CLINICAL STUDY PROTOCOL

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
Study Short Title:	TD-0903 for ALI Associated with COVID-19
Sponsor Study No.:	TD-0903-0188
Date:	18 September 2020— [redacted]
Test Product:	TD-0903
US IND:	149220
EudraCT No.:	2020-001807-18
Sponsor:	Theravance Biopharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
Clinical Study Director:	[redacted] Theravance Biopharma US, Inc. Telephone: [redacted] Email: [redacted]

This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and 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

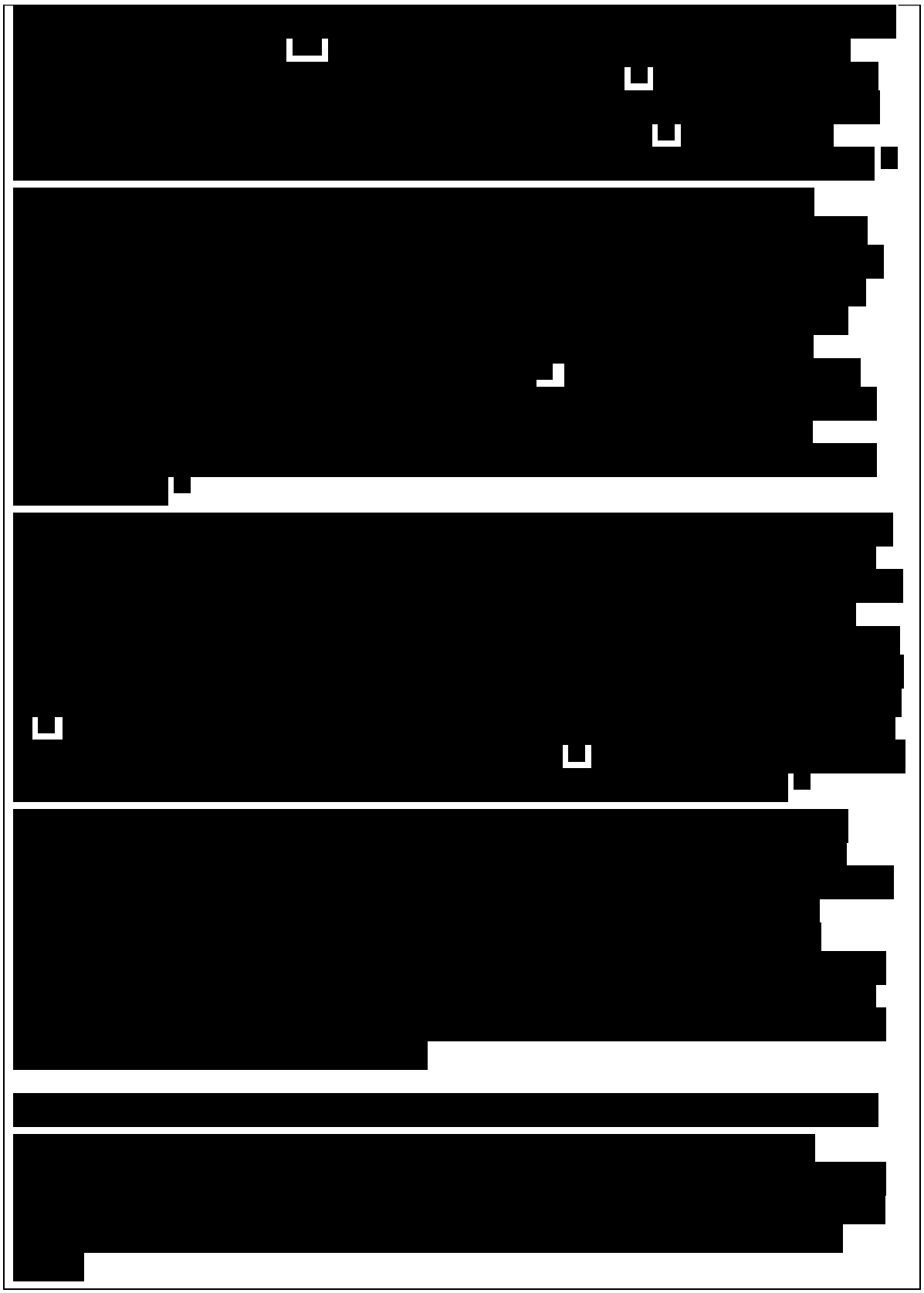
Study Short Title: TD-0903 for ALI Associated with COVID-19

Estimated Number of Study Centers and Countries or Regions:

[redacted]

Background and Rationale:

[redacted]



[redacted]

Objectives

Part 1:

The objectives are:

- Evaluate the safety and tolerability of inhaled TD-0903 in subjects with COVID-19
- Assess the plasma pharmacokinetics (PK) of TD-0903 in subjects with COVID-19
- Characterize the effect of TD-0903 on reducing the acute lung injury (as measured by SaO2/FiO2 ratio) associated with COVID-19
- Explore the effect of TD-0903 on swab viral infection status, SARS-CoV-2 antibody levels, blood cytokine levels, and biomarkers of inflammation, thrombosis and lung injury

Part 2:

The primary objective is to characterize the efficacy of TD-0903 as measured by respiratory failure-free days (RFDs) through Day 28.

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

- Reducing the acute lung injury (as measured by 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

[redacted]

Study Design: This is a two-part study.

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.

Up to three ascending-dose cohorts, each comprised of 8 subjects, will be dosed at [redacted] total daily dose of TD-0903 or matched placebo. Six subjects in each cohort will be randomized to receive TD-0903 and 2 subjects in each cohort will be randomized to receive placebo (3:1 randomization). Each dose level cohort will be initiated once the corresponding healthy volunteer cohort in Study TD-0903-0183 has completed dosing and the Dose Level Review Committee (DLRC) has recommended escalation. Dosing will be either once or twice a day in divided doses, as informed by emerging data from Study TD-0903-0183 and prior cohorts in this study.

Eligible subjects will be randomized and dosed for up to 7 days or until discharge from the hospital, whichever is earlier. 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. The blinding of subjects' treatment assignments will be maintained for Theravance personnel who are directly involved with the ongoing operational activities of the study, for all subjects, and for all site personnel until the study is concluded. The activities and composition of DLRC will be described in a charter.

The DLRC will recommend the final dose to carry forward into Part 2, including the potential to dose twice daily.

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 ratio of peripheral oxygen saturation to the fraction of inspired oxygen (SaO2/FiO2 ratio) will be measured to guide dose selection for Part 2.

Subject follow-up after the dosing period will continue until Day 28.

Part 2

Part 2 is a randomized, double-blind, parallel-group study evaluating efficacy and safety of one dose 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. [redacted] The study drug will be administered once-daily or twice daily in divided doses (as determined by results from Study TD-0903-0183 and from Part 1 of this study) for up to 7 days or until discharge

from the hospital, whichever is earlier. Subjects will be followed for up to 28 days or until death, whichever is earlier.

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

Parts 1 and 2

Subjects will provide informed consent upon study entry; consent can be provided by the subject or legally authorized representative, or as assent/proxy consent via both a clinician and second health professional attesting that the subject understands the risks and potential benefits and elects to proceed. 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.

Oxygenation will be assessed via SaO2/FiO2 ratio. Use of ventilatory and oxygen 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.

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 [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. A Safety Assessment Committee will meet regularly to review safety data.

Duration of Study Participation: 28 days or until death, whichever is earlier.

[redacted]

Study Population:

Inclusion Criteria:

1. Willing and able to provide written informed consent on their own prior to performing study procedures

   In the U.K., subject assent or proxy consent as per local site procedures, may also be acceptable if both a clinician and second health professional attest that the subject understands the risks and potential benefits of the study and elects to proceed.

   Outside the U.K., written informed consent may only be obtained from the subject or legally authorized representative.

   In the event the subject loses capacity during the study, the subject consents to continued participation, except where this is not clinically indicated.
2. Willing and able to comply with study-related procedures/assessments
3. Age 18 to 80 years old
4. Hospitalized (or documentation of a plan to admit to the hospital if the subject is in an emergency department) and requiring supplemental oxygen to maintain saturation > 90%
5. A diagnosis of symptomatic COVID-19 defined as a positive test for SARS-CoV-2 RNA detected by RT-PCR on a sample from the upper respiratory tract (e.g. nasopharyngeal, nasal, or oropharyngeal swab) collected < 72 hours prior to randomization
6. Onset of COVID-19 -related symptoms > 2 days and $\leq$ 14 days prior to hospital admission

Exclusion Criteria:

1. Subjects currently receiving invasive mechanical ventilation.
2. Presence or suspicion of active malignancy with the exception of cancer in situ (e.g., skin cancer)
3. Evidence of serious active infections other than COVID-19
4. Current diagnosis of human immunodeficiency virus, hepatitis B or C
5. In the opinion of the investigator, unlikely to survive for > 24 hours from enrollment
6. Women who are pregnant or might be pregnant, or who are currently breast-feeding

   Subjects must agree to not donate ova or sperm through 30 days after the last dose of study medication.

7. Presence of significant comorbidity that, in the opinion of the investigator, predisposes the subject to mortality. Such conditions might include:
   a. New York Heart Association class IV Heart Failure
   b. Hepatic dysfunction (i.e., AST or ALT >3x upper limit of normal)
   c. Renal dysfunction (i.e., estimated glomerular filtration rate (eGFR) <50 mL/min) or receiving renal replacement therapy
8. Presence of septic shock at time of enrollment
9. Hemoglobin < 80 g/L
10. Evidence of neutropenia (i.e., absolute neutrophil count < 1000 cells/μL), lymphopenia (i.e., absolute lymphocyte count < 200 cells/μL) or thrombocytopenia (i.e., platelets < 50×10^9/L)
11. Hypersensitivity to TD-0903 or its components, or to other JAK inhibitors
12. Treatment with anti-IL 6 (e.g., tocilizumab, sarilumab), anti-IL-1, anti-T cell (e.g., abatacept) antibodies, anti-IL-6R antagonists, JAK inhibitors (e.g., baricitinib, tofacitinib) supplemental interferon therapy, or tyrosine kinase inhibitors (e.g., erlotinib, gefinitib) in the past 30 days, or plans to receive a JAK inhibitor during the study period
13. Current treatment with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs)/immunosuppressive agents including:
   a. Methotrexate, cyclosporine, mycophenolate, tacrolimus, penicillamine, or sulfasalazine within 2 weeks prior to enrollment
   b. Azathioprine or cyclophosphamide within 12 weeks prior to enrollment
   c. Monoclonal antibodies targeting B cells (eg rituximab) within 12 weeks prior to enrollment
   d. Tumor necrosis factor-alpha (TNFα) inhibitors within 4 weeks prior to enrollment
14. Participating in other clinical trials involving any other experimental treatment for COVID-19, except in the context of a single-arm antiviral or convalescent plasma compassionate-use protocol
15. Subjects with active or incompletely treated pulmonary tuberculosis, or known history of non-tuberculosis mycobacterium over past 12 months
16. Subject requires continuous oxygen supplementation for underlying cardiorespiratory history in the past 90 days
17. Body Mass Index ≥ 40 kg/m^2
18. Receipt of any live vaccine (i.e., live attenuated) in the 4 weeks prior to visit 1 or plans to receive a live vaccine (or live attenuated) during the study period.

    Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.

19. History of venous thromboembolism (VTE), deep venous thrombosis (DVT), Pulmonary Embolism (PE) or known hypercoagulable disorder (e.g. factor V Leiden, antiphospholipid antibody syndrome, protein C or S deficiency).

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment: TD-0903 [redacted] up to a maximum of [redacted] total daily dose either once or twice daily in divided doses for up to 7 days, will be administered via inhalation using the [redacted] nebulizer system.

For the [redacted] and/or [redacted] doses, a loading dose of [redacted] and/or [redacted] respectively, will be given as the total dose on Day 1 based on emerging PK and safety data from Study TD-0903-0183.

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment: Matching placebo will be administered once or twice daily for up to 7 days via inhalation using the [redacted] nebulizer system.

Study Evaluations

Subjects will be assessed daily while hospitalized, with evaluations performed according to the Protocol Schedule of Events. In Part 2, if subjects are discharged from the hospital before Days 14, 21 or 28 and are known to be alive at discharge, they will undergo a telephonic study visit on Days 14, 21, and/or 28 to provide data relating to clinical status, adverse events and concomitant medications.

Safety Assessments:

Subject safety will be assessed throughout the subject's stay in hospital using standard measures, including clinical status, AE monitoring, physical examinations, vital signs, clinical laboratory tests and concomitant medication usage.

Efficacy Assessments:

- Pulse oximetric saturation analyses
- Use of ventilatory and oxygen support
- ICU days
- Modified Borg Dyspnea Score
- Clinical status
- Modified HScore
- Vital signs

Biomarker Assessments:

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

[redacted]

Pharmacokinetic Assessments:

- In Part 1, serial blood samples for assessment of TD-0903 plasma concentrations will be collected predose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after the dose on Day 1 and Day 7. If the dose on Day 1 occurs in the evening (after 1:00 pm / 13:00), Day 1 serial PK samples may be collected on Day 2 and Day 3.
- In Part 2, sparse sampling for assessment of TD-0903 plasma concentrations may be collected for population PK analysis pre-dose and within 30 to 120 minutes post-dose on Day 7; and additional sample on Day 5 can be taken at any time postdose.
- [redacted]

Statistical Methods

[redacted]

[redacted]

Study Endpoints:

Part 1:

Endpoints (through Day 7)

Safety

- Change from baseline in vital signs and clinical laboratory results
- Incidence and severity of treatment-emergent AEs (TEAEs)

Pharmacokinetics

- Plasma PK parameters on Day 1 and Day 7

Pharmacodynamics (PD)

- Change from baseline in SaO2/FiO2 ratio

Additional Endpoints (through Day 28)

Safety

- Change from baseline in vital signs and clinical laboratory results
- Incidence and severity of TEAEs

[redacted]

[redacted]

Part 2:
The primary endpoint is the number of RFDs from randomization through 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

[redacted]

[redacted]

The safety endpoints are:

- Change from baseline in vital signs and clinical laboratory results
- Incidence and severity of TEAEs

The PK endpoints are population PK parameters for TD-0903.

Analysis:

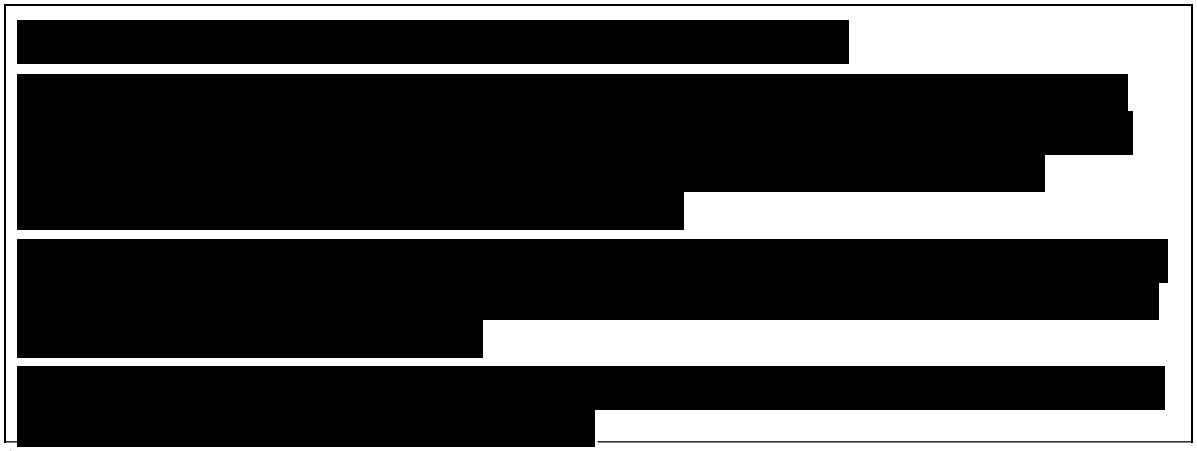
Parts 1 and 2:

[redacted]

Part 2:

[redacted]

[redacted]


[redacted]

SCHEDULE OF STUDY PROCEDURES

Table 1: 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[n]	X[n]	X	X[n]
Randomization		X										
Study Drug Dosing		X	X	X	X	X	X	X				

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
Adverse Events	X	X	X	X	X	X	X	X	X[n]	X[n]	X	X[n]
Concomitant Medications		X	X	X	X	X	X	X	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; 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 may be collected on Day 2 and the 24-hour sample may 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 28 and known to be alive at discharge, this information will be collected via telephone at any time between Day 25 and Day 35; other assessments for this day will not be performed for these subjects.

Table 2: 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 2019FiO2, fraction of inspired oxygen; HR, heart rate; PCR, polymerase chain reaction; RR, respiratory rate; SARS-CoV-2; Severe Acute Respiratory Syndrome-associated Coronavirus-2TBili, 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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AE	adverse event
ALI	Acute lung injury
Alk Phos	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	blood pressure
CBC	Complete blood count
CCL	Chemokine (C-C motif) ligand
CFR	(United States) Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
(e)CRF(s)	(electronic)case report form(s)
CRP	C-reactive protein
DLRC	Dose Level Review Committee
DMARD	Disease-modifying anti-rheumatic drug
eGFR	Estimated glomerular filtration rate
ECMO	Extracorporeal membrane oxygenation
FiO2	Fraction of inspired oxygen
GCP	Good Clinical Practice
HLH	Hemophagocytic lymphohistocytosis
HR	Heart rate
HScore	Diagnostic score that generates a probability for the presence of secondary hemophagocytic lymphohistocytosis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit

Abbreviation	Description
IEC	Independent Ethics Committee
IFN(γ)	Interferon(-gamma)
IL	interleukin
IRB	Institutional Review Board
JAK	Janus kinase
MERS-Co-V	Middle East Respiratory Syndrome-associated coronavirus
MMRM	Mixed-model repeated measures
NOAEL	No-observed-adverse effect level
PASS	Power Analysis and Sample Size
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per-protocol
REB	Research Ethics Board
RFD	Respiratory failure-free day
(RT-) PCR	(Real-time) polymerase chain reaction
RTSM	Randomized Trial Supply Management
SaO2	peripheral oxygen saturation
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV(-2)	Severe Acute Respiratory Syndrome-associated Coronavirus (-2) (SARS-CoV-2 is the virus attributed to COVID-19)
SOP	Standard operating procedure
(p)STAT	(phosphorylated) Signal transducers and activators of transcription
TBili	Total bilirubin
TEAE	Treatment-emergent adverse event

1. INTRODUCTION

1.1. Background and Rationale

[redacted]

[redacted]

1.2. Nonclinical Profile

A review of the nonclinical profile of TD-0903 can be found in the current version of the TD-0903 Investigator's Brochure (IB). The following is a brief summary of the pertinent findings.

1.2.1. Pharmacology

[redacted]

[redacted]

1.2.2. Toxicology

[redacted]

1.2.3. Pharmacokinetics

[redacted]

1.3. Clinical Experience

[redacted]

1.4. Risks and Benefits

There is a high unmet need for COVID-19 patients with ALI as there are no approved treatments for COVID-19. Given the high potency of TD-0903 in inhibiting cytokine activation in human cells, and its formulation as an inhaled agent, TD-0903 may be a potentially effective treatment of inflammatory lung diseases.

Nonclinical safety studies did not reveal any adverse safety findings [redacted]

[redacted]

2. OBJECTIVES

The objectives are based on a subject population hospitalized with confirmed symptomatic COVID-19 and requiring supplemental oxygen.

Part 1:

The objectives are:

- Evaluate the safety and tolerability of inhaled TD-0903 in subjects with COVID-19
- Assess the plasma pharmacokinetics (PK) of TD-0903 in subjects with COVID-19
- Characterize the effect of TD-0903 on reducing the acute lung injury (as measured by SaO2/FiO2 ratio) associated with COVID-19
- Explore the effect of TD-0903 on swab viral infection status, SARS-CoV-2 antibody levels, blood cytokine levels and biomarkers of inflammation, thrombosis and lung injury.

Part 2:

The primary objective is to characterize the efficacy of TD-0903 as measured by respiratory failure-free days (RFDs) through Day 28.

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

- Reducing the acute lung injury (as measured by 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

[redacted]

3. STUDY DESIGN

3.1. Overview

This is a two-part study.

3.1.1. Part 1: Multiple Ascending Dosing

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.

Up to three ascending-dose cohorts, each comprised of 8 subjects, will be dosed at [redacted] total daily dose of TD-0903 or matched placebo. Six subjects in each cohort will be randomized to receive TD-0903 and 2 subjects in each cohort will be randomized to receive placebo (3:1 randomization). Each dose level cohort will be initiated once the corresponding healthy volunteer cohort in Study TD-0903-0183 has completed dosing and the Dose Level Review Committee (DLRC) has recommended escalation. Dosing will be either once or twice a day in divided doses, as informed by emerging data from Study TD-0903-0183 and any prior cohorts in this study.

Eligible subjects will be randomized and dosed for up to 7 days or until discharge from the hospital, whichever is earlier. 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. The blinding of subjects' treatment assignments will be maintained for Theravance personnel who are directly involved with the ongoing operational activities of the study, for all subjects, and for all site personnel until the study is concluded. The activities and composition of DLRC will be described in a charter.

The DLRC will recommend the final dose to carry forward into Part 2, including the potential to dose twice daily.

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 ratio of peripheral oxygen saturation to the fraction of inspired oxygen (SaO2/FiO2 ratio) will be measured to guide dose selection for Part 2.

Subject follow-up after the dosing period will continue until Day 28.

3.1.2. Part 2: Parallel Group

Part 2 is a randomized, double-blind, parallel-group study evaluating efficacy and safety of one dose 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. Approximately 99 subjects per group (198 subjects total) will be enrolled in Part 2.

[redacted]

(Table 3). The study drug will be administered once-daily or twice daily in divided doses (as determined by results from Study TD-0903-0183 and from Part 1 of this study) for up to 7 days or until discharge from the hospital, whichever is earlier. Subjects will be followed for up to 28 days or until death, whichever is earlier.

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

3.1.3. Parts 1 and 2

Subjects will provide informed consent upon study entry; consent can be provided only by the subject or legally authorized representative outside the United Kingdom (U.K.), or, within the U.K., as assent/proxy consent via both a clinician and second health professional attesting that the subject understands the risks and potential benefits and elects to proceed. Baseline assessments (Day1) 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.

Oxygenation will be assessed via SaO2/FiO2 ratio. Use of ventilatory and oxygen 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.

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 [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. A Safety Assessment Committee will meet regularly to review safety data.

3.2. Rationale for Study Design

[redacted]

[redacted]

3.3. Selection of Dose and Duration of Treatment

[redacted]

3.4. Study Endpoints

Part 1:

Endpoints (through Day 7)

Safety

- Change from baseline in vital signs and clinical laboratory results
- Incidence and severity of treatment-emergent AEs (TEAEs)

Pharmacokinetics

- Plasma PK parameters on Day 1 and Day 7

Pharmacodynamics (PD)

- Change from baseline in SaO2/FiO2 ratio

Additional Endpoints (through Day 28)

Safety

- Change from baseline in vital signs, and clinical laboratory results
- Incidence and severity of TEAEs

[redacted]

Part 2:

The primary endpoint is the number of RFDs from randomization through 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

[redacted]

The safety endpoints are:

- Change from baseline in vital signs and clinical laboratory results
- Incidence and severity of TEAEs

The PK endpoints are population PK parameters for TD-0903.

3.5. Minimization of Bias

3.5.1. Blinding

Part 1 and Part 2 of this study will be conducted as a double-blind, placebo-controlled study. Part 1 will be unblinded to the DLRC after 7-day dosing is completed for all subjects in each cohort.

3.5.1.1. Part 1

For Part 1, randomization and treatment assignment will be via the Randomization Trial Supply Management System (RTSM).

Subjects will be assigned in random order to TD-0903 or placebo according to the randomization schedule. All study subjects, study investigators and their staff, and the Sponsor's staff involved in the conduct of the study will be blinded to treatment assignment Unblinded study staff will include dose administration staff at the research site and the site pharmacist and/or designee[s], neither of whom will be involved in direct subject care, or collection or analysis of data. Following the final Day 7 dosing of all subjects in each cohort, the DLRC (as described in Section 6.4) will review the data in an unblinded manner; any data reviewed by Sponsor personnel before that point will be performed in a blinded manner.

Additionally, to facilitate PK analysis, the analyst at the PK bioanalytical lab may be unblinded, however, any PK data provided to the Sponsor for analysis will be provided in a blinded fashion (i.e., PK data cannot be linked to an individual subject).

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject. If breaking the blind is required because of a medical emergency, the treatment identity will be revealed by the investigator or designee for that subject only. In the event that the emergency

is one in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects dosed at that dose level. The unblinding will be properly documented in the study file and captured in the RTSM. The responsibility to break the blind resides solely with the investigator (or designee), however, it is requested that the investigator or designee will make every effort to contact the Medical Monitor or designee to notify him/her of the medical emergency and the breaking of the blind as soon as it is practicable, granting that these efforts should not stall or delay the unblinding of trial subject treatment in emergency situations.

In the absence of a medical emergency, the blinded randomization for this study will not be revealed to any blinded person until all data are entered in the database, edits checks are performed, queries closed, electronic case report forms (eCRFs) signed by the investigator(s) or designee, and the database is officially locked.

3.5.1.2. Part 2

For Part 2, randomization and treatment assignment will be via the Randomization Trial Supply Management System.

In the event of an untoward safety observation, the investigator may unblind a subject's treatment assignment using the RTSM. The blind should be broken only if knowledge of the subject's study medication would affect subsequent treatment and such knowledge is required for the clinical management of the subject. Any investigator unblinding will be documented within the appropriate section of the subject's case report from (CRF) and will, for Part 2, be captured in the RTSM.

Unblinding of individual study subjects or study center staff on the basis of results from the study procedures (i.e., self-unblinding) is considered to be improbable.

3.5.2. Treatment Assignment

3.5.2.1. Part 1

Within each cohort, subjects will be randomized 3:1, TD-0903 to placebo.

3.5.2.2. Part 2

[redacted]

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects who meet the following criteria will be eligible for study enrollment:

1. Willing and able to provide written informed consent on their own prior to performing study procedures

   In the U.K., subject assent, or proxy consent as per local site procedures, may also be acceptable if both a clinician and second health professional attest that the subject understands the risks and potential benefits of the study and elects to proceed.

   Outside the U.K., written informed consent may only be obtained from the subject or legally authorized representative.

   In the event the subject loses capacity during the study, the subject consents to continued participation, except where this is not clinically indicated.
2. Willing and able to comply with study-related procedures/assessments
3. Age 18 to 80 years old
4. Hospitalized (or documentation of a plan to admit to the hospital if the subject is in an emergency department) and requiring supplemental oxygen to maintain saturation > 90%
5. A diagnosis of symptomatic COVID-19 defined as a positive test for SARS-CoV-2 RNA detected by RT-PCR on a sample collected from the upper respiratory tract (e.g. nasopharyngeal, nasal, or oropharyngeal swab) collected < 72 hours prior to randomization
6. Onset of COVID-19-related symptoms > 2 days and $\leq$ 14 days prior to hospital admission

4.2. Exclusion Criteria

Subjects who satisfy any of the following criteria are not eligible for study enrollment:

1. Subjects currently receiving invasive mechanical ventilation
2. Presence or suspicion of active malignancy with the exception of cancer in situ (e.g., skin cancer)
3. Evidence of serious active infections other than COVID-19
4. Current diagnosis of human immunodeficiency virus, hepatitis B or C
5. In the opinion of the investigator, unlikely to survive for > 24 hours from enrollment
6. Women who are pregnant or might be pregnant, or who are currently breast-feeding

   Subjects must agree to not donate ova or sperm through 30 days after the last dose of study medication.
7. Presence of significant comorbidity that, in the opinion of the investigator, predisposes the subject to mortality. Such conditions might include:
   a. New York Heart Association class IV Heart Failure
   b. Hepatic dysfunction (i.e., AST or ALT >3x upper limit of normal)
   c. Renal dysfunction (i.e., estimated glomerular filtration rate (eGFR) <50 mL/min) or receiving renal replacement therapy
8. Presence of septic shock at time of enrollment
9. Hemoglobin < 80 g/L
10. Evidence of neutropenia (i.e., absolute neutrophil count < 1000 cells/μL), lymphopenia (i.e., absolute lymphocyte count < 200 cells/μL) or thrombocytopenia (i.e., platelets < 50×10^9/L)
11. Hypersensitivity to TD-0903 or its components, or to other JAK inhibitors
12. Treatment with anti-IL 6, (eg tocilizumab, sarilumab), anti-IL-1, anti-T cell (e.g., abatacept) antibodies, anti-IL-6R antagonists, JAK inhibitors (e.g., baricitinib, tofacitinib), supplemental interferon therapy, or tyrosine kinase inhibitors (e.g.,umatibib, genfinitib) in the past 30 days, or plans to receive a JAK inhibitor during the study period
13. Current treatment with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs)/immunosuppressive agents including:
    a. Methotrexate, cyclosporine, mycophenolate, tacrolimus, penicillamine, or sulfasalazine within 2 weeks prior to enrollment
    b. Azathioprine or cyclophosphamide within 12 weeks prior to enrollment
    c. Monoclonal antibodies targeting B cells (eg rituximab) within 12 weeks prior to enrollment
    d. Tumor Necrosis Factor-alpha (TNFα) inhibitors within 4 weeks prior to enrollment

14. Participating in other clinical trials involving any other experimental treatment related to COVID-19, except in the context of a single-arm antiviral or convalescent plasma compassionate-use protocol
15. Subjects with active or incompletely treated pulmonary tuberculosis, or known history of non-tuberculosis mycobacterium over past 12 months
16. Subject requires continuous oxygen supplementation for underlying cardiorespiratory history in the past 90 days
17. Body Mass Index $\geq$40 kg/m^2
18. Receipt of any live vaccine (i.e., live attenuated) in the 4 weeks prior to visit 1 or plans to receive a live vaccine (or live attenuated) during the study period

    Note: Use of non-live (inactivated) vaccinations is allowed for all subjects.
19. History of venous thromboembolism (VTE), deep venous thrombosis (DVT), Pulmonary Embolism (PE) or known hypercoagulable disorder (e.g. factor V Leiden, antiphospholipid antibody syndrome, protein C or S deficiency).

5. STUDY DRUGS

All study drug supplied by the Sponsor must be stored in a secure location accessible only to designated study personnel.

5.1. Description of Study Drugs

5.1.1. TD-0903

[redacted]

5.1.2. TD-0903 Matching Placebo

[redacted]

5.2. Dosage and Administration

For blinding purposes, study drug will be prepared and administered to the subject by clinical study staff who are designated as unblinded dosing personnel and who will not have any responsibilities for clinical assessment of the subject except during the dose administration procedure. Further details are described in the pharmacy manual.

5.2.1. TD-0903

TD-0903 [redacted] total daily dose either once or twice daily in divided doses for up to 7 days, will be administered via inhalation using the [redacted] nebulizer system.

[redacted]

5.2.2. TD-0903 Matching Placebo

Matching placebo will be administered once or twice daily for up to 7 days via inhalation using the [redacted] nebulizer system.

5.3. Treatment Compliance

Subjects will receive study drug (TD-0903 or placebo) from medical personnel as inpatients. Compliance will be defined as subjects who received at least 1 dose on 4 of the 7 days.

Receipt of less than 4 doses will be documented in the CRF as to reasons why, the number of doses that were outside this range, and whether any AE occurred as a result of the non-compliance.

5.4. Drug Accountability and Reconciliation

The investigator or designee is responsible for maintaining accountability records for all study drug(s) received from the Sponsor, in accordance with applicable government regulations and study procedures. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s). Unused and expired study drugs will be disposed of in accordance with written instructions from the Sponsor.

Study drug reconciliation for each subject will not be performed because subjects will receive study drug as inpatients.

6. STUDY PROCEDURES

6.1. Schedule of Study Procedures

The schedule of study procedures for Part 1 and for Part 2 is summarized in Table 1 and Table 2, respectively.

6.2. Procedures by Visit

6.2.1. Part 1

6.2.1.1. Day 0

Written informed consent can be provided on Day 0 after the nature of the study has been explained and before any study procedure is performed. In the U.K., subject assent, or proxy consent as per local site procedures, may also be acceptable if both a clinician and second health professional attest that the subject understands the risks and potential benefits of the study and elects to proceed. Outside the U.K., written informed consent may only be obtained from the subject or legally authorized representative.

Informed consent/subject assent may be obtained 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.

If informed/proxy consent is obtained on Day 0, there is no need to obtain it on Day 1.

Subjects who provide informed/proxy consent on Day 0, will be assessed for AEs.

6.2.1.2. Day 1

For purposes of this study, Day 1 is the day of enrollment. The following procedures will be performed on Day 1.

- If not provided on Day 0, written informed consent (signed and dated by the subject) after the nature of the study has been explained and before any study procedure is performed.

  Informed consent may be obtained 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.

  Subject assent, or proxy consent as per local site procedures, may also be acceptable if both a clinician and second health professional attest that the subject understands the risks and potential benefits of the study and elects to proceed.
- Review of inclusion and exclusion criteria
- Medication and medical history (including known immunosuppression and source of immunosuppression i.e., disease or medication)
- Vital signs (prior to dosing; BP, HR, RR, body temperature)

- Complete physical examination (including height and weight, and hepato- or splenomegaly at a minimum)
- Serum pregnancy test (for female subjects of childbearing potential)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Blood collection
  - CBC with differential (within 24 hours before dosing inclusive of those collected prior to informed consent inclusive of those collected prior to informed consent)
  - Serum chemistry including renal function, liver function tests, triglycerides, ferritin, and fibrinogen (within 24 hours before dosing inclusive of those collected prior to informed consent)
  - PK: Serial blood samples for assessment of TD-0903 plasma concentrations will be collected pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours (i.e., on Day 2) after the dose. If the dose on Day 1 occurs in the evening (after 1:00 pm / 13:00), Day 1 serial PK samples may be collected on Day 2.
  - Biomarkers, and antibodies (if feasible) at pre-dose.
- Swab for SARS-CoV-2 viral PCR at pre-dose (oropharyngeal and/or nasal [anterior nares or nasopharyngeal] consistent with site standard of care)
- Clinical status
- Randomization
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.1.3. Day 2

The following procedures will be performed on Day 2:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Blood sample for PK: If feasible, the 24-hour sample following the Day 1 dose can be collected. If the dose on Day 1 occurs in the evening (after 1 pm / 13:00), Day 1 serial PK samples may be collected on Day 2.
- Clinical status
- Study drug dosing
- Adverse events

- Concomitant medications

6.2.1.4. Day 3

The following procedures will be performed on Day 3:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Blood sample for PK: If feasible, the 24-hour sample following the Day 2 dose can be collected if the dose on Day 1 occurs in the evening (after 1 pm / 13:00) and Day 1 serial PK samples are collected on Day 2.
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.1.5. Day 4

The following procedures will be performed on Day 4:

- Vital signs (prior to first daily dose, or morning vital signs; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.1.6. Day 5

The following procedures will be performed on Day 5:

- Vital signs (prior to first daily dose, or morning vital signs; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons

- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.1.7. Day 6

The following procedures will be performed on Day 6:

- Vital signs (prior to first daily dose, or morning vital signs; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.1.8. Day 7

The following procedures will be performed on Day 7:

- Vital signs (prior to first daily dose, or morning vital signs; BP, HR, RR, body temperature)
- Physical examination (including hepato- or splenomegaly at a minimum)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Blood collection
  - CBC with differential, predose
  - Serum chemistry, including renal function, liver function tests, triglycerides, ferritin, and fibrinogen; predose
  - PK: Serial blood samples for assessment of TD-0903 plasma concentrations will be collected pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours (i.e., Day 8) after the dose
  - Biomarkers and antibodies (if feasible; collected at 3 hours ± 2 hours postdose)
- Swab for SARS-CoV-2 viral PCR (oropharyngeal and/or nasal [anterior nares or nasopharyngeal] consistent with site standard of care)

- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.1.9. Day 14 and Day 21 (Chart Review)

The following results will be recorded at Day 14 and Day 21 via chart review:

- Vital signs (BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Record results of blood work done for clinical reasons
- Clinical status
- Adverse events
- Concomitant medications

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6.2.1.10. Hospital Discharge

The following procedures will be performed prior to discharge from the hospital:

- Morning vital signs (BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Record results of blood work done for clinical reasons
- Clinical status
- Adverse events
- Concomitant medications

6.2.1.11. Day 28 (Follow-up)

For subjects discharged prior to Day 28 and known to be alive at time of discharge, information on clinical status, AEs, and concomitant medications will be collected via telephone at any time between Day 25 and Day 35. No additional procedures will be conducted for these subjects.

The following procedures will be performed at Day 28 for subjects who remain hospitalized:

- Morning vital signs (BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Record results of blood work done for clinical reasons
- Clinical status
- Adverse events

- Concomitant medications

6.2.2. Part 2

6.2.2.1. Day 0

Written informed consent can be provided on Day 0 after the nature of the study has been explained and before any study procedure is performed. In the U.K., subject assent, or proxy consent as per local site procedures, may also be acceptable if both a clinician and second health professional attest that the subject understands the risks and potential benefits of the study and elects to proceed. Outside the U.K., written informed consent may only be obtained from the subject or legally authorized representative.

Informed/proxy consent may be obtained 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.

If informed/proxy consent is obtained on Day 0, there is no need to obtain it on Day 1.

Subjects who provide informed consent on Day 0, will be assessed for AEs.

6.2.2.2. Day 1

For purposes of this study, Day 1 is the day of enrollment. The following procedures will be performed on Day 1.

- If not provided on Day 0, written informed consent (signed and dated by the subject) after the nature of the study has been explained and before any study procedure is performed.

  Informed consent may be obtained 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.

  Subject assent, or proxy consent as per local site procedures, may also be acceptable if both a clinician and second health professional attest that the subject understands the risks and potential benefits of the study and elects to proceed.
- Review of inclusion and exclusion criteria
- Medication and medical history (including known immunosuppression and source of immunosuppression i.e., disease or medication)
- Vital signs (prior to dosing; BP, HR, RR, body temperature
- Complete physical examination (including height and weight, and hepato- or splenomegaly at a minimum)
- Serum pregnancy test (for female subjects of childbearing potential)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Blood collection

  - CBC with differential (within 24 hours before dosing, inclusive of those collected prior to informed consent)
  - Serum chemistry including renal function, liver function tests, triglycerides, ferritin, and fibrinogen (within 24 hours before dosing inclusive of those collected prior to informed consent)
  - Biomarkers and antibodies (if feasible) at pre-dose
- Swab for SARS-CoV-2 viral PCR at pre-dose (oropharyngeal and/or nasal [anterior nares or nasopharyngeal] consistent with site standard of care)
- Clinical status
- Randomization
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.2.3. Day 2

The following procedures will be performed on Day 2:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.2.4. Day 3

The following procedures will be performed on Day 3:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Oxygen saturation via pulse Oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Clinical status
- Study drug dosing
- Adverse events

- Concomitant medications

6.2.2.5. Day 4

The following procedures will be performed on Day 4:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.2.6. Day 5

The following procedures will be performed on Day 5:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Oxygen saturation via pulse Oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Record results of blood work done for clinical reasons
- Blood collection for biomarkers and antibodies (if feasible; collected at 3 hours ± 2 hours postdose)
- Blood sample for PK (if feasible) postdose
- Swab for SARS-CoV-2 viral PCR (oropharyngeal and/or nasal [anterior nares or nasopharyngeal] consistent with site standard of care)
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.2.7. Day 6

The following procedures will be performed on Day 6:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)

- Record results of blood work done for clinical reasons
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.2.8. Day 7

The following procedures will be performed on Day 7:

- Vital signs (prior to first daily dose; BP, HR, RR, body temperature)
- Physical examination (including hepato- or splenomegaly at a minimum)
- Oxygen saturation via pulse Oximetry / Record FiO2
- Modified Borg Dyspnea Score (collected while subject is at rest)
- Blood collection
  - CBC with differential, predose
  - Serum chemistry, predose, including renal function, liver function tests, triglycerides, ferritin, and fibrinogen
  - PK: blood samples for plasma PK analyses may be collected pre-dose and within 30 to 120 minutes postdose
  - Biomarkers and antibodies (if feasible; collected at 3 hours ± 2 hours postdose)
- Swab for SARS-CoV-2 viral PCR (oropharyngeal and/or nasal [anterior nares or nasopharyngeal] consistent with site standard of care)
- Clinical status
- Study drug dosing
- Adverse events
- Concomitant medications

6.2.2.9. Days 8 to 13

The following assessments will be performed while the subject remains hospitalized:

- Clinical status
- Adverse events
- Concomitant medications

6.2.2.10. Day 14

For subjects discharged prior to Day 14 and known to be alive at time of discharge, information on clinical status, AEs, and concomitant medications will be collected via telephone on this day (±3 days). No additional procedures will be conducted for these subjects.

The following procedures will be performed at Day 14 for subjects who remain hospitalized:

- Morning vital signs (BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Record results of blood work done for clinical reasons
- Clinical status
- Adverse events
- Concomitant medications

6.2.2.11. Days 15 to 20

The following assessments will be performed while the subject remains hospitalized:

- Clinical status
- Adverse events
- Concomitant medications

6.2.2.12. Day 21

For subjects discharged prior to Day 21 and known to be alive at time of discharge, information on clinical status, AEs, and concomitant medications will be collected via telephone on this day (±3 days). No additional procedures will be conducted for these subjects.

The following procedures will be performed at Day 21 for subjects who remain hospitalized:

- Morning vital signs (BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Record results of blood work done for clinical reasons
- Clinical status
- Adverse events
- Concomitant medications

6.2.2.13. Days 22 to 27

The following assessments will be performed while the subject remains hospitalized:

- Clinical status
- Adverse events

- Concomitant medications

6.2.2.14. Hospital Discharge

The following procedures will be performed prior to discharge from the hospital:

- Morning vital signs (BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Record results of blood work (hematology and serum chemistry) done for clinical reasons
- Blood collection for biomarkers and antibodies (if feasible)
- Swab for SARS-CoV-2 viral PCR (oropharyngeal and/or nasal [anterior nares or nasopharyngeal] consistent with site standard of care)
- Clinical status
- Adverse events
- Concomitant medications

6.2.2.15. Day 28 (Follow-up)

For subjects discharged prior to Day 28 and known to be alive at time of discharge, information on clinical status, AEs, and concomitant medications will be collected via telephone on this day (±3 days). No additional procedures will be conducted for these subjects.

The following procedures will be performed at Day 28 for subjects who remain hospitalized:

- Morning vital signs (BP, HR, RR, body temperature)
- Oxygen saturation via pulse oximetry / Record FiO2
- Record results of blood work done for clinical reasons
- Clinical status
- Adverse events
- Concomitant medications

6.3. Description of Study Assessments

6.3.1. Demographic and Baseline Assessments

Subjects will provide informed consent (or assent/proxy consent as per local site procedures via both a clinician and second health professional) upon admission to the hospital. Each subject will be asked to provide a relevant medical history (with the aid of medical records if available) including review of COVID-19 symptoms that lead to hospital administration, medication history, concomitant medications, known immunosuppression and source of

immunosuppression (i.e., disease or medication) and demographic information including year of birth, sex, race, and ethnicity. The subject will also undergo a physical examination including vital signs (BP, HR, RR, and body temperature) and height and weight, presence of hepato- or splenomegaly, and will also have the following assessments measured: pulse oximetry, FiO2, modified Borg Dyspnea Score and clinical status. Female subjects of childbearing potential will have blood collected for a serum pregnancy test. Blood will be collected for serial PK assessments (for subjects enrolled in Part 1), CBC with differential, and serum chemistry including renal function, liver function tests, triglycerides, ferritin, and fibrinogen.

6.3.2. Efficacy Assessments

Subjects will be evaluated for peripheral oxygen saturation on Day 1 through Day 7. Pulse oximetry will be measured 3 times over 5 minutes and the average value recorded. Data will be used to calculate SaO2/FiO2 ratio.

The Modified Borg Dyspnea Score is based on a 10-point scale that measures shortness of breath. Scores range from 0 (nothing at all, no shortness of breath) to 10 (maximal shortness of breath).[30] Subjects will record their resting modified Borg Dyspnea Score on Day 1 through Day 7.

Clinical outcomes will be assessed as follows:

- Use of ventilatory and oxygen support
- ICU days
- For Part 1, clinical status assessed by the investigator on Day 1 through Day 7 inclusive, on Day 14, Day 21, prior to hospital discharge, and on Day 28, based on an 8-point scale as summarized in Table 3
- For Part 2, clinical status assessed by the investigator daily on Day 1 through Day 28 inclusive, during hospitalization and at hospital discharge, based on an 8-point scale as summarized in Table 3. If subjects are discharged from the hospital before Days 14, 21 or 28 and are known to be alive at discharge, they will undergo a telephonic study visit on Days 14, 21, and/or 28 to provide data relating to clinical status.

Table 3: Clinical Status Score

Status / Criteria	Score
Death	8
Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation	7
Hospitalized, on non-invasive ventilation or high-flow oxygen devices	6
Hospitalized, requiring supplemental oxygen	5
Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (whether or not related to COVID-19)	4
Hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care (including subjects hospitalized for infection control)	3
Not hospitalized, but with limitation on activities and/or requiring home oxygen	2
Not hospitalized, no limitations on activities	1

Note: High-flow devices include high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5).

[redacted]

[redacted]

6.3.3. Pharmacokinetic Assessments

In Part 1, serial blood samples for assessment of TD-0903 plasma concentrations will be collected predose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after the dose on Day 1 and Day 7. If the dose on Day 1 occurs in the evening (after 1:00 pm / 13:00), Day 1 serial PK samples may be collected on Day 2 and Day 3.

In Part 2, sparse sampling for assessment of TD-0903 plasma concentrations will be collected for population PK analysis pre-dose and within 30 to 120 minutes post-dose on Day 7; an additional sample on Day 5 can be taken at any time postdose.

6.3.4. Biomarker Assessments

[redacted]

6.3.5. Safety Assessments

6.3.5.1. Adverse Events

Adverse events will be reviewed and recorded beginning at Day 0 or Day 1 (i.e., after signing the Informed Consent Form [ICF] or providing assent/proxy consent as per local site procedures up to and including Day 21, and prior to discharge from the hospital. Adverse events will also be reviewed and recorded at the follow-up contact at Day 28. For subjects who discontinue due to a nonserious AE, follow-up information on these events will be collected at Day 28. For subjects who discontinue due to a serious AE, follow-up information will be obtained as described in Section 7.3.3.

Adverse events may be observed by the study center personnel or spontaneously reported by the subject. Subjects will be reminded to call the study center to report AEs that occur between discharge from the hospital, and the Day 28 follow-up contact.

6.3.5.2. Medical History

To the extent possible, medical history on Day 1 will include evaluation for past and present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, substance abuse, surgical history, or any other diseases or disorders, including known immunosuppression and source of immunosuppression (i.e., disease or medication).

6.3.5.3. Physical Examination

Physical examinations will include an assessment of hepato- or splenomegaly in order to obtain the subjects modified HScore (Table 4). To the extent possible, physical examinations at enrollment on Day 1 will include height and weight, and examination of the following: general appearance; head, ears, eyes, nose, and throat; neck, skin, cardiovascular system, respiratory system, abdominal system, lymphatic system, dermatologic system, musculoskeletal system, and nervous system.

Physical examinations on subsequent days will assess changes since the previous examination, which may be recorded as AEs, if appropriate.

6.3.5.4. Vital Signs

6.3.5.4.1. Part 1

Vital signs (BP, HR, RR, and body temperature) will be collected on Day 1 through Day 7 prior to the subject's first dose, prior to hospital discharge (first vital signs of the morning), and Day 28 (for subjects still hospitalized; first vital signs of the morning). All measurements will be taken after the subject has been resting in a semirecumbent position for approximately 5 minutes.

On Day 14 and Day 21, this information will be collected via a review of the subject's chart.

6.3.5.4.2. Part 2

Vital signs (BP, HR, RR, and body temperature) will be collected on Day 1 through Day 7, Day 14, Day 21, prior to hospital discharge, and Day 28 (for subjects still hospitalized). Measurements will be taken after the subject has been resting in a semirecumbent position for approximately 5 minutes.

6.3.5.5. Laboratory Tests

Blood samples for routine clinical laboratory evaluation will be collected on Day 1 and Day 7. At all other times, this information will be recorded if these tests were performed for clinical purposes.

6.3.5.5.1. Hematology

Hematology assessments will include, at a minimum, a CBC with differential.

6.3.5.5.2. Serum Chemistry

Serum chemistry assessments will include, at a minimum, renal function (creatinine, blood urea nitrogen), liver function tests (AST, ALT, Alk Phos, and TBili), triglycerides, ferritin, and fibrinogen.

Additional blood samples may be collected to explore PD effects by evaluating the biomarkers described in Section 6.3.4.

6.3.5.5.3. Serum Pregnancy Test

Female subjects of childbearing potential will have a serum pregnancy test performed on Day 1. If the result is positive, the subject will not be enrolled into the study.

6.4. Dose Escalation Stopping Rules (Part 1 Only)

A decision to proceed to the next higher dose administration or initiate Part 2 will be made by the site investigator(s) and the DLRC. The DLRC will include the Sponsor's Medical Monitor, Study Director, Clinical Pharmacologist, and an independent statistician; other representatives may be considered on a case-by-case basis if additional expertise is required.

All pertinent safety/tolerability data (e.g., physical examinations, vital signs assessments, clinical laboratory tests, and AEs) and pharmacodynamic data (e.g., SaO2/FiO2 ratio)

through 7 days of dosing will be captured in a database snapshot and analyzed as described in Section 8. Results of these analyses will be reviewed to inform dose escalation decisions. In addition, available PK data from previous cohorts will be included in the review, for context.

Sponsor personnel (i.e., the DLRC) will review available data in the electronic data capture system that has been source document verified.

[redacted]

Following dose escalation review, and if none of the stopping rules are met, a decision will be made to continue the dose escalation as planned, and/or to initiate Part 2. Dose escalation to a level higher than planned will not occur without a protocol amendment.

Part 2 of the study will be initiated following the recommendation of the DLRC. The decision to initiate Part 2 will be based on evidence of predictable PK response, acceptable safety profile, and evidence of improved oxygenation at a dose lower than [redacted]

[redacted]

6.5. Concomitant Medications

[redacted]

All concomitant medications, including name of medication, date started and stopped, route of administration, indication, and dose will be recorded in the source documentation and on the CRF. The Sponsor must be notified in advance (or as soon as possible thereafter) of any administration of a prohibited medication. Administration of a prohibited medication may result in the subject being discontinued from the study.

[redacted]

[redacted]

6.6. Restrictions

Restrictions regarding subject care will be based on hospital standards and the subject's clinical course during the study.

6.6.1. Females of Childbearing Potential

Females of childbearing potential must have documentation of a negative serum pregnancy test prior to randomization on Day 1.

To be considered a female of non-childbearing potential, the subject must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

- bilateral salpingectomy;
- hysterectomy;
- bilateral oophorectomy.

A female subject will also be considered to be of non-childbearing potential if the subject is postmenopausal with amenorrhea for at least 12 months prior to dosing without an alternative medical cause. FSH levels will be measured only in cases when postmenopausal status is in question.

6.6.2. Contraception Measures for Male and Female Subjects

All female subjects of childbearing potential and male subjects with partners of childbearing potential must agree to use a highly effective method of birth control during the study and for at least 30 days after the last dose of study drug to prevent conception. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., < 1% per year) when used consistently and correctly. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device

- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized male partner

  Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has documented medical assessment of the surgical success.

- sexual abstinence

  True abstinence is defined as refraining from heterosexual intercourse in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Birth control methods which may not be considered highly effective are as follows:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

Male subjects must agree to use condoms to prevent potential fetal or partner exposure through seminal fluid, in addition to the use of highly effective pregnancy prevention measures during the study and through 30 days after the last dose of study medication.

6.7. Discontinuation

6.7.1. Subject Discontinuation

[redacted]

Any subject may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. Subjects will be asked if they can be contacted at Day 28; if they do not consent to this contact, tests and evaluations listed for the termination visit should be performed at the time of withdrawal.

A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

The Sponsor will be notified of all subject withdrawals.

Reasons for which the investigator or the Sponsor may withdraw a subject from the study or a subject may choose to terminate participation before completion of the study include, but are not limited to, the following:

- Adverse event
- Subject choice
- Major violation of the protocol
  - Did not receive a dose on at least 4 days of the treatment period
  - Received a prohibited concomitant medication
- Termination of the study by the Sponsor
- Other

If a subject is discharged prior to Day 28 and there are 3 documented, unsuccessful attempts to reach the subject by telephone at any time between Day 25 and Day 35 (during Part 1), or Days 14, 21, and/or 28 (± 3 days; during Part 2), the subject will be considered lost to follow-up.

6.7.2. Subject Replacement

[redacted]

6.7.3. Study Discontinuation

The Sponsor reserves the right to discontinue this study at any time for any reason.

6.8. Pregnancy

Given the inpatient setting and the disease being studied, pregnancies during the study are not anticipated.

However, if a female subject or a female partner of a subject discovers she is pregnant within 30 days of dosing, the Sponsor clinical study director (or designee) must be notified immediately. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Subjects must agree to not donate ova or sperm through 30 days after receiving the last dose of study medication (Section 4.2).

6.9. Safety Assessment Committee

[redacted]

7. ADVERSE EVENTS

7.1. Definitions

The definitions below are based on International Conference on Harmonization (ICH) guideline E2A, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".

7.1.1. Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- AEs may be new events
- Preexisting events that increase in frequency, severity or change in nature or seriousness during or as a consequence of participation in clinical studies.
- Pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).
- AEs may result from an overdose of the study medication.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE.
- Preexisting diseases or conditions present or detected before signing an ICF that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the ICF is considered to be preexisting and should be documented in the medical history CRF.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, Theravance Biopharma, Inc. (TBPH) will be notified according to the procedures for SAE reporting as outlined in Section 7.3.3. Follow-up information regarding

the outcome of the pregnancy and any fetal or neonatal sequelae will be obtained and documented.

7.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation. "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- New Inpatient hospitalization or prolongation of existing hospitalization.
  - Note: New inpatient hospitalization refers to a subsequent hospitalization after the subject's current hospitalization for COVID-19. To meet this criteria the subject must be formally admitted to a hospital for medical reasons for any length of time; it may or may not be overnight. It does not include presentation and care within an emergency department nor does it include preplanned hospitalizations. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- Disability- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.3. Additional Considerations for Serious Adverse Events

- Death is an outcome of an AE and not an AE in itself. Deaths of unknown cause for which the investigator cannot identify a cause of death will be captured as death of unknown cause or death not otherwise specified.
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.

7.2. Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the CRF, including the dates of onset and resolution, severity, relationship to study drug, outcome, and action taken with study medication.

7.2.1. Severity

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

- **Mild**: the AE is noticeable to the patient and/or the investigator, but does not interfere with routine activity.
- **Moderate**: the AE interferes with routine activity, but responds to symptomatic therapy or rest.
- **Severe**: the AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

7.2.2. Causal Relationship to Study Medication

The investigator's assessment of causality is based on clinical judgment regarding the reasonable possibility that the study medication caused the event and may include consideration of some or all of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, comorbid conditions, other drugs, and environmental factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study medication.
- Whether the AE resolved or improved with decreasing the dose or stopping the study medication ("dechallenge") or recurred or worsened upon re-exposure to the study medication ("rechallenge").

The causal relationship between the study medication and the AE will be described using one of the following categories:

- **Not Related:** Evidence exists that the AE has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the

drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

7.3. AE Reporting and Recording

7.3.1. AE Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and is mandated by regulatory agencies. Sponsor has established SOPs in compliance with regulatory requirements worldwide to ensure appropriate reporting of safety information. All clinical trials sponsored by TBPH will be conducted in accordance with these procedures.

7.3.2. AE and SAE Recording

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded from signing an ICF/providing assent through the last study visit (or last subject contact in the case of a follow-up telephone call). AEs will be recorded on the AE page of the CRF. SAEs, regardless of relationship to study medication will be recorded from signing an ICF/providing assent through the last study visit (or last subject contact in the case of a follow-up telephone call). All SAEs will be recorded on both the SAE Report Form and the AE page of the CRF and should include the following:

Description of event:

- Signs and symptoms due to a common etiology should be reported as a single diagnosis; for example, cough, runny nose, sneezing, sore throat, and head congestion would be reported as “upper respiratory infection”.
- A diagnosis or description must be as specific and as complete as possible (e.g., “lower extremity edema” instead of “edema”).
- “Death” should not be used as an AE term unless the cause of death is unknown. For events with a fatal outcome, the cause of death should be the AE term (e.g., if a subject died of an acute myocardial infarction, the AE term should be recorded as “Myocardial Infarction” and the event outcome as fatal).

Relationship to study medication: The investigator will assess the causal relationship of the study medication to the AE using the guidelines in Section 7.2.2.

Severity: The severity of the AE will be assessed using the guidelines in Section 7.2.1.

Outcome: The outcome of AEs will be recorded.

Therapeutic measures: Measures taken for the treatment or management of the AEs will be recorded.

7.3.3. SAE Reporting Timeline

SAEs will be reported to Global Safety and Pharmacovigilance or designee within 24 hours of the time the investigator or his/her designee becomes aware that an SAE has occurred, whether or not the event is considered to be related to study medication. A written report signed by the investigator should be submitted within 24 hours.

The SAE Report Form must be completed in accordance with the SAE Report Form Completion Guidelines. If all information on the SAE Report Form is not available at the time of the initial report, follow-up SAE reports will be completed and submitted.

To report an SAE, complete and fax or email the Serious Adverse Event Report Form to the following:

Theravance Biopharma Global Safety
Fax: [redacted]
Email: [redacted]

For medical questions regarding an SAE, contact the Sponsor medical monitor by telephone as follows:

Sponsor Medical Monitor Contact Information:
[redacted]

Telephone: [redacted]
Email: [redacted]

For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents if available. Additional information may be requested from the investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current TD-0903 IB. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.4. Adverse Event Follow-up

A subject experiencing an AE will be followed by the investigator or his/her trained delegate(s) through the follow-up period until Day 28. All SAEs will be followed until the investigator and/or the Sponsor has determined that the SAE has resolved or a stable clinical endpoint is reached, whichever is longer. The Sponsor may request follow-up of certain AEs until resolution and documentation of assessments made during this period.

Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the CRF.

8. STATISTICAL CONSIDERATIONS

8.1. General Considerations

[redacted]

8.2. Sample Size and Power

[redacted]

8.3. Analysis Sets

Parts 1 and 2:

The safety analysis set will include all subjects who receive at least one dose of study drug. Subjects will be analyzed according to their treatment actually received. The safety analysis set will be the primary analysis set for general and safety analyses.

The Pharmacokinetic (PK) analysis set will include all randomized subjects who received at least one dose of active TD-0903 study drug and have at least one measurable plasma PK concentration. The PK analysis set will be used for PK analyses.

The intent-to-treat (ITT) analysis set is the primary analysis set for efficacy and will include all subjects who are randomized into the study. Subjects will be analyzed according to their randomized treatment group.

The per-protocol (PP) analysis set will include all subjects in the ITT analysis set with no major analysis protocol deviations. Treatment assignment will be based on actual treatment.

All safety endpoints will be summarized descriptively using summary statistics or frequency distributions.

8.3.1. Examination of Subgroups

The following subgroups are pre-defined for the purposes of analyses:

[redacted]

8.3.2. Major Protocol Analysis Deviations

The following protocol deviations are defined as major and would be considered to have an impact on the analysis of efficacy data

[redacted]

8.4. General Analyses

8.4.1. Demographics Characteristics

Demographics and baseline characteristics (including age, sex, race, ethnicity, height, weight, and Body Mass Index) will be summarized for the safety analysis set.

8.4.2. Screening Summaries

Not applicable

8.4.3. Baseline Clinical Characteristics

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

8.4.4. Analysis of Efficacy

8.4.4.1. Efficacy endpoints

Part 1 (Exploratory):

[redacted]

Part 2:

The primary endpoint is the number of RFDs from randomization through 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

[redacted]

[redacted]

8.4.4.2. Primary Efficacy Evaluation

[redacted]

[redacted]

8.4.5. Secondary and Exploratory Efficacy Evaluations

[redacted]

[redacted]

8.4.6. Multiplicity Adjustment

[redacted]

8.4.7. Analysis of Pharmacokinetics

[redacted]

8.4.8. Analysis of Pharmacodynamics

[redacted]

8.5. Safety Analyses

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include vital signs, AEs, and clinical laboratory results (hematology, serum chemistry). Vital signs will be summarized in terms of observed values and changes from baseline.

8.5.1. Extent of Exposure

A subject's data for the extent of exposure to study drug will be generated from the study drug administration page of the CRF. Dosing information for individual subjects will be listed. Using drug administration data, estimates of exposure to TD-0903 will be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

8.5.2. Adverse Event Data

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities. Summaries will present system organ class (SOC), preferred term (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 plus up to 21 days of follow-up post-dose. AEs observed during the period from obtaining informed/proxy consent to the start of administration of study drug will be regarded separately from TEAEs.

[redacted]

A listing will be provided for all subjects who experience an SAE. Data listings will also be provided for subjects who discontinued the study due to any AE, as well as for a SAE.

8.5.3. Concomitant Medications

Medications will be summarized both prior to and during the treatment period.

8.5.4. Laboratory Data

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. Listings will flag laboratory values that are outside of normal range.

Clinical laboratory test results will be listed by subject. Reference ranges provided by the laboratory for each parameter 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 listed in a separate listing.

8.5.5. Vital Signs Data

Vital signs data will be summarized in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages within appropriately defined categories (Table 5).

[redacted]

8.6. Missing Data Handling

[redacted]

8.7. Adjudication Committee

Not applicable.

8.8. Data Monitoring Committee

[redacted]

9. STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1. Principal Investigator Responsibilities

Before beginning the study, the principal investigator at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 (or equivalent) and a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [e.g., associates, residents, research fellows].)

The principal investigator will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in Code of Federal Regulations Title 21 (21 CFR) Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required. He or she will also ensure that site-specific requirements for obtaining subject assent/ proxy consent (per the investigative site's procedures) are met.
- He or she will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64 and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required.
- He or she has read and understands the information in the TD-0903 IB, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that there are adequate and accurate records in accordance with 21 CFR 312.62 and will make those records available for inspection in accordance with 21 CFR 312.68 and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required.
- He or she will ensure that the IRB/IEC complies with the with the local and international regulatory requirements (for example in the US, compliance with 21 CFR 56 is required and outside of the US, compliance with ICH E6 and/or local regulatory requirements is required), and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will

also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312, and outside of the US, ICH E6 and/or local regulatory requirements.

9.2. Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and Good Clinical Practice (GCP) requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, ICF, IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by the Sponsor or its designee. If possible, the approval document should refer to the study by study protocol title and the Sponsor study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and the Sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3. Informed Consent

A properly written and executed ICF, in compliance with-ICH E6 (GCP Guideline, Section 4.8), 21 CFR Part 50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the study. In the U.K, informed consent can be provided as proxy consent via a clinician and another health professional attesting that the subject understands the risks and potential benefits and elects to proceed. Outside the U.K., written informed consent may only be obtained from the subject or legally authorized representative.

The investigator will prepare the ICF or revise the template ICF and provide the documents to the Sponsor (or designee) for approval before submission to the IRB/IEC/REB. The Sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

The investigator will provide copies of the signed ICF to each subject (or the subject's LAR) and will maintain the original in the subject's record file.

9.4. Data Recording and Quality Assurance

As used in this protocol, a CRF should be understood to refer to be an electronic data record.

Electronic data capture technology will be used for this study. All clinical information requested in this protocol will be recorded on the eCRFs approved by the Sponsor, or via other data collection methods, e.g., electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (e.g., correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks will be sent to the site for retention with other study documents after full completion of the study, i.e., after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5. Document Retention

Until otherwise notified by the Sponsor, an investigative site must retain in a controlled manner all study documents required by the Sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult the Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location or disposition of the study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6. Confidentiality

The investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study Sponsor, the study Sponsor's affiliated companies, the study Sponsor's designated service providers, regulatory agencies, and the IRB or IEC. The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject. If permission to use confidential medical information is withdrawn, the investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by the subject identification number, subject initials, date of birth, and study number, and not by the subject's full name, except the subject consent form or documentation of subject assent, which is archived at the study center only. The subject's name will not be used in any public report of the study.

During the course of the study, a confidential subject identification list will be maintained by the investigator and archived at the investigative site.

Before and during the conduct of the study, no study-related details may be disclosed, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7. Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to the Sponsor, representatives of the Sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed/proxy consent.

9.8. Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and SOPs for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the Sponsor immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation) and all study files are available, if requested.

Non-compliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued non-compliance may result in termination of the investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9. Publication

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The Sponsor will retain the ownership of the data collected in this study. The investigator will provide any proposed manuscript or abstract to the Sponsor before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between the Sponsor and the investigator.

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APPENDIX 1. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	TD-0903-0188
Protocol 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
Version:	[redacted]
Version Date:	18 September 2020 (FINAL)

I have read the protocol described above and agree to conduct this study in accordance with procedures described therein. I also agree to conduct the study in compliance with all applicable regulations.

Investigator's Name (print)

Investigator's Signature Date