.

3.4. Exploratory Endpoint(s) Analyses

[redacted]

[redacted]

3.5. Safety Analyses

For all safety analyses, the Safety analysis set will be used.

3.5.1. Extent of Exposure

A subject's data for the extent of exposure (i.e., duration of dosing within each period) to study drug will be summarized by treatment using an 8-point descriptive summary.

Dosing information for individual subjects will be listed. Discontinuation of dosing and reasons for discontinuation will be listed and summarized.

3.5.2. Treatment Compliance

[redacted]

3.5.3. Adverse Events

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus with Theravance review and approval of the coding. MedDRA, version 23.0 or later will be used.

Summaries will present SOC, PT, and severity, and the frequency and percentage of subjects reporting each observed event. Adverse events observed during the period from obtaining informed/proxy consent to the start of administration of study drug will be regarded separately from AEs observed after study drug administration (i.e., TEAEs).

A TEAE will be defined as any AE that begins on or after the date (and time) of first dose of study drug up to the date/time of last dose of study drug during the study period. Any AEs observed during the period from obtaining informed/proxy consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject. The frequency of subjects who experience TEAEs will be summarized overall and by treatment group. All AEs will also be summarized by relationship to treatment (study drug) and severity. All SAEs will be summarized.

The following TEAE summaries will be generated:

- Overall Summary of Adverse Events
- The overall summary of adverse events will include the following summary lines: (any AE, any AE related to Study Drug, moderate or severe AEs, moderate or severe AEs related to study drug, SAEs, SAEs related to study drug, AEs leading to discontinuation, deaths during study).
- TEAEs by primary SOC and PT
- Drug-related TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- Drug-related TEAEs by SOC, PT, and severity

- Moderate or severe TEAEs by SOC and PT
- Moderate or severe drug related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Drug-related serious TEAEs by SOC and PT
- Adverse events leading to premature study drug discontinuation
- TEAEs by PT with Overall Frequency > 10% of Overall Population

Separate analyses will be performed for TEAEs occurring during the 7-day treatment period and the 28-day duration of Part 1.

3.5.3.1. Adverse Events of Special Interest

Not applicable.

3.5.4. Additional Safety Assessments

3.5.4.1. Clinical Laboratory Parameters

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges (i.e.., shifts from normal to abnormal high/low). Listings will flag laboratory values that are outside of normal range.

Clinical laboratory test results will be listed by subject. Reference ranges for each parameter provided by the laboratory will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged, as appropriate, in the data listings. Abnormalities in clinical laboratory test results will be provided in a separate listing.

3.5.4.2. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, heart rate, respiratory rate, temperature and weight) and changes from baseline values at each visit will be presented by treatment group.

Vital signs data will be summarized in terms of counts and percentages within appropriately defined categories (Table 6).

A listing of subjects' vital sign (systolic and diastolic blood pressures, heart rate, respiratory rate) and change from baseline at each visit will be provided. Marked abnormalities as defined in Table 6 will be flagged in the listing.

Table 6: Criteria for Marked Abnormalities in Vital Signs

Heart Rate (bpm)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3.6. Other Analyses

Not applicable.

3.6.1. Other Variables and/or Parameters

Not applicable.

3.6.2. Subgroup Analyses

Not applicable.

3.7. Interim Analyses

No interim analyses are planned.

3.7.1. Data Monitoring Committee

[redacted]

4. REFERENCES

Not applicable

5. SUPPORTING DOCUMENTATION

5.1. Appendix 1: Changes to Protocol-Planned Analyses

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

STATISTICAL ANALYSIS PLAN

PHASE 2

(Part 2)

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Multi-center Study of an Inhaled Pan-Janus Kinase Inhibitor, TD-0903, to Treat Symptomatic Acute Lung Injury Associated with COVID-19
Short Study Title:	TD-0903 for ALI Associated with COVID-19
Sponsor Study Number:	TD-0903-0188
Test Product:	TD-0903
Sponsor:	Theravance Biopharma Ireland Limited
Legal Registered Address:	Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland

Regulatory Agency Identifier Number(s)

EudraCT No.	2020-001807-18
US IND:	149220

This study will be conducted in compliance with Good Clinical Practice.

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SAP (Part 2)

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HR	ITT
LOD	Lower limit of quantitation/limit of detection
MedDRA	Medical Dictionary For Regulatory Activities Terminology
ND	Not Detected
PT	Preferred Term
SaO2/FiO2 ratio	Ratio of peripheral oxygen saturation to the fraction of inspired oxygen
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

SAP VERSION HISTORY

1. INTRODUCTION

This statistical analysis plan (SAP) provides a detailed description of the statistical analyses of the efficacy and safety data specified in the protocol for Part 2 of study TD-0903-0188.

This is a Phase 2 (2-part), randomized, double-blind, placebo-controlled, parallel-group, multi-center study of an inhaled pan-Janus kinase inhibitor, TD-0903, to treat symptomatic acute lung injury associated with Coronavirus Disease 2019 (COVID-19). The Phase 2 study was designed with separate data reporting for Parts 1 and 2. Part 1 was completed, and Part 2 dosing was chosen based upon Dose Level Review Committee (DLRC) dose-escalation review of safety and tolerability.

The SAPs for [redacted]

Specifications of tables, figures, and data listings are contained in a separate document.

1.1. Objectives and Endpoints

1.1.1. Primary Objective and Endpoint

Based on a subject population hospitalized with confirmed COVID-19 and requiring supplemental oxygen, the primary objective is to characterize the efficacy of TD-0903 as measured by respiratory failure-free days (RFDs) through Day 28.

The **primary endpoint** is the number of RFDs from randomization through Day 28.

1.1.2. Secondary Objectives and Endpoints

The **secondary objectives** are to evaluate the effect of TD-0903 on:

- Reducing the acute lung injury (as measured by the ratio of peripheral oxygen saturation to the fraction of inspired oxygen [SaO2/FiO2 ratio]) associated with COVID-19
- Safety and tolerability
- Clinical outcomes as measured by an 8-point clinical status scale
- The proportion of subjects alive and respiratory failure-free on Day 28

Secondary Endpoints are:

- Change from baseline in SaO2/FiO2 ratio on Day 7
- Proportion of subjects in each category of the 8-point clinical status scale on Days 7, 14, 21 and 28
- Proportion of subjects alive and respiratory-failure free on Day 28

1.1.3. Exploratory Objectives and Endpoints

[redacted]

1.2. Study Design

This is a two-part study; this SAP applies only to Part 2.

Part 2 is a randomized, double-blind, parallel-group study evaluating efficacy and safety of 3 mg of TD-0903 (selected based on the data from Part 1) as compared with placebo in hospitalized subjects with confirmed symptomatic COVID-19 who require supplemental oxygen.

Sparse sampling for assessment of TD-0903 plasma concentrations may be collected for population PK analysis.

Subjects will provide informed consent upon study entry. Baseline assessments (Day 1) will include medical and medication history, vital signs (blood pressure, heart rate, respiratory rate [BP, HR, RR], and body temperature), a physical examination (including height and weight, and hepato- or splenomegaly at a minimum), and measures of oxygenation (pulse oximetry, FiO2). Female subjects of childbearing potential will undergo a serum pregnancy test. Blood samples will be collected from all subjects for hematology (complete blood count [CBC] with differential at a minimum), and serum chemistry (renal function [creatinine, blood urea nitrogen], liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (Alk Phos), and total bilirubin (TBili), and triglycerides, ferritin and fibrinogen. The investigator will also evaluate the subject's clinical status and review inclusion/exclusion criteria.

Oxygenation will be assessed via SaO2/FiO2 ratio. Use of ventilatory and oxygen support, presence in the Intensive Care Unit (ICU), clinical status (including mortality), and date of discharge will be recorded for all subjects as appropriate.

Clinical status will be assessed for all subjects using the 8-point scale.

Changes in swab SARS-CoV-2 viral infection status, SARS-CoV-2 antibody levels, blood cytokine levels, and biomarkers of inflammation, thrombosis, and lung injury will be explored.

Subject safety will be assessed throughout the study using standard measures, including adverse event (AE) monitoring, physical examinations (including hepato- or splenomegaly at a minimum), vital signs (at a minimum, temperature, BP, HR, and respiratory rate [RR]), clinical laboratory tests (at a minimum, CBC with differential, renal function, and liver function tests), and concomitant medication usage. A Safety Assessment Committee (SAC) will meet regularly to review blinded safety data.

1.3. Treatment Assignment

[redacted]

Table 3: Schedule of Study Procedures (Part 2)

Procedure	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8-13	Day 14	Days 15-20	Day 21	Days 22-27	Hospital Discharge	Day 28
Informed Consent[a]	X	X													
Review Inclusion/Exclusion Criteria		X													
Medication and Medical History[b]		X													
Vital Signs		X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]		X[d]		X[d]		X[d]	X[d]
Physical Examination[e]		X						X							
Height and Weight		X[f]													
Serum Pregnancy Test		X													
Pulse Oximetry[g]		X	X	X	X	X	X	X		X		X		X	X
Modified Borg Dyspnea Score[h]		X	X	X	X	X	X	X							
Hematology (CBC with Diff)[i]		X	Record results of any lab evaluations performed for clinical purposes.					X	Record results of any lab evaluations performed for clinical purposes only on Day 14, 21, 28 (while hospitalized) and at discharge.						
Serum Chemistry[j]		X						X							
Plasma PK samples[k]						X		X							
Serum and plasma for biomarkers and antibodies, and for storage for future analysis (if feasible)[l]		X				X		X						X	
Swab for SARS-CoV-2 viral PCR[m]		X				X		X						X	
Clinical Status		X	X	X	X	X	X	X	X[n]	X[n]	X[n]	X[n]	X[n]	X	X[n]
Randomization		X													
Study Drug Dosing		X	X	X	X	X	X	X							
Adverse Events	X	X	X	X	X	X	X	X	X[n]	X[n]	X[n]	X[n]	X[n]	X	X[n]
Concomitant Medications		X	X	X	X	X	X	X	X[n]	X[n]	X[n]	X[n]	X[n]	X	X[n]

Abbreviations: Alk Phos, alkaline phosphatase, ALT, alanine aminotransferase; AST, aspartate aminotransferase, BP, blood pressure; CBC, complete blood count; COVID-19. Coronavirus Disease 2019; FiO2, fraction of inspired oxygen; HR, heart rate; PCR, polymerase chain reaction; RR, respiratory rate; SARS-CoV-2; Severe Acute Respiratory Syndrome-associated Coronavirus-2 TBili, total bilirubin

[a] Informed consent may be obtained on either Day 0 or Day 1 up to 1 week prior to study enrollment in subjects undergoing testing for COVID-19, but with milder symptoms that, in the investigator's opinion, may worsen.

[b] Including known immunosuppression and source of immunosuppression i.e., disease or medication)

[c] Includes BP, HR, RR, and body temperature. Measured before dosing (first daily dose if study drug given twice daily).

[d] Morning vital signs

[e] Including hepato-or splenomegaly at a minimum

[f] If not available from subject's chart

[g] Oxygen saturation via pulse oximeter is considered equivalent to arterial oxygen saturation (SaO2) for this study. Record FiO2 at each assessment.

[h] Collected while subject is at rest.

[i] At a minimum. Day 1 samples must be collected within 24 hours before dosing, inclusive of those collected prior to informed consent; Day 7 samples must be collected predose. Laboratory testing as per local hospital protocols will be followed.

[j] Including renal function, liver function tests (AST, ALT, Alk Phos, TBili), triglycerides, ferritin, and fibrinogen. Day 1 samples on must be collected within 24 hours before dosing, inclusive of those collected prior to informed consent; Day 7 samples must be collected predose. Laboratory testing as per local hospital protocols will be followed.

[k] Blood samples for plasma PK analyses will be collected predose and within 30 to 120 minutes postdose on Day 7. Additional sample on Day 5 can be taken at any time postdose.

[l] Blood samples for biomarkers and antibodies (if feasible) will be collected predose on Day 1, and at 3 hours ± 2 hours postdose on Day 5 and Day 7, and at hospital discharge.

[m] Swab can be oropharyngeal and/or nasal (anterior nares or nasopharyngeal) consistent with site standard of care.

[n] For subjects discharged prior to Day 28 inclusive and known to be alive at discharge, this information will be collected via telephone as follows:

- Days 14, 21, and 28 (±3 days) for subjects discharged on Days 8 through 13
- Days 21 and 28 (±3 days) for subjects discharged on Days 15 through 20
- Day 28 (±3 days) for subjects discharged on Days 22 through 27

The other assessments for these days will not be performed for these subjects.

1.4. Sample Size Determination

[redacted]

2. ANALYSIS SETS

The analysis sets are defined below and the treatment assignments that will be used for each type of analysis are shown in Table 4.

Table 4: Analysis Sets

Analysis Set	Definition	Treatment Assignment
Safety	All subjects who received at least one dose of study drug. This analysis set will be used for all safety analyses.	Treatment received
Intent-to-Treat (ITT)	All subjects who are randomized into the study. This analysis set will be used for all efficacy analyses.	Randomized treatment
Per-Protocol (PP; membership to be determined before unblinding)	Intent-to-Treat subjects with no protocol deviations during the study that would affect the primary efficacy analyses. This analysis set will be used for primary and key secondary efficacy analyses.	Treatment received

3. STATISTICAL ANALYSES

3.1. General Considerations

[redacted]

[redacted]

3.1.1. Visit Windows

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3.2. Study Subjects

[redacted]

3.2.4. Protocol Deviations

The following protocol deviations are defined as major for primary analysis:

[redacted]

A summary of protocol deviations by site and overall by treatment group based on the ITT analysis set will be provided.

A subject listing with all protocol deviations identified prior to database lock will be provided. In addition, a subject listing with newly identified nonmajor protocol deviations identified during site closeout visits following database lock will be provided as applicable. Moreover, a listing of all major analysis protocol deviations will be provided. All subject listings will be based on the ITT analysis set.

Subjects with major analysis protocol deviations will be identified before unblinding.

3.2.5. Medical History

Medical history is defined as conditions with onset dates prior to the first dose of study medication and will be coded using the Medical Dictionary for Regulatory Activities [MedDRA] version 23.1 or newer.

The number and percentage of subjects with medical history in each system organ class (SOC) and for each preferred term (PT) will be summarized by treatment group using the Safety analysis set.

To the extent possible, medical history on Day 1 will include evaluation for past and present conditions, or any other disease disorders, including known immunosuppression and source of immunosuppression (i.e., disease or medication).

A listing of subjects' clinical characteristics, medical history of comorbidity, as well as concurrent use of antiviral therapy at baseline using the Safety analysis set will be provided.

3.2.6. Prior/Concomitant Medications

Prior medications include all medications taken prior to the first dose of study medication, regardless of medication end date. Concomitant medications prescribed and over the counter, encompass all non-study medicinal products that the subject was taking prior to Day 1 that are ongoing at the visit, in addition to all medications that have a start date on or after the first dose of investigational product of the treatment period.

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) with Theravance review and approval of the mappings. The 3Q2020 C3 or later version of the WHODD will be used.

A listing of subjects' prior and concomitant medications will be provided.

3.3. Primary Efficacy Endpoint Analysis

[redacted]

[redacted]

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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]

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[redacted]

[redacted]

3.4. Secondary Endpoint Analyses

[redacted]

[redacted]

3.5. Exploratory Endpoints

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.6. Safety Analyses

For all safety analyses, the Safety analysis set will be used.

3.6.1. Extent of Exposure

A subject's data for the extent of exposure (i.e., duration of dosing) to study drug will be summarized for each treatment group using an 8-point descriptive summary.

Dosing information for individual subjects will be listed. Discontinuation of dosing and reasons for discontinuation will be listed and summarized.

3.6.2. Treatment Compliance

[redacted]

3.6.3. Adverse Events

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus with Theravance clinical review and approval of the coding. MedDRA version 23.0 or later will be used.

A treatment-emergent adverse event (TEAE) is defined as any AE that begins on or after the date (and time) of first dose of study drug up to the date/time of last dose of study drug during the study period. Any AEs observed during the period between obtaining informed/proxy consent and the start of study drug administration will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject.

Summaries will present SOC, PT, and severity, and the frequency and percentage of subjects within each treatment group reporting each observed event. The frequency of subjects who experience TEAEs will be summarized overall and by treatment group. All AEs will also be summarized for each treatment group by relationship to treatment (study drug) and severity. All SAEs will be summarized for each treatment group.

The following TEAE summaries will be generated:

- Overall Summary of Adverse Events

  The overall summary of adverse events will include the following summary lines: (any AE, any AE related to Study Drug, moderate or severe AEs, moderate or severe AEs related to study drug, SAEs, SAEs related to study drug, AEs leading to discontinuation, deaths during study).
- TEAEs by primary SOC and PT
- Drug-related TEAEs by SOC and PT
- TEAEs by SOC, PT, and severity
- Drug-related TEAEs by SOC, PT, and severity
- Moderate or severe TEAEs by SOC and PT

- Moderate or severe drug related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Drug-related serious TEAEs by SOC and PT
- Adverse events leading to premature study drug discontinuation
- TEAEs by PT with Overall Frequency > 10% of Overall Population

Separate analyses will be performed for TEAEs occurring during the 7-day treatment period and the 28-day duration.

Of note, SAEs include serious and life-threatening conditions such as: pulmonary embolism, dysrhythmia, secondary infections, stroke, hemodynamic instability requiring vasopressor support, acute renal failure, acute liver failure as well as other acute events, including those that have been associated with underlying disease.

3.6.3.1. Adverse Events of Special Interest

Not applicable.

3.6.4. Additional Safety Assessments

3.6.4.1. Clinical Laboratory Parameters

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges (i.e., shifts from normal to abnormal high/low). Listings will flag laboratory values that are outside of the normal range.

Clinical laboratory test results will be listed by subject. Reference ranges for each parameter provided by the laboratory will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged in the data listings. Abnormalities in clinical laboratory test results will be provided in a separate listing.

3.6.4.2. Vital Signs

Vital signs (systolic and diastolic blood pressures, heart rate, respiratory rate, temperature and weight) and changes from baseline values at each visit will be summarized for each treatment group using descriptive statistics.

Vital signs data will also be summarized in terms of counts and percentages within appropriately defined categories (Table 7).

A listing of subjects' vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate) and change from baseline at each visit will be provided. Marked abnormalities as defined in Table 7 will be flagged in the listing.

Table 7: Criteria for Marked Abnormalities in Vital Signs

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3.7. Other Analyses

Not applicable.

3.7.1. Other Variables and/or Parameters

Not applicable.

[redacted]

3.8. Interim Analyses

No interim analyses are planned.

3.8.1. Data Monitoring Committee

[redacted]

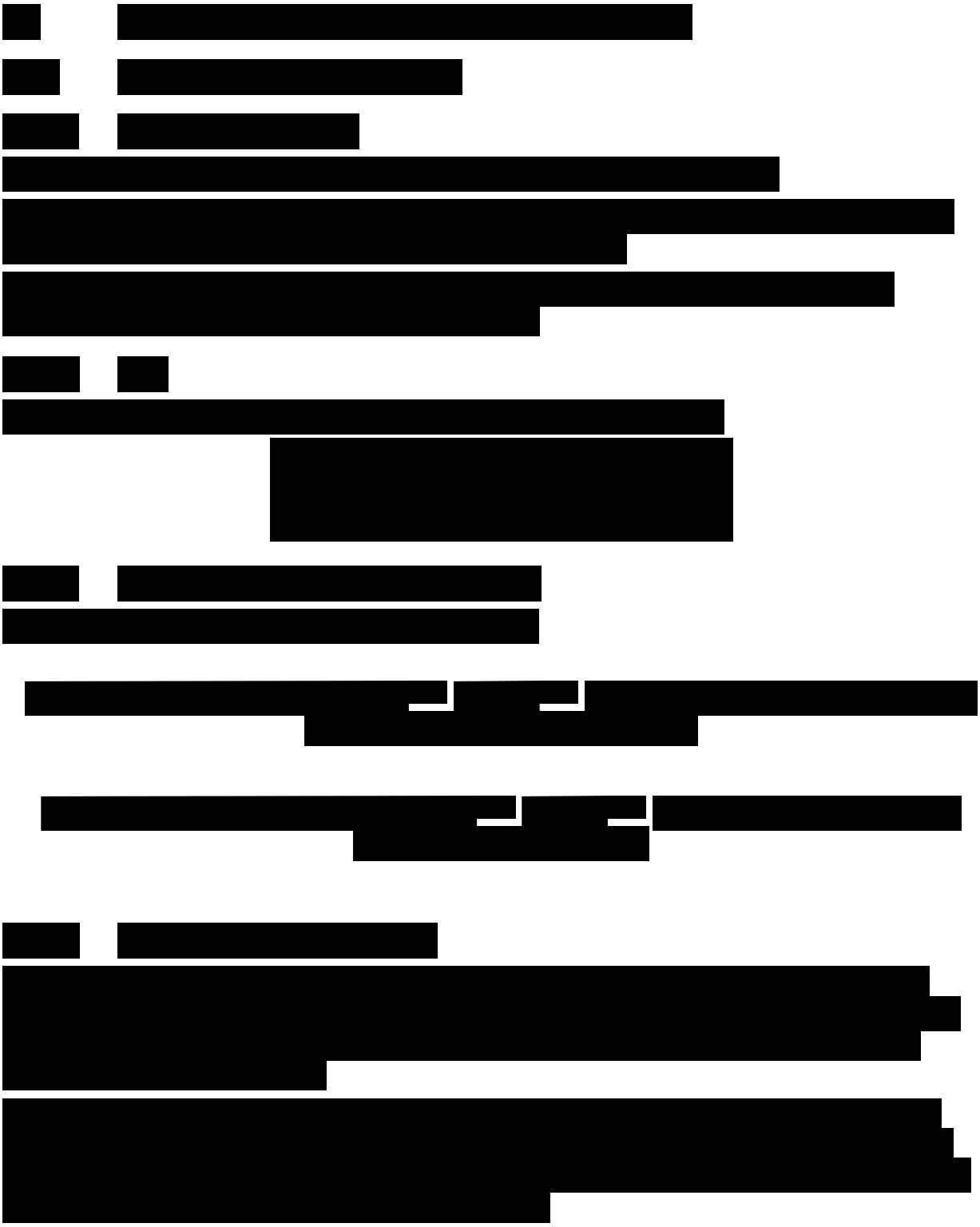
4. REFERENCES

1. Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients with COVID 19. - Full Text - ClinicalTrials.gov [cited 2020 Mar 16]. Available from: https://clinicaltrials.gov/ct2/show/NCT04315298?cond=covid+19&draw=2&rank=6
2. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology. 2020 Feb 19;200432.
3. Adapted from Vannucchi AM et al (2020). Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a prospective observational study. Leukemia. 2020 Aug 19:1–13. doi: 10.1038/s41375-020-01018-y. Epub ahead of print. PMID: 32814839; PMCID: PMC7437386.
4. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;**94**:496–509. doi: 10.1080/01621459.1999.10474144.

SOFTWARE

5. PASS Version 14 (NCSS, LLC, Kaysville, Utah) was used for planned sample size and power calculation.
6. SAS Version 9.4 (SAS Institute Inc., Cary, NC.) or newer is to be used for all programming of tables, listings, and figures.

[redacted]



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4.4. Supplementary Support for Sample Size Estimation

[redacted]