PROTOCOL

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF MSTT1041A OR UTTR1147A IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	GA42469
VERSION NUMBER:	4
EUDRACT NUMBER:	2020-002713-17
IND NUMBER:	149507
NCT NUMBER:	NCT04386616
TEST PRODUCTS:	MSTT1041A (RO7187807) UTTR1147A (RO7021610)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
16-Sep-2020 00:19:11	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	10 April 2020
2	27 May 2020
3	3 August 2020

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GA42469 has been amended to change the primary endpoint and increase the sample size. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The primary endpoint has been changed to "Time to recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first)" (Sections 2.1.1, 6.1, and 6.4.1). The previous primary endpoint, "Clinical status assessed using a 7-category ordinal scale at Day 28," has been moved to the secondary efficacy endpoints (Sections 2.1.2 and 6.4.2). On the basis of published data from other clinical trials for COVID-19 pneumonia (Beigel et al. 2020; McCreary and Angus 2020), there appears to be growing consensus that time to recovery reflects a clinically meaningful outcome measurement for the targeted patient population. Additionally, given the variable time course of COVID-19, a fixed time endpoint could miss recognition of clinical benefit and therefore may not be optimal (Dodd et al. 2020).
- The incidence of mechanical ventilation and extracorporeal membrane oxygenation has been combined into a single secondary efficacy endpoint (Sections 2.1.2 and 6.4.2), as both represent a worsening of the clinical status and choice of management may vary between institutions.
- Clarifications have been made to the reporting requirements for possible UTTR1147A-mediated dermatologic reactions (Sections 4.6.1, 5.1.3.3, 5.2.3, and 5.3.5.2).
- The sample size was increased to allow for enrollment of approximately 390 patients with severe COVID-19 pneumonia, which will provide approximately 80% power to detect a difference between treatment groups for the new primary endpoint, "time to recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first)" (Sections 3.1.1, 4.1, and 6.1).
- Language has been updated to clarify that homeopathic remedies, IV fluids, or nutritional supplements (e.g., vitamins and minerals) do not need to be reported on the Concomitant Medications eCRF (Section 4.4).
- Language has been added to clarify that historic standard-of-care assessments are acceptable if performed within 2 days prior to Day 1, unless otherwise specified (Appendix 1).
- Language has been updated to clarify the window for central and local lab assessments (Appendix 1).
- Language has been added to clarify that visit days in the post-discharge schedule of activities should be based on days on study and not on days post-discharge (Appendix 2).
- Language regarding the discharge day has been updated to state that certain specified assessments do not need to be repeated if performed the day prior to discharge (Appendix 2).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF MSTT1041A OR UTTR1147A IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA**
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IND NUMBER:	149507
NCT NUMBER:	NCT04386616
TEST PRODUCTS:	MSTT1041A (RO7187807) UTTR1147A (RO7021610)
PHASE:	II
INDICATION:	Severe COVID-19 pneumonia
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with standard of care (SOC), for the treatment of severe coronavirus disease 2019 (COVID-19) pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoint:

- *Time to recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first)*

The ordinal scale categories are as follows:

1. Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$2 L supplemental oxygen)
2. Non–intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2 L supplemental oxygen)
- Duration of supplemental oxygen
- Proportion of patients alive and free of respiratory failure (requiring non-invasive ventilation, high-flow oxygen, mechanical ventilation, or ECMO) at Day 28
- *Clinical status assessed using a 7-category ordinal scale at Days 14 and 28*
- Incidence of *invasive* mechanical ventilation *or* ECMO
- Ventilator-free days to Day 28
- Incidence of ICU stay
- Duration of ICU stay
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal of care (whichever occurs first). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one category worsening on the ordinal scale, withdrawal, or death.
- Mortality rate at Days 14 *and* 28
- Time to clinical improvement, defined as a National Early Warning Score 2 of ≤ 2 maintained for 24 hours

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoints:

- Incidence of vasopressor use
- Duration of vasopressor use
- Incidence of starting hemodialysis
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load on Day 15 and Day 28
- Proportion of patients with secondary bacterial infections

Safety Objective

The safety objective for this study is to evaluate the safety of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs, targeted clinical laboratory test results, and targeted ECG parameters

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to characterize the MSTT1041A and UTTR1147A PK profiles on the basis of the following endpoints:

- Serum concentration of MSTT1041A at specified timepoints
- Serum concentration of UTTR1147A at specified timepoints

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of MSTT1041A and UTTR1147A on the basis of the following endpoints:
  - Relationship between serum concentration or PK parameters for MSTT1041A and efficacy and safety endpoints

- Relationship between serum concentration or PK parameters for UTTR1147A and efficacy and safety endpoints

- To evaluate potential relationships between selected covariates and exposure to MSTT1041A or UTTR1147A on the basis of the following endpoint:
  - Relationship between selected covariates and serum concentration or PK parameters for MSTT1041A
  - Relationship between selected covariates and serum concentration or PK parameters for UTTR1147A

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to UTTR1147A and MSTT1041A, individually, on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to MSTT1041A or UTTR1147A (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of MSTT1041A or UTTR1147A activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood and other fluid and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Study Design

Description of the Study

Overview of Study Design

This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, in patients hospitalized with severe COVID-19 pneumonia. Approximately 390 adult hospitalized patients who have been diagnosed with COVID-19 pneumonia (defined by a positive polymerase chain reaction [PCR] and evidence of pneumonia by chest X-ray or computed tomography [CT] scan) are expected to be enrolled.

Patients will be randomized after screening at a 2:2:1:1 ratio to receive blinded treatment of either MSTT1041A, UTTR1147A, or their matching placebos. Study treatment will be given in combination with SOC as defined by the site, including, but not limited to, anti-virals, host-directed therapies, convalescent plasma, low-dose corticosteroids, and supportive care. Randomization will be stratified by need for invasive mechanical ventilation (yes vs. no) and region. Enrollment of patients with a need for invasive mechanical ventilation will be capped at approximately 25% of the overall study population.

Patients assigned to the MSTT1041A or UTTR1147A arm will receive one infusion of MSTT1041A 700 mg or UTTR1147A 90 μg/kg on Day 1, respectively, and patients assigned to the placebo arm will receive one infusion of matching placebo. A second dose of MSTT1041A 350 mg, UTTR1147A 90 μg/kg, or matching placebo will be given on Day 15 if the patient still remains hospitalized with a requirement for supplemental oxygen therapy. For patients who are being discharged or transferred to a different care facility prior to Day 60, a discharge visit should be performed. Subsequently, patients will be followed up remotely (via phone or video visit), and should return to the clinic for Day 28 and a study completion visit (Day 60) or early discontinuation visit, if possible. Depending on patient findings during the phone/video visit, patients may need to be seen in person within 48 hours at the discretion of the investigator.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the

investigator's discretion. The investigator will record the reasons for screen failure in the screening log.

Patients who are eligible to be re-screened will be required to repeat assessments as follows:

- Within the 2-day screening window: Repeat only the assessments that triggered screen failure.
- Outside the 2-day screening window: Repeat all assessments. The consent process does not need to be repeated if re-screening is completed within 7 days after completion of initial informed consent.

Note: Historic standard of care test results are acceptable for CT scan or chest X-ray if performed within 7 days prior to randomization, and for influenza and SARS-CoV-2 virology if performed within 14 days of randomization.

Number of Patients

Approximately 390 adult patients hospitalized with severe COVID-19 pneumonia will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Documented informed consent
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- For sites at an altitude ≤ 5000 feet: peripheral capillary oxygen saturation (SpO_2) $\leq 93\%$ or partial pressure of oxygen/fraction of inspired oxygen ≤ 300 mmHg or requirement for supplemental oxygen to maintain $SpO_2 > 93\%$
- For sites at an altitude > 5000 feet: requirement for supplemental oxygen to maintain SpO_2 at an acceptable level per local standard of care
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 95 days after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 95 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 95 days after the final dose of study drug

  Women of childbearing potential must have a negative pregnancy test at screening.
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Participating in another clinical drug trial
- Treatment with investigational therapy (other than for COVID-19) within 5 half-lives or 30 days (whichever is longer) prior to initiation of study drug
- Use of Janus kinase inhibitor within 30 days or 5 drug elimination half-lives (whichever is longer) prior to screening
- Have received high-dose systemic corticosteroids ($\geq$ 1 mg/kg/day methylprednisolone or equivalent) within 72 hours prior to Day 1
- Known HIV infection with CD4 $<$ 200 cells/μL or $<$ 14% of all lymphocytes
- ALT or AST $>$ 10 $\times$ upper limit of normal (ULN) detected at screening
- History of anaplastic large-cell lymphoma or mantle-cell lymphoma
- History of cancer within the previous 5 years unless it has been adequately treated and considered cured or remission-free in the investigator's judgment
- Clinical evidence of active or unstable cardiovascular disease (e.g., acute myocardial ischemia or decompensated heart failure) as assessed by the investigator
- Elevated cardiac troponin indicative of a recent cardiac event or myocarditis/pericarditis, as defined below:
  1. If high-sensitivity immunoassay is available locally: high-sensitivity troponin (hs-troponin) I or T $>$ ULN (as per local standard for ULN), unless certain additional criteria are met, as outlined below:
     - If the local laboratory reports "indeterminate" or "intermediate" hs-troponin results: Patients with hs-troponin in the "intermediate" or "indeterminate" range (per local laboratory) may be enrolled if an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%–55%) without evidence of hypokinesis; if an echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.
     - If the local laboratory does not report "indeterminate" or "intermediate" hs-troponin results: Patients with hs-troponin $>$ ULN to $<$ 5 $\times$ ULN may be enrolled if an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%–55%) without evidence of hypokinesis; if an

echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.

2. If high-sensitivity immunoassay is not available locally: conventional cardiac troponin I or T > ULN, (based on local standard for ULN)
   - Patients with screen failure due to conventional troponin >ULN may be re-screened and enrolled if a repeat conventional troponin is ≤ULN and an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%–55%) without evidence of hypokinesis; if an echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.

- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- Sustained prolongation of QT interval corrected through use of Fridericia's formula (QTcF), defined as repeated demonstration of QTcF >480 ms (NCI CTCAE Grade 1)

  Patients with prolonged QTcF due to a reversible cause (e.g., electrolyte abnormalities) may be re-tested after the underlying cause has been corrected.

  For patients with a ventricular pacemaker, there should be appropriate correction for heart rate and pacing when determining baseline QTcF (as per Chakravarty et al. 2015); absolute QTcF values should not exceed 490 ms.
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), or family history of sudden unexplained death or long QT syndrome
- History of moderate or severe allergic, anaphylactic, or anaphylactoid reactions or hypersensitivity to any component of study treatment

End of Study

The end of this study is defined as the date when the last patient, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 10 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

- MSTT1041A 700 mg IV on Day 1, and a second dose of 350 mg IV on Day 15 for patients remaining hospitalized with a requirement for supplemental oxygen therapy at that time
- UTTR1147A 90 μg/kg IV on Day 1, and a second dose of 90 μg/kg IV on Day 15 for patients remaining hospitalized with a requirement for supplemental oxygen therapy at that time

Comparator

- Placebo for MSTT1041A via IV on Day 1, and a second dose on Day 15 for patients remaining hospitalized with a requirement for supplemental oxygen therapy at that time
- Placebo for UTTR1147A via IV on Day 1, and a second dose on Day 15 for patients remaining hospitalized with a requirement for supplemental oxygen therapy at that time

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoint:

- *Time to recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first)*

The ordinal scale categories are as follows:

1. Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen)
2. Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

Time to recovery will be analyzed using the stratified log-rank test, adjusting for stratification factors. The Kaplan-Meier plot, median time to event, and their 95% CI and p-value from the stratified log-rank test will be presented. A Cox proportional hazards regression model will be used to estimate the hazard ratio comparing MSTT1041A or UTTR1147A with placebo, respectively, adjusting for stratification factors. Hazard ratios and 95% CIs will be presented. In addition, the p-value from unstratified log-rank test, unadjusted hazard ratio, and 95% CI will also be presented. Further details on the primary endpoint analysis will be included in the Data Analysis Plan.

Determination of Sample Size

A total of approximately *390* patients will be randomly allocated in a 2:2:1:1 ratio to receive MSTT1041A, UTTR1147A, or their matching placebos. The sample size provides approximately 80% power using a log-rank Chi-square test to detect a *7*-day difference between treatment groups in time to *recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first),* under the following assumptions: median time to improvement in the placebo group is *21* days, with 28 days follow-up, and using a one-sided 5% alpha. The minimal detectable difference is expected to be approximately *5.3 days.*

Optional Interim Analyses

Other than the cumulative data review by the Data Monitoring Committee (DMC) for benefit/risk assessment, no formal efficacy interim analyses are planned at this time. The DMC, after reviewing unblinded data, may recommend that a formal efficacy interim analysis be performed. Furthermore, to adapt to information that may emerge during the course of this study, the Sponsor may choose to add a formal interim analysis at the recommendation of the DMC.

The interim analysis will be conducted by DMC. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The DMC Charter will be updated to document potential recommendations the DMC can make as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ARDS	acute respiratory distress syndrome
AUC	area under the concentration–time curve
$AUC_{0\text{-}28\ d}$	area under the concentration–time curve from 0 to 28 days
BNP	brain natriuretic peptide
C_{max}	maximum concentration observed
COPD	chronic obstructive pulmonary disease
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRP	C-reactive protein
CRSwNP	chronic rhinosinusitis with nasal polyps
CT	computed tomography
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic Case Report Form
ECHO	echocardiogram
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
Fc	fragment crystallizable
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
hs-troponin	high-sensitivity troponin
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
ICU	intensive care unit
IL	interleukin
IL-1RAcP	interleukin-1 receptor accessory protein
IL-22BP	IL-22 binding protein
IL-22Fc	interleukin-22 immunoglobulin fusion protein
IL-22R	interleukin-22 receptor
IMP	investigational medicinal product

Abbreviation	Definition
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
JAK	Janus kinase
LPS	lipopolysaccharide
MAD	multiple ascending dose
mITT	modified intent-to-treat
MOF	multiple organ failure
ms	millisecond
MTD	maximum tolerated dose
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NEWS2	National Early Warning Score 2
NOAEL	no-observed-adverse-effect level
NT-proBNP	N-terminal pro-brain natriuretic peptide
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PEEP	positive-end expiratory pressure
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected through use of Fridericia's formula
SAD	single ascending dose
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	standard of care
SpO_2	*peripheral capillary oxygen saturation*
sST2	soluble form of ST2
UC	ulcerative colitis
ULN	upper limit of normal
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON COVID-19 PNEUMONIA

Coronaviruses (CoVs) are positive-stranded RNA viruses that are important human and animal pathogens and usually cause mild to moderate respiratory illnesses such as the common cold. In the past two decades, Middle East respiratory syndrome coronavirus (MERSCoV) and severe acute respiratory syndrome coronavirus (SARS-CoV-) emerged from animal reservoirs to cause more serious respiratory illness leading to death. A third novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in China at the end of 2019, causing the coronavirus disease 2019 (COVID-19). The COVID-19 outbreak was categorized as a pandemic by the WHO on March 11, 2020, and globally more than 4 million confirmed cases have been reported (WHO 2020a).

The majority of patients with COVID-19 present with symptoms ranging from asymptomatic transmission via respiratory droplets to mild disease with fever, cough, and shortness of breath that resolve with supportive care. However, approximately 20% of patients develop severe disease requiring hospitalization, and up to 10% of the total infected population require intensive care unit (ICU) admission. The dominant finding in patients critically ill with COVID-19 is interstitial pneumonia, which progresses to acute respiratory distress syndrome (ARDS) and hypoxemic respiratory failure. Complications of COVID-19 include acute kidney injury, elevated liver enzymes, pericarditis, multiple organ failure (MOF), and death (WHO 2020b), with in-hospital mortality rates of approximately 25% (Cao et al. 2020; Zhou et al. 2020). Risk factors for progression to severe COVID-19 include advanced age, cardiovascular disease, diabetes mellitus, chronic lung disease, and chronic kidney disease (Liang et al. 2020; Wu et al. 2020; Zhou et al. 2020).

ARDS, which is characterized by increased epithelial and endothelial permeability leading to alveolar edema, has been observed in 16%–42% of patients with severe COVID-19 (Guan et al. 2020; Huang et al. 2020; Wu et al. 2020; Zhou et al. 2020). Typical imaging findings are consistent with viral pneumonia, showing rapidly worsening bilateral pulmonary opacities and ground glass opacification with or without consolidation (Bhatraju et al. 2020). Early phase ARDS with epithelial desquamation, hyaline membrane formation, and edema was seen in lung pathology in a patient who died of COVID-19 (Xu et al. 2020). Hyperinflammatory responses, including increased pro-inflammatory cytokines (interleukin [IL]-6) and other inflammatory markers (ferritin and D-dimer) are associated with increased mortality in patients with COVID-19 (Zhou et al. 2020). Approximately 10% of patients with COVID-19 develop secondary bacterial infections, and 50% of those patients have died (Zhou et al. 2020).

COVID-19 is a serious public health risk. To date, limited anti-viral and host-directed therapies have been shown to be effective for treating COVID-19 and there is no

vaccine. There is a significant unmet medical need for novel therapies to treat the complications of COVID-19 pneumonia.

1.2 BACKGROUND ON MSTT1041A (ANTI-ST2)

MSTT1041A (RO7187807, also known as astegolimab) is a fully human, IgG2 monoclonal antibody that binds with high affinity to ST2 (IL-33 receptor, also referred to as IL-1 receptor-like 1 [IL1RL1]), thereby blocking the signaling of IL-33, an inflammatory cytokine of the IL-1 family and member of the "alarmin" class of molecules. MSTT1041A has subnanomolar affinity and potency, is active in whole blood, and lacks agonistic activity.

1.2.1 Background on Interleukin-33/ST2

IL-33 is released from epithelial cells in response to allergens, irritants, and infection in the various tissues and organs, including the lung and skin (Cevikbas and Steinhoff 2012; Lambrecht and Hammad 2015). High levels of IL-33 are found in stromal cells, particularly at barrier surfaces such as the lung and gastrointestinal (GI) tract. Within the lung, IL-33 is detected in multiple cell types, including epithelial cells, endothelial cells, and fibroblasts (Liew et al. 2016). IL-33 bioavailability is tightly regulated, and under homeostatic conditions, this protein is sequestered in the nuclei of these cells. Cellular damage, caused by injury, mechanical stress, or death, leads to the release of bioactive IL-33 into circulation, where it initiates and propagates innate and adaptive immune responses. Environmental triggers that promote IL-33 release include allergens, irritants, and viral and bacterial infections. The receptor for IL-33, ST2, is expressed on multiple cell types implicated in pulmonary inflammation and disease, including mast cells, eosinophils, basophils, innate lymphoid cells, T lymphocytes, macrophages, and endothelial cells. Akin to other IL-1 cytokines, IL-33 activates cells by binding to its cognate receptor, which allows for association with interleukin-1 receptor accessory protein (IL-1RAcP), the shared receptor for this family. The formation of the IL-33–ST2–IL-1RAcP receptor complex in turn activates the MyD88 signalosome to induce the transcription of genes with pro-inflammatory functions.

Given the diverse nature of signals that lead to IL-33 release and the wide range of target cells, IL-33 is implicated in a number of pathological pathways. IL-33 release can trigger acute exacerbations and/or disease progression in asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, ARDS, and atopic dermatitis. IL-33 activity is elevated following viral infections, and inhibition of this pathway reduces virus-induced exacerbations in rodent models of asthma and COPD (Werder et al. 2018; Ravanetti et al. 2019). ST2- or IL-33–deficient mice exposed to cigarette smoke have decreased inflammatory responses in response to subsequent respiratory viral infections without compromising anti-viral host defense (Kearly et al. 2015). The absence of the IL-33 pathway significantly reduced viral induced leukocyte migration into the lung, inflammatory cytokine expression, and subsequent pulmonary pathology. Furthermore, IL-33 is elevated in the serum of patients with ARDS and pulmonary etiology (Lin et al.

2016). Blockade of IL-33 activity, either in preventative or therapeutic treatment regimens, has demonstrated efficacy in reducing inflammation and ameliorating disease preclinical models of ARDS (Yin et al. 2011; Martin-Gonzalez et al. 2013; Lin et al. 2016; Liang et al. 2018). Inhibition of this pathway effectively reduced induction of pro-inflammatory cytokines, including IL-6 and tumor necrosis factor-α, inflammatory cell infiltrates, and protected the lung tissues from lipopolysaccharide (LPS) or bleomycin-induced injury. For these reasons, anti-ST2 is hypothesized to confer clinical benefit to patients with COVID-19 pneumonia by limiting excessive inflammatory sequelae while preserving anti-viral responses.

1.2.2 Summary of Nonclinical Studies

The toxicology program was designed to support IV and SC administration of MSTT1041A in clinical studies. MSTT1041A has been shown to have a favorable overall nonclinical safety profile. In 28-day and 6-month repeat–dose toxicity studies, no adverse effects were observed in cynomolgus monkeys following biweekly IV or SC administration at doses up to 300 mg/kg (the highest dose tested). There were no adverse findings at the injection sites as evidenced by macroscopic and microscopic analysis following SC administration at doses up to 300 mg/kg. In an ex vivo human tissue cross reactivity study, biotin-labeled MSTT1041A staining was not observed in any human tissues evaluated by immunohistochemistry.

Refer to the RO7187807 Investigator's Brochure for details on nonclinical studies.

1.2.3 Summary of Clinical Studies

MSTT1041A has been investigated in four completed studies, with three Phase I studies (single ascending dose [SAD] AMG Study 20110235, multiple ascending dose [MAD] AMG Study 20110236, and single-dose pharmacokinetic (PK) AMG Study 2011236 in subjects of Japanese heritage, and a Phase IIb study in patients with asthma (GB39242 [ZENYATTA]). Additionally, a Phase II study in patients with atopic dermatitis (Study GS40965 [ZARNIE]) and an investigator-initiated study in patients with COPD (Study GB40568) are ongoing.

The pharmacokinetics of MSTT1041A were characterized after single and multiple (SC and IV) doses in two studies (AMG Studies 20110235 and 20110236). [redacted] Overall MSTT1041A was well tolerated in each of these healthy volunteer studies. There were no serious adverse events, deaths, or adverse events that led to treatment or study discontinuation.

In the Phase IIb Study GB39242 in patients with severe asthma, the primary endpoint (reduction over placebo in incidence of asthma exacerbations at Week 52) was met for the MSTT1041A 490-mg dose. For the secondary efficacy endpoints, a nominally

significant benefit over placebo in time to first asthma exacerbation were seen with the highest MSTT1041A dose (490 mg). A total of approximately 451 patients and 109 healthy subjects have been exposed to at least one dose of MSTT1041A. MSTT1041A has been generally well tolerated with adverse events being mostly non-serious and of mild to moderate intensity. Adverse events rates were generally similar between the three treatment arms and the placebo arm. Adverse events leading to withdrawal have generally occurred at a rate similar to what would be expected for clinical trials in the studies' respective indications. [redacted] None of the incidences of potential MACE were considered related to the study drug. No clinically meaningful changes were observed in laboratory parameters, vital signs, or ECG results in the MSTT1041A treatment groups. To date, there are no identified risks associated with MSTT1041A.

Refer to the RO7187807 Investigator's Brochure for details on clinical studies.

1.3 BACKGROUND ON UTTR1147A (IL-22FC)

UTTR1147A (RO7021610) is a human IL-22 fusion protein in which the cytokine IL-22 is linked with the fragment crystallizable (Fc) portion of IgG4 to improve the cytokine's PK characteristics. The Fc portion of the fusion protein incorporates a mutation that minimizes the potential for Fc effector function.

1.3.1 Background on Interleukin-22

IL-22 belongs to the IL-10 cytokine family (Ouyang et al. 2019) and binds specifically to the IL-22 receptor (IL-22R) heterodimer. IL-22R is expressed on a variety of epithelial and stromal tissues, including lung ciliated epithelial and endothelial cells, GI tract epithelium, epidermal keratinocytes, liver hepatocytes, pancreatic acinar epithelium, and renal tubular epithelium. IL-22 binding results in activation of receptor-associated Jak1/Tyk2 kinases and the transcription factor STAT3 (Dudakov et al, 2015). IL-22 modulates innate immunity through multiple different regenerative and protective mechanisms in epithelial tissues, including the GI tract mucosal epithelium, epidermal keratinocytes, and lung epithelial cells (Whittington et al. 2004; Wolk et al. 2004; Aujla et al. 2008; Sugimoto et al. 2008; Zheng et al. 2008; Hoegl et al. 2011; Pociask et al. 2013). Nonclinical studies have demonstrated that IL-22 promotes endothelial and epithelial proliferation, barrier function, and anti-microbial host defense (Ouyang and Valdez 2008). Specifically, IL-22 signaling has been shown to increase lung epithelial cell proliferation and wound healing (Barthelemy et al. 2017; Nguyen et al. 2020), to decrease apoptosis of epithelial and endothelial cells in acute lung injury models (Ren et al. 2017; Wu et al. 2017), and to increase expression of tight junction proteins (Barthelemy et al. 2017; Abood et al. 2019; Hebert et al. 2020). IL-22 directly increases endothelial barrier function by stabilizing intracellular junction proteins, reducing endothelial permeability following LPS, reducing apoptosis, and increasing proliferation (He et al. 2016; Hu et al. 2018; Wu et al. 2018). IL-22 also plays a role in protecting and

repairing damage to lung epithelial tissue caused by high-pressure ventilation-induced damage (Hoegl et al. 2011) and angiotensin II-induced acute lung injury and edema (Wu et al. 2017). IL-22 decreases levels of cytokines (IL-6, interferon-γ, IL-17A) and chemokines (MCP-1, MIP-1α/β) in bronchoalveolar lavage, which correlates with decreased numbers of lung neutrophils and lymphocytes and reduced alveolitis in viral infection models (Abood et al. 2019; Hebert et al. 2020). Moreover, treatment with post-viral murine IL-22 immunoglobulin fusion protein (IL-22Fc), a fusion protein with prolonged half-life in vivo, promotes repair of the lung epithelial barrier, reduces inflammation, and mitigates the pathological consequences of bacterial superinfections (Barthelemy et al. 2018).

In acute lung injury murine models, IL-22 was shown to be protective against multiple viral and bacterial respiratory pathogens and enhanced recovery (Ivanov et al. 2013; Pociask et al. 2013; Trevejo-Nunez et al. 2016; Barthelemy et al. 2018; Abood et al. 2019; Hebert et al. 2020). IL-22 signaling increases expression of anti-microbial proteins, including β-defensin and Reg3γ (the murine homolog of the human *Reg3a* gene) (Pichavant et al. 2015; Ito et al. 2017). In a murine model of bacterial superinfection post-influenza, treatment with murine IL-22Fc following viral infection increased pulmonary barrier function and decreased inflammation and systemic dissemination of bacteria (Barthelemy et al. 2018). Pretreatment of small intestinal epithelial cells with porcine IL-22 prior to infection with swine enteric alpha CoVs showed dose-dependent inhibition of viral infection (Xue et al. 2017). IL-22 treatment of lung epithelial cells induces anti-microbial protein production such as Reg3γ (Pichavant et al. 2015; Ito et al. 2017) and protects against influenza virus-bacterial co-infection (Ivanov et al. 2013; Abood et al. 2019) and coronavirus infection (Xue et al. 2017).

IL-22 induces expression of mucin genes and activation of goblet cells, increasing mucus production in the gut, which in turn may contribute to decreased intestinal inflammation (Sugimoto et al. 2008, Turner et al. 2013). This raises the question whether goblet cells also promote increased mucus production in the lung, which may not be beneficial. However, internal and external evidence to date suggests that IL-22 does not promote increased mucin production in the airways. Different types of mucins are expressed in GI and respiratory mucosa. Lung secretory cells secrete MUC5B and MUC5AC, which are important for mucociliary clearance of pathogens. Studies conducted by the Sponsor showed that IL-22Fc treatment of primary human bronchial epithelial cells grown at air-liquid interface for 24 hours did not significantly increase expression of mucin or secretory cell genes nor alter the ratio of the *MUC5AC:MUC5B* gene expression, generally considered a measure of pathogenic mucus. Similar results were seen in the lungs of mice administered murine IL-22Fc intranasally or intravenously after 24 hours. In addition, in mice were exposed to cigarette smoke for 8 weeks and then treated with IL-22Fc for a week prior to infection with influenza and a week post-infection, at which time no lung goblet cell hyperplasia was seen by periodic acid-Schiff/Alcian Blue histology staining (unpublished data). Moreover, neither

increased mucus nor lung goblet cell hyperplasia have been reported following IL-22 treatment in respiratory infection studies (Barthelemy et al. 2018).

Although IL-22 levels in COVID-19 have not yet been studied, IL-22 levels were shown to be reduced in the bronchoalveolar lavage of patients with ARDS compared with post-operative patients on mechanical ventilation without lung injury (Whittington et al. 2004).

1.3.2 Summary of Nonclinical Studies

The toxicology program in rats, cynomolgus monkeys, and minipigs identified the potential clinical safety risks of UTTR1147A. [redacted] The nonclinical PK profile observed for UTTR1147A in rats, cynomolgus monkeys, and minipigs is consistent with that expected for a cytokine fusion protein with a humanized IgG4 Fc, demonstrating that fusion of recombinant IL-22 to an antibody Fc fragment extends the half-life of IL-22, leading to improved IL-22 exposure (Lee et al. 2018).

[redacted]

1.3.3 Summary of Clinical Studies

In a Phase Ia, first-in-human, placebo-controlled SAD study in 68 healthy volunteers (Study GA29468), UTTR1147A demonstrated linear and dose-proportional pharmacokinetics and was adequately tolerated following IV doses of up to 90 μg/kg (Rothenberg et al. 2019). The most common adverse events were on-target dermatologic events that were monitorable, manageable with topical emollients, and reversible. Single IV doses of UTTR1147A at 30 μg/kg and above produced dose-related dermatologic effects such as dry scaly lips, dry skin, erythema, pruritus, and skin discomfort, all of which appeared within the first month of dosing and resolved within 1 week to 3 months after onset. No clinically significant changes or findings were noted from vital sign measurements, 12-lead ECGs, or body weight measurements. All other abnormal clinical laboratory results reported as treatment-emergent adverse events were assessed by the investigator as mild or moderate in intensity and not related to UTTR1147A.

[redacted]

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Up to approximately 20% of patients with COVID-19 have severe disease, with 25% of those patients requiring ICU admission. Patients with severe COVID-19 develop an interstitial pneumonia that progresses to ARDS and hypoxic respiratory failure requiring respiratory support, MOF, and death (Guan et al. 2020, Zhou et al. 2020, Wu et al. 2020, Ma et al. 2020, WHO 2020b). To date there are no vaccines, anti-viral therapies, or host-directed therapies shown in randomized controlled trials to be effective in preventing or reducing the risk of progression of COVID-19. There remains a significant unmet need to develop novel therapies to treat patients with severe COVID-19 pneumonia.

1.4.1 MSTT1041A (Anti-ST2)

MSTT1041A, an anti-ST2 monoclonal antibody that acts as a pure competitive antagonist to block IL-33 signaling, is hypothesized to have the potential to treat severe COVID-19 pneumonia by reducing the maladaptive hyper-inflammatory responses to the virus, reducing disease progression to ARDS and promoting convalescence, without inhibiting the development of protective adaptive immunity and viral clearance (Kearley

et al. 2015). Nonclinical and clinical studies have demonstrated that MSTT1041A has a well-tolerated safety profile and potential for efficacy to treat severe COVID-19 pneumonia, supporting further clinical development. To date, there are no identified risks associated with MSTT1041A. Although not seen in the four completed and two ongoing clinical trials to date, as with all protein therapies, there is the possibility that administration of MSTT1041A may lead to the development of anti-MSTT1041A antibodies, which could lead to adverse events and/or decreased exposure. [redacted] Like all monoclonal antibodies, MSTT1041A carries a potential risk of hypersensitivity reactions and anaphylaxis/hypersensitivity-like reactions. [redacted]

The mechanism of action of MSTT1041A suggests the possibility of decreased Th2 response to certain infections, particularly helminthic infections. [redacted]

Finally, in mice models of cardiovascular disease, a protective role for IL-33/ST2 has been described, and $ST2^{-/-}$ mice had more left ventricular hypertrophy, more fibrosis, and impaired survival relative to their wild-type littermates in an experimentally induced acute left-ventricular pressure overload model. However, the translatability of those findings to humans remains unknown, [redacted]

Combined, nonclinical and clinical studies have demonstrated that MSTT1041A has a well-tolerated safety profile and strong theoretical rationale supporting its potential benefit in COVID-19 pneumonia, supporting further clinical development in this indication. The potential risks for MSTT1041A will be mitigated by stringent pre-enrollment screening for patients with evidence of clinically apparent or insipient cardiovascular disease, including cardiac enzyme elevations that are caused by COVID-19, which have been described in 8%–12% of the hospitalized patients with

severe COVID-19 pneumonia (Lippi and Plebani 2020). In addition, cardiac enzymes will be monitored closely while patients are hospitalized, and cardiovascular complications will be subject to expedited reporting requirements.

1.4.2 UTTR1147A (IL-22Fc)

Based on non-clinical studies, UTTR1147A, an IL-22 fusion protein, has the potential to treat severe COVID-19 pneumonia by increasing epithelial and endothelial integrity, increasing epithelial regeneration, and preventing secondary bacterial infections (Ivanov et al. 2013; Pociask et al. 2013; Trevejo-Nunez et al. 2016; Barthelemy et al. 2018; Abood et al. 2019; Hebert et al. 2020).

Clinical studies have demonstrated that UTTR1147A has an adequately tolerated safety profile. At the dose proposed in this study (90μg/kg IV Q2W for two doses), the most common adverse events associated with UTTR1147A were dermatologic effects, including pruritus, dry lips, erythema, and skin discomfort. Consequently, dermatologic reactions are considered an identified risk of UTTR1147A. These are expected on-target effects and have been non-serious and manageable with topical emollients and moisturizers, monitorable, and reversible.

[redacted] However, the overall incidence of treatment-emergent ADAs in the Phase Ia study was low and neutralizing antibodies have not been detected to date. Moreover, in patients with non-infected diabetic foot ulcers who received multiple doses of UTTR1147A subcutaneously, there was no increased infection rate between treated and placebo patients and no opportunistic or fungal infections were reported.

Finally, based on the ability to stimulate mucins in the GI tract, UTTR1147A treatment may induce mucus hypersecretion in the lung. To date, lung goblet cell hyperplasia has not been reported following IL-22 treatment in studies of the respiratory tract (Barthelemy et al. 2018) [redacted]

[redacted] Development of UTTR1147A as a therapeutic for

patients with severe COVID-19 pneumonia is further supported by [redacted] The identified and potential risks of UTTR1147A will be mitigated by excluding patients with a history of active malignancy, by restricting the duration of UTTR1147A exposure (all patients will receive one dose and only patients who are higher risk due to remaining hospitalized with a requirement for oxygen support will receive a second dose of study drug).

Furthermore, the study will include safety monitoring, including a Data Monitoring Committee comprised of external experts in COVID-19 pneumonia that will frequently monitor adverse events including dermatologic reactions, use of supplemental oxygen, ventilation use, and death between the treatment and placebo arms. The DMC can recommend modifications to the study, including the need for additional safety monitoring and measures, dose modification, discontinuation of a treatment arm, and halting or stopping the trial if the risk/benefit profile is no longer favorable.

In summary, there are currently no drugs that have demonstrated efficacy in patients with COVID-19 pneumonia in adequate and well-controlled studies. Given the scientific rationale provided above, UTTR1147A in combination with standard of care (SOC) treatment has the potential to improve morbidity and mortality in hospitalized patients with severe COVID-19 pneumonia. Safety data from randomized controlled trials collected for UTTR1147A to date demonstrate that the drug is well tolerated within the described exposure limits. The dermatologic events that have been observed can be closely monitored in a hospital setting. Given that severe COVID-19 pneumonia is considered an acute life-threatening event without proven therapy, the potential benefit of UTTR1147A counterbalances the risks associated with 1 to 2 doses of UTTR1147A, thereby justifying the need for a randomized, placebo-controlled study.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, for the treatment of severe COVID-19 pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoint:

- *Time to recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first)*

The ordinal scale categories are as follows:

1. Discharged (or “ready for discharge” as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen)
2. Non-ICU hospital ward (or “ready for hospital ward”) not requiring supplemental oxygen
3. Non-ICU hospital ward (or “ready for hospital ward”) requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to hospital discharge or “ready for discharge” (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen)
- Duration of supplemental oxygen
- Proportion of patients alive and free of respiratory failure (requiring non-invasive ventilation, high-flow oxygen, mechanical ventilation, or ECMO) at Day 28
- *Clinical status assessed using a 7-category ordinal scale at Days 14 and 28*
- Incidence of *invasive* mechanical ventilation *or* ECMO
- Ventilator-free days to Day 28
- Incidence of ICU stay
- Duration of ICU stay
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal of care (whichever occurs first). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one category worsening on the ordinal scale, withdrawal, or death.
- Mortality rate at Days 14 *and* 28
- Time to clinical improvement, defined as a National Early Warning Score 2 (NEWS2) of ≤2 maintained for 24 hours

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoints:

- Incidence of vasopressor use
- Duration of vasopressor use
- Incidence of starting hemodialysis
- SARS-CoV-2 viral load on Day 15 and Day 28
- Proportion of patients with secondary bacterial infections

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs, targeted clinical laboratory test results, and targeted ECG parameters

2.3 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to characterize the MSTT1041A and UTTR1147A PK profiles on the basis of the following endpoints:

- Serum concentration of MSTT1041A at specified timepoints
- Serum concentration of UTTR1147A at specified timepoints

The exploratory PK objectives for this study are as follows:

- To evaluate potential relationships between drug exposure and the efficacy and safety of MSTT1041A and UTTR1147A on the basis of the following endpoints:
  - Relationship between serum concentration or PK parameters for MSTT1041A and efficacy and safety endpoints
  - Relationship between serum concentration or PK parameters for UTTR1147A and efficacy and safety endpoints
- To evaluate potential relationships between selected covariates and exposure to MSTT1041A or UTTR1147A on the basis of the following endpoint:
  - Relationship between selected covariates and serum concentration or PK parameters for MSTT1041A
  - Relationship between selected covariates and serum concentration or PK parameters for UTTR1147A

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to UTTR1147A and MSTT1041A, individually, on the basis of the following endpoint:

- Prevalence of ADAs at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.5 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to MSTT1041A or UTTR1147A (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of MSTT1041A or UTTR1147A activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in blood and other fluid (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, in patients hospitalized with severe COVID-19 pneumonia. Approximately *390* adult hospitalized patients who have been diagnosed with COVID-19 pneumonia (defined by a positive polymerase chain reaction [PCR] and evidence of pneumonia by chest X-ray or computed tomography [CT] scan) are expected to be enrolled.

Patients will be randomized after screening at a 2:2:1:1 ratio to receive blinded treatment of either MSTT1041A, UTTR1147A, or their matching placebos. Study treatment will be given in combination with SOC as defined by the site, including, but not limited to, anti-virals, host-directed therapies, convalescent plasma, low-dose corticosteroids, and supportive care. Randomization will be stratified by need for invasive mechanical ventilation (yes vs. no) and region. Enrollment of patients with a need for invasive mechanical ventilation will be capped at approximately 25% of the overall study population.

Patients assigned to the MSTT1041A or UTTR1147A arm will receive one infusion of MSTT1041A 700 mg or UTTR1147A 90 μg/kg on Day 1, respectively, and patients

assigned to the placebo arm will receive one infusion of matching placebo (see Section 4.3). A second dose of MSTT1041A 350 mg, UTTR1147A 90 μg/kg, or matching placebo will be given on Day 15 if the patient still remains hospitalized with a requirement for supplemental oxygen therapy. For patients who are being discharged or transferred to a different care facility prior to Day 60, a discharge visit should be performed. Subsequently, patients will be followed up remotely (via phone or video visit), and should return to the clinic for Day 28 and a study completion visit (Day 60) or early discontinuation visit, if possible. Depending on patient findings during the phone/video visit, patients may need to be seen in person within 48 hours at the discretion of the investigator.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. The investigator will record the reasons for screen failure in the screening log (see Section 4.5.1).

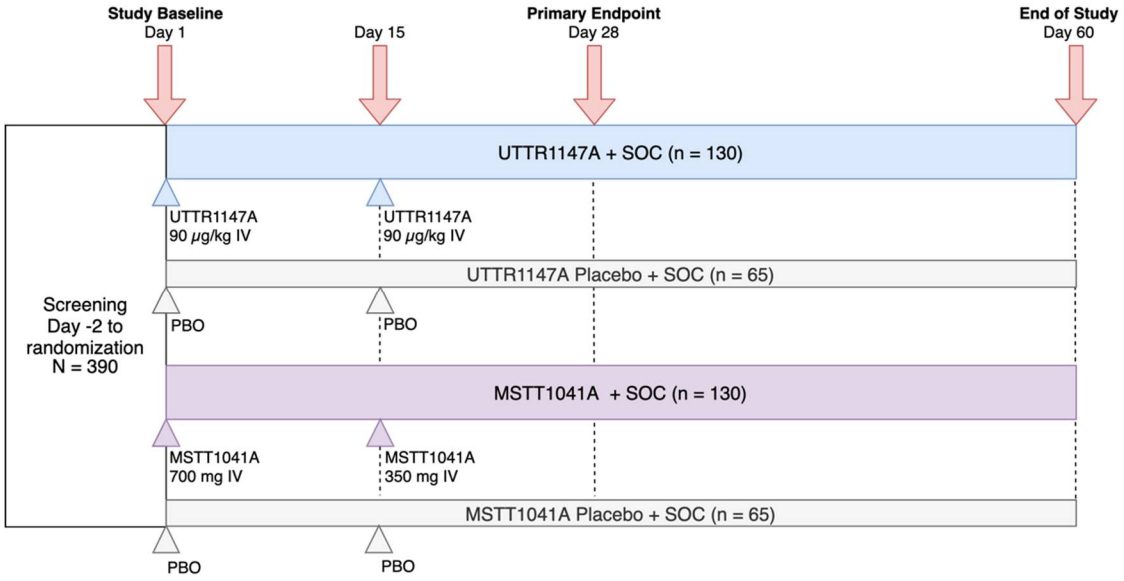
Patients who are eligible to be re-screened will be required to repeat assessments as follows:

- Within the 2-day screening window: Repeat only the assessments that triggered screen failure.
- Outside the 2-day screening window: Repeat all assessments. The consent process does not need to be repeated if re-screening is completed within 7 days after completion of initial informed consent.

Note: Historic standard of care test results are acceptable for CT scan or chest X-ray if performed within 7 days prior to randomization, and for influenza and SARS-CoV-2 virology if performed within 14 days of randomization (see Appendix 1).

Figure 1 presents an overview of the study design. A schedule of activities for patients in the hospital is provided in Appendix 1. A schedule of activities for patients who will be discharged from the hospital *or transferred to a different care facility* prior to Day 60 is provided in Appendix 2.

Figure 1 Study Schema



PBO = placebo; SOC = standard of care.

Screening period will be up to 2 days.

A second dose of study drug will be given on Day 15 if the patient remains hospitalized with a requirement for supplemental oxygen therapy, unless the patient meets the study drug discontinuation criteria (see Section 4.6.1).

3.1.2 Data Monitoring Committee

A DMC will review unblinded safety and efficacy data to assess whether treatment with MSTT1041A or UTTR1147A is associated with toxicity or worsening disease. Members of the DMC will include representatives from Clinical Science and Drug Safety who are not directly involved in the study and representatives from Biostatistics and Statistical Programming and Analysis and may invite representatives from other functional areas on an ad-hoc basis when additional expertise is required (e.g., Clinical Pharmacology, Research). The DMC will also include at least two external experts in the field, and additional experts may be added during the course of the study.

The DMC will review cumulative safety data through at least Day 14 after the first 30 patients have been enrolled or after the first 30 days from the first patient enrolled (whichever occurs first). Subsequently, the DMC will review cumulative safety and efficacy data after each additional 75 patients have been enrolled or 3 months (whichever occurs first); for example, once *approximately* 75, 150, 225*, and 300* patients have enrolled. Ad hoc meetings may be held at the request of the DMC or Sponsor at any time to address potential safety concerns. The DMC will have access to all available data at each review to perform an overall benefit/risk assessment. Data to be reviewed will include demographics, concomitant medications, study drug administration, ECGs, laboratory data, adverse events, serious adverse events, adverse events of special interest, and deaths.

At the time of each review, the DMC can make one of the following recommendations: the trial continues as planned, additional analyses need to be performed, enrollment is held pending further safety evaluations or other study modifications, the MSTT1041A or UTTR1147A arm of the trial is stopped, or the trial is stopped. Final decisions will rest with the Sponsor's study team.

Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Board (IRB) or Ethics Committee (EC).

A detailed description of the procedures, data flow, and meeting schedule will be provided in the DMC Charter.

3.1.3 Safety Monitoring Committee

An SMC consisting of internal team members will review blinded safety and efficacy data to assess whether treatment with MSTT1041A or UTTR1147A is associated with toxicity or worsening disease. The SMC will meet to review safety and efficacy data at least as frequently as the DMC. The SMC may also meet to assess the significance of other adverse events or safety findings at any time following a request from either an investigator or the Sponsor.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 10 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for MSTT1041A (Anti-ST2) Dose and Schedule

For the MSTT1041A arm, 700 mg IV will be administered for the first dose. For patients who remain in hospital and on oxygen 2 weeks after the first dose (Day 15), a second dose of 350 mg IV will be administered.

The proposed dose is based on clinical experience in healthy subjects (safety, pharmacokinetics, and pharmacodynamics) observed in the SAD study (AMG Study 20110235) and in the MAD study (AMG Study 20110236), as well as in the Phase IIb study GB39242 in patients with severe asthma (safety, efficacy, pharmacokinetics, and pharmacodynamics). In Study 20110235, at least 3 subjects (per SC cohort) or at least 6 subjects (per IV cohort) received SC doses of MSTT1041A up to 420 mg or IV doses

of MSTT1041A up to 700 mg. In Study 20110236, at least 6 subjects per cohort received multiple SC or IV doses of MSTT1041A, Q2W or every 4 weeks (Q4W), up to 700 mg IV.

A small number of patients with mild asthma (n = 6) or chronic rhinosinusitis with nasal polyps (CRSwNP; n = 1) were also enrolled in Phase I studies. MSTT1041A was well tolerated in Phase I studies, with no significant safety issues identified, including at the highest doses (700 mg IV of MSTT1041A administered as a single dose or Q4W for three doses).

In Study GB39242, 502 patients with severe asthma were randomized in a 1:1:1:1 ratio to receive 1 of 3 doses of MSTT1041A (70 mg, 210 mg, or 490 mg SC) or placebo Q4W for 52 weeks, for a total of 13 doses. In this study, the 490 mg Q4W dose showed a significant reduction over placebo in incidence of asthma exacerbations and met the primary endpoint. MSTT1041A was well tolerated. Rates of adverse events were generally similar between the three treatment arms and the placebo arm, and were mostly mild or moderate in intensity.

The available evidence suggests that circulating levels of the secreted soluble form of ST2 (sST2) are significantly increased in patients with ARDS compared with healthy subjects or patients with severe asthma. A median concentration of sST2 of 534 ng/mL has been reported in patients with ARDS (Alladina et al. 2016),

As sST2 acts as a decoy to bind and inhibit released IL-33, higher sST2 concentrations in patients with ARDS suggest that higher doses of MSTT1041A may be required to achieve efficacy in ARDS compared with severe asthma.

[redacted]

3.3.2 Rationale for UTTR1147A (IL-22Fc) Dose and Schedule

For the UTTR1147A arm, up to two doses of 90 μg/kg Q2W IV will be administered on Day 1 and Day 15. The proposed dose is supported by the safety, PK, and PD results from a completed Phase Ia SAD study in healthy volunteers (Study GA29468), a completed Phase Ib MAD study in healthy volunteers and patients with IBD (Study GA29469), and an ongoing double-blinded, placebo-controlled 5-arm Phase II study in patients with moderate to severe UC (Study GA39925). In the completed Phase I studies, 73 subjects have received at least one IV dose of UTTR1147A. [redacted]

In the Phase Ia SAD study, the MTD in 26 healthy volunteers was 90 μg/kg IV due to serious on-target effects of IL-22 causing non-serious dermatologic events, including dry skin, dry lips, pruritus, moderate erythema, and skin hyperesthesia, which are

manageable, monitorable, and reversible. [redacted]

Serum PD biomarkers REG3A and CRP demonstrated dose-dependent pharmacological activity of UTTR1147A, implying increased target engagement at 90 mg/kg compared with 30 μg/kg and 60 μg/kg in the Phase Ia SAD and Phase Ib MAD, respectively. [redacted]

[redacted] The observation of a different PK profile in patients with UC as compared with healthy volunteers is consistent with studies with infliximab and other biologics (Brandse et al. 2015; Fausel and Afzali 2015; Rosen et al. 2015) where patients with GI damage had faster drug clearance than in healthy volunteers.

[redacted], patients with severe COVID-19 pneumonia are predicted to have decreased UTTR1147A exposure as compared to healthy volunteers due to alveolar tissue damage and pulmonary vascular leakage leading to faster clearance.

In previous studies, patients with infections have shown faster antibody clearance than healthy volunteers. In a Phase II trial, patients hospitalized with severe influenza A treated with MHAA4549A, a monoclonal antibody against influenza A, showed faster clearance than healthy volunteers (Lim et al, submitted). Similarly, faster clearance of DSTA4637S, an antibody antibiotic conjugate, was observed in hospitalized patients with *Staphylococcus aureus* bacteremia than in healthy volunteers (Peck et al., data not published).

Based on the tolerability profile in patients with UC to date and a potential lower PK exposure in the target population, 90 μg/kg Q2W was chosen as the dose regimen with the highest benefit–risk ratio for patients with severe COVID-19 pneumonia. In patients randomized to UTTR1147A, 90 μg/kg IV will be administered on Day 1. For patients who remain hospitalized on supplemental oxygen on Day 15, a second dose at 90 μg/kg IV will be given. The first dose of 90 μg/kg is targeted to maximize the drug exposure in patients with severe COVID-19 pneumonia. The second dose is targeting the epithelial barrier repair and protective mechanisms to help patients with ongoing lung damage and pulmonary dysfunction.

3.3.3 Rationale for Patient Population

Approximately 15%–20% of patients with COVID-19 pneumonia have severe disease requiring hospitalization and supplemental oxygen and 5% of patients with COVID-19 pneumonia will be admitted to the ICU (WHO 2020b). Risk factors for progression to severe COVID-19 pneumonia are common and include advanced age, cardiovascular disease, diabetes mellitus, chronic lung disease, and chronic kidney disease (Liang et al. 2020; Wu et al. 2020; Zhou et al. 2020). In a study of 138 hospitalized patients with COVID-19 pneumonia in China, 26% of patients required transfer to the ICU and 4.3% of patients died (Wang et al. 2020). In a second study of 1099 Chinese patients with

COVID-19 pneumonia, 5% of patients were admitted to the ICU, 2.3% of patients underwent invasive mechanical ventilation, and 1.4% of patients died (Guan et al. 2020). Patients with severe COVID-19 pneumonia requiring hospitalization and supplemental oxygen have significant morbidity and mortality and despite multiple experimental therapies in wide use, there are no treatments with proven efficacy to date. This study will enroll patients hospitalized with severe COVID-19 pneumonia requiring supplemental oxygen at high risk of developing ARDS, hypoxic respiratory failure and death.

3.3.4 Rationale for Control Group

The study will compare the efficacy and safety of MSTT1041A or UTTR1147A IV compared with matching placebos in combination with SOC for the treatment of patients with severe COVID-19 pneumonia. In this study, the SOC regimen will be based on institutional guidelines for treatment of severe COVID-19 pneumonia. Due to the lack of proven efficacious treatments for COVID-19, SOC treatment generally includes supportive care. Experimental therapies include anti-viral agents (e.g., hydroxychloroquine, ritonavir/lopinavir, remdesivir) and host-directed therapies (i.e., anti–IL-6, low-dose corticosteroids). The treatment of all patients with SOC therapy ensures that all patients will receive therapy for COVID-19. This control treatment is based on consideration of safety, ethics, and efficacy for treatment of severe COVID-19 pneumonia.

3.3.5 Rationale for Biomarker Assessments

PD biomarkers will be assessed to demonstrate evidence of biologic activity of MSTT1041A and of UTTR1147A in patients with severe COVID-19 pneumonia, to characterize PK/PD relationships, and to support selection of a recommended dose and dosing regimen selection for future studies. The exploratory biomarkers will be assessed to identify those patients who are most likely to respond to MSTT1041A or UTTR1147A, to characterize MSTT1041A and UTTR1147A mechanisms of action, to provide further evidence of MSTT1041A and UTTR1147A efficacy, and to understand progression of COVID-19. The relationship between biomarkers and safety, immunogenicity, and other biomarker endpoints may also be explored.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 390 hospitalized patients with severe COVID-19 pneumonia will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Documented informed consent as described in Section 4.5.1
- Age $\geq$ 18 years at time of signing Informed Consent Form

- Ability to comply with the study protocol
- Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- For sites at an altitude $\leq$5000 feet: peripheral capillary oxygen saturation (SpO_2) $\leq$ 93% or partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) $\leq$300 mmHg or requirement for supplemental oxygen to maintain $SpO_2 > 93\%$
- For sites at an altitude $>$5000 feet: requirement for supplemental oxygen to maintain SpO_2 at an acceptable level per local standard of care
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 95 days after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 95 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug

exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 95 days after the final dose of study drug

  Women of childbearing potential must have a negative pregnancy test at screening.
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Participating in another clinical drug trial
- Treatment with investigational therapy (other than for COVID-19) within 5 half-lives or 30 days (whichever is longer) prior to initiation of study drug
- Use of Janus kinase (JAK) inhibitor within 30 days or 5 drug elimination half-lives (whichever is longer) prior to screening
- Have received high-dose systemic corticosteroids (≥ 1 mg/kg/day methylprednisolone or equivalent) within 72 hours prior to Day 1
- Known HIV infection with CD4 < 200 cells/μL or $< 14\%$ of all lymphocytes
- ALT or AST $> 10 \times$ upper limit of normal (ULN) detected at screening
- History of anaplastic large-cell lymphoma or mantle-cell lymphoma
- History of cancer within the previous 5 years unless it has been adequately treated and considered cured or remission-free in the investigator's judgment
- Clinical evidence of active or unstable cardiovascular disease (e.g., acute myocardial ischemia or decompensated heart failure) as assessed by the investigator
- Elevated cardiac troponin indicative of a recent cardiac event or myocarditis/pericarditis, as defined below:
  1. If high-sensitivity immunoassay is available locally: high-sensitivity troponin (hs-troponin) I or T $>$ ULN (as per local standard for ULN), unless certain additional criteria are met, as outlined below:
     - If the local laboratory reports "indeterminate" or "intermediate" hs-troponin results: Patients with hs-troponin in the "intermediate" or "indeterminate" range (per local laboratory) may be enrolled if an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%–55%) without evidence of hypokinesis; if an echocardiogram

cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.

- If the local laboratory does not report "indeterminate" or "intermediate" hs-troponin results: Patients with hs-troponin $>$ULN to $<5\times$ULN may be enrolled if an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%–55%) without evidence of hypokinesis; if an echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.

2. If high-sensitivity immunoassay is not available locally: conventional cardiac troponin I or T $>$ULN, (based on local standard for ULN)

   - Patients with screen failure due to conventional troponin $>$ULN may be re-screened and enrolled if a repeat conventional troponin is $\leq$ULN and an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%–55%) without evidence of hypokinesis; if an echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.

- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- Sustained prolongation of QT interval corrected through use of Fridericia's formula (QTcF), defined as repeated demonstration of QTcF $>$480 ms (NCI CTCAE Grade 1)

  Patients with prolonged QTcF due to a reversible cause (e.g., electrolyte abnormalities) may be re-tested after the underlying cause has been corrected.

  For patients with a ventricular pacemaker, there should be appropriate correction for heart rate and pacing when determining baseline QTcF (as per Chakravarty et al. 2015); absolute QTcF values should not exceed 490 ms.
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), or family history of sudden unexplained death or long QT syndrome
- History of moderate or severe allergic, anaphylactic, or anaphylactoid reactions or hypersensitivity to any component of study treatment

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind, placebo-controlled study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of four treatment arms: MSTT1041A, UTTR1147A, or their matching placebos. Randomization will occur in a 2:2:1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to need for invasive mechanical ventilation (yes vs. no) and region. The proportion of patients with a need for invasive mechanical ventilation will be capped at approximately 25% of the overall study population.

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment of MSTT1041A and UTTR1147A versus their respective placebos during the study. The Sponsor and its agents will also be blinded to treatment assignment of MSTT1041A and UTTR1147A versus their respective placebos, with the exception of IxRS service provider, and prespecified personnel (e.g., DMC members).

PK samples may be used to assess immunogenicity. While PK samples must be collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the placebo arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples will be analyzed for all patients. Postbaseline ADA samples from patients assigned to the placebo arm will not be analyzed for ADAs except by request. Baseline and postbaseline samples will be collected for all patients.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are MSTT1041A and matching placebo, and UTTR1147A and matching placebo.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 MSTT1041A, UTTR1147A, and Placebos

MSTT1041A and UTTR1147A will be supplied by the Sponsor as a sterile, clear, and colorless to slightly yellow solution in single-use 5-mL and 2-mL vials, respectively. Matching placebos will be supplied by the Sponsor as a sterile solution in respective single-use 5-mL and 2-mL vials. The UTTR1147A diluent will also be supplied by the Sponsor. For information on the MSTT1041A and UTTR1147A formulations, see the pharmacy manual and RO7187807 (MSTT1041A) and RO7021610 (UTTR1147A) Investigator's Brochures.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.13.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 MSTT1041A, UTTR1147A, and Placebo

Doses of MSTT1041A, UTTR1147A, or matching placebo will be prepared per the instructions outlined in the pharmacy manual and delivered over 60 (±10) minutes.

Weight-based infusions of UTTR1147A, with a maximum dose given to be based on 100 kg total body weight, will be prepared per the instructions outlined in the pharmacy manual.

Patients who experience an infusion-associated adverse event with the initial infusion may be premedicated for the next infusion.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by

each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the RO7187807 (MSTT1041A) and RO7021610 (UTTR1147A) Investigator's Brochures for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to MSTT1041A or UTTR1147A

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMPs (MSTT1041A or UTTR1147A) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing MSTT1041A or UTTR1147A in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, *or* herbal remedies) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the study completion/discontinuation visit. For concomitant therapy used by a patient >7 days prior to initiation, only concomitant therapy for treatment of COVID-19 will be recorded. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. *Homeopathic remedies, IV fluids, or nutritional supplements (e.g., vitamins and minerals) do not need to be reported.*

4.4.1 Permitted Therapy

All patients will receive SOC per local practice for the treatment of severe COVID-19 pneumonia, with the exception of treatments listed under Section 4.4.3. The SOC for severe COVID-19 pneumonia may include, but is not limited to, anti-viral treatment, host-directed therapies, convalescent plasma, low-dose corticosteroids, and supportive care. Participation in another clinical drug trial is prohibited for the duration of this study.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

4.4.2.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during the study as described below:

- Treatment with any investigational agent (other than for COVID-19), cell-depleting therapies, JAK inhibitors (e.g., tofacitinib, baricitinib, upadacitinib), alkylating agents (e.g., chlorambucil, cyclophosphamide), TNF inhibitors, anti–IL-1 agents, thalidomide, anti-thymocyte globulin, and azathioprine
- High-dose systemic corticosteroids (≥ 1 mg/kg/day methylprednisolone or equivalent for more than 1 day)
- Plasmapheresis or extracorporeal photopheresis

- Immunization with a live or attenuated vaccine

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Records

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Due to the pandemic situation and restricted hospital access, the patient's legally authorized representative may consent remotely with appropriate documentation by the investigator or the authorized designee in accordance with applicable regulatory guidance. Where informed consent from the patient or the legally authorized representative is not feasible, exception from regulatory informed consent requirements may be permitted under certain circumstances in accordance with applicable law and IRB/EC policies.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a record of all patients screened and will confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and home oxygen use will be recorded at screening. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, *or* herbal remedies) used by the patient within 7 days prior to initiation of study treatment will be recorded. For concomitant therapy used by a patient $>$7 days prior to initiation, only concomitant therapy for treatment of COVID-19 will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs and Oxygen Saturation

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature. Peripheral oxygen saturation should also be measured at the same time as vital signs. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) should be recorded. For patients requiring non-invasive or invasive mechanical ventilation, the positive-end expiratory pressure (PEEP) and FiO_2 or oxygen flow rate (L/min) should be recorded.

To allow assessment of the NEWS2 score (see Appendix 4), site personnel should record *one* representative set of vital sign and oxygen saturation measurements from a single timepoint, ideally within 1 hour prior to treatment administration at the baseline visit (Day 1) and between 8 a.m. and 12 p.m. at subsequent visits during patient hospitalization. When possible, the patient should be assessed at approximately the same time each day. Following hospital discharge, patients may be provided with a personal pulse oximeter, which will be used to measure oxygen saturation and pulse rate at home.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Assessments Specific to National Early Warning Score 2

In addition to the vital measurements, the patient's consciousness level and the presence or absence of respiratory support must be recorded. The NEWS2 parameter for respiratory support is the selection of either air or "oxygen" and can include other forms of ventilation to maintain oxygen saturation (see Appendix 4). The form of ventilation used should be recorded on the appropriate eCRF.

These should be recorded at the same timepoints as the vital sign measurements.

NEWS2 values do not need to be calculated by the site, but will be calculated electronically by the Sponsor based on vital sign parameters and NEWS2-related assessments recorded by the investigator in the appropriate eCRF.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Arterial blood gases (oxygen, partial pressure of carbon dioxide, PaO_2, pH, FiO_2, bicarbonate)

  For sites at an altitude $>$5000 ft, a correction factor should be applied to the PaO_2 value by using the following equation:

  $$\frac{PaO_2}{FiO_2 \times \text{barometric pressure} / 760}$$

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered SOC for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, and/or AST, urate, LDH, and ferritin
- Coagulation: INR, PT, aPTT, fibrinogen, and D-dimer
- Cardiac hs-troponin I or T via high-sensitivity immunoassay; or conventional cardiac troponin I or T, if high-sensitivity immunoassay is not available locally

  The same assay should be used for all samples for each patient, if possible.

- N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP)

  The same assay should be used for all samples for each patient, if possible.

- CRP
- Lactate
- SARS-CoV-2 local virology test (PCR): nasopharyngeal swab, oropharyngeal swab, bronchoalveolar lavage, or other respiratory specimen; blood; urine; stool; or other bodily fluid
- Influenza A and influenza B virology test (PCR or rapid antibody test)
- Pregnancy test (urine or serum) for women of childbearing potential, including those who have had a tubal ligation

  Positive urine test results will be confirmed with a serum pregnancy test. Study drug can be administered only if the initial urine or serum pregnancy test result is negative or if a positive urine pregnancy test is followed by a negative serum pregnancy test.

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for PK analysis

  Serum ADA may be measured using PK samples if ADA samples have not been collected at the same timepoint.
- Serum samples for ADA analysis
- Serum samples for exploratory biomarker research
- Blood PAXgene® RNA for RNA sequencing or quantitative PCR
- Nasopharyngeal swabs for SARS-CoV-2 central virology tests (viral load and exploratory analysis)

Exploratory biomarker research may include, but will not be limited to, analysis of sST2, IL-22, IL-22 binding protein (IL-22BP), CRP, and REG3A, inflammatory mediators, and ARDS-related variables.

Research may involve extraction of RNA and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation and biomarker measurements; therefore, these samples will be destroyed no later than 15 years after the final Clinical Study Report has been completed.
- Serum, blood PAXgene, and fluid samples (nasopharyngeal swabs, if applicable) collected for biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis including data on genomic variants will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes if possible. All ECGs should be obtained prior to other procedures scheduled at that same time (e.g., blood draws) if possible. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. SOC treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.3.4. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, medications known to prolong the QT interval including chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir).

4.5.8 Chest X-Rays and CT Scans

Chest X-ray or CT scan should be performed during screening per inclusion criteria. A chest CT scan should be performed on Day 60 if a patient is still hospitalized or if an in-clinic follow-up visit is performed. Chest X-ray and/or CT findings should be recorded

on the appropriate eCRF. If additional chest X-rays/CT scans are performed per local practice during the patient's hospitalization or after discharge through Day 60, these findings should be provided in the appropriate eCRF. Upon completion of the study, imaging reports and DICOM® files for chest X-rays and CT scans obtained during the study period may be requested by the Sponsor.

4.5.9 Ordinal Scale Determination

Assessment of clinical status using a 7-category ordinal scale will be recorded *prior to dosing* at baseline on Day 1 and then again once daily every morning (ideally, between 8 a.m. and 12 p.m.) *at subsequent visits* during patient hospitalization. When possible, the patient should be assessed at approximately the same time each day. The ordinal scale categories are as follows:

1. Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen)
2. Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

In general, patients with oxygen saturation consistently ≤90% should be considered for escalation to a higher clinical status category, while patients with oxygen saturation consistently ≥96% should be considered for de-escalation to a lower category. However, actual clinical status category should be recorded on the eCRF. Please refer to the additional guidance for investigators regarding assessment of clinical status using the 7-category ordinal scale.

Patients on supplemental oxygen should be evaluated at least daily and considered for reduction or discontinuation of oxygen support. Actual changes in level of support will be at the discretion of the clinician(s) treating the patient based on the patient's overall condition and may be dictated by other clinical and non-clinical considerations.

Normal body temperature is defined as oral, rectal, axillary, temporal, or tympanic temperature 36.1°C–38.0°C. Normal respiratory rate is defined as 12–20 breaths per minute.

4.5.10 Optional Blood Samples for Whole Genome Sequencing (Patients at Participating Sites)

At participating sites, optional blood samples will be collected from consenting patients for DNA extraction to enable whole genome sequencing (WGS) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this section of the protocol (Section 4.5.10) will not be applicable at that site.

The Informed Consent Form will contain a separate section that addresses optional blood samples for WGS. A separate, specific signature will be required to document a patient's agreement to provide optional blood samples. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Whole Genome Sequencing Informed Consent eCRF.

Genomics is increasingly informing researchers understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.6 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Grade ≥ 4 dermatologic *reactions (as described in Section 5.1.3.3)*
- Major adverse cardiovascular event
- Hs-troponin I or T in the "intermediate" or "indeterminate" range or hs-troponin $>$ ULN to $< 5 \times$ ULN (and above baseline) AND either reduced ejection fraction or new hypokinesis by echocardiogram or evidence of myocarditis and/or pericarditis (as described in Section 5.1.3.3)
- Hs-troponin I or T at a level indicative of myocardial ischemia, $\geq 5 \times$ ULN, or category above "intermediate" or "indeterminate" (as described in Section 5.1.3.3)
- Conventional cardiac troponin I or T $>$ ULN, if high-sensitivity immunoassay is not available locally (as described in Section 5.1.3.3)
- QTcF prolongation or torsades des pointes as described in Section 5.1.3.4, unless there is a clear alternative cause for the changes
- Grade ≥ 3 infusion-related reaction as described in Section 5.1.3.3
- Use of prohibited therapy as described in Section 4.4.3

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients will remain in study and complete all study visits and assessments (with the exception of the study drug administration).

4.6.2 Patient Discontinuation from the Study

Hospitalized patients who discontinue the study prematurely should perform a study discontinuation visit. Discharged patients who discontinue study prematurely should return to the clinic for a study discontinuation visit, if possible, or have a remote (phone or video) visit.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MSTT1041A and UTTR1147A are not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with MSTT1041A and UTTR1147A in completed and ongoing studies. The anticipated

important safety risks for MSTT1041A and UTTR1147A are outlined below. Please refer to the RO7187807 (MSTT1041A) and RO7021610 (UTTR1147A) Investigator's Brochures for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria treatment discontinuation, are provided below.

5.1.1 Risks Associated with MSTT1041A (Anti-ST2)

5.1.1.1 Identified Risks

No risks have been identified yet for MSTT1041A.

5.1.1.2 Potential Risks

5.1.1.2.1 Adverse Effects Related to Immunogenicity

Administration of MSTT1041A, a protein therapeutic, may lead to the development of anti-MSTT1041A antibodies, which could lead to adverse events and/or decreased exposure. For details about immunogenicity rates and associated adverse events, refer to the MSTT1041A Investigator's Brochure.

5.1.1.2.2 Hypersensitivity Reactions and Anaphylaxis/ Hypersensitivity-Like Reactions

Hypersensitivity reactions and anaphylaxis have been described with SC administration of monoclonal antibodies (Corominas et al. 2014). Signs and symptoms may include acute onset (minutes to several hours) of one or more of the following: respiratory compromise, reduced blood pressure, skin-mucosal involvement, or GI symptoms (Sampson et al. 2006). The potential for hypersensitivity to MSTT1041A in humans is unknown. However, as with any large-molecule therapeutic, administration of MSTT1041A may result in systemic reactions. Systemic reactions to large-molecule therapeutics can be IgE or non-IgE mediated or due to the release of cytokines and are generally characterized by signs and symptoms such as skin rash, urticaria, pruritus, local or diffuse erythema, angioedema, fever, chills, cough, dyspnea, wheezing, bronchospasm, nausea, vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can be severe or life threatening. Effects typically occur during or within several hours after drug administration, but they may be delayed.

Refer to the MSTT1041A Investigator's Brochure for details about reports of adverse events of hypersensitivity reactions and anaphylaxis/hypersensitivity-like reactions.

5.1.1.2.3 Infection

The intended mechanism of action of MSTT1041A suggests inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of a decrease in the

protective response to infection, particularly helminthic infections (Molofsky et al. 2015). However, as described in Section 5.3 of the MSTT1041A Investigator's Brochure, a lack of significant differences in levels of exploratory biomarkers fractional exhaled nitric oxide (reflecting airway IL-4/IL-13 activity) and serum IL-5 between MSTT1041A-treated and placebo patients in Study GB39242 (patients with asthma) may reflect a limited effect on Type 2 inflammation. Refer to the MSTT1041A Investigator's Brochure for details about infections related to study treatment.

5.1.1.2.4 Exacerbation of Cardiovascular Disease

Published studies involving mouse models of cardiovascular disease or in vitro culture systems describe potential cardioprotective and atheroprotective roles of the IL-33/ST2 axis (Sanada et al. 2007; Miller et al. 2008; Seki et al. 2009; McLaren et al. 2010; Wasserman et al. 2012). For example, after experimentally induced acute left ventricular pressure overload, which could be relevant to clinical scenarios involving increased afterload (e.g., left-sided congestive heart failure or acute hypertension), $ST2^{-/-}$ mice had more left ventricular hypertrophy, more fibrosis, and impaired survival relative to their wild-type littermates (Sanada et al. 2007). However, the translatability of these findings remains uncertain. In addition, studies with conflicting data exist (Demyanets et al. 2011; Abston et al. 2012; Martin et al. 2015).

Evidence has shown that the sST2 receptor is a prognostic biomarker of cardiovascular disease outcome (Sabatine et al. 2008; Shah et al. 2009; Weir et al. 2010). Although published findings suggest a possible risk of exacerbation of existing cardiovascular disease in humans, there are no identified cardiovascular risks associated with inhibiting the IL-33/ST2 axis in humans.

Refer to the MSTT1041A Investigator's Brochure for details about the preclinical and clinical experience associated with the potential risk of cardiovascular disease.

5.1.2 Risks Associated with UTTR1147A (IL-22Fc)

5.1.2.1 Identified Risks

5.1.2.1.1 Dermatologic Reactions

In nonclinical and clinical studies, UTTR1147A caused on-target dose-dependent reversible skin changes, including pruritus, dry lips and skin, patchy erythema, skin exfoliation (primarily on the face and upper body), and skin discomfort. In the Phase I SAD study GA29468 in healthy volunteers, the MTD of 90 μg/kg IV was determined on the basis of the intensity of erythema, pruritus, and skin hyperesthesia reported by 3 of 4 subjects who received UTTR1147A at 120 μg/kg IV. Most dermatologic manifestations at doses of up to 90 μg/kg were mild (Grade 1) or moderate (Grade 2). Dermatologic findings appeared within a week of dosing, were manageable with topical emollients, and resolved within approximately 2 weeks of onset.

In the Phase Ib MAD in healthy volunteers and patients with IBD (Study GA29469), similar dermatologic findings have been observed at all dose levels tested (30 μg/kg IV

Q2W, 60 μg/kg IV Q2W, 60 μg/kg IV Q4W, and 90 μg/kg IV Q2W) after the first or second dose of UTTR1147A. In healthy volunteers, two doses of UTTR1147A at 90 μg/kg IV Q2W caused severe (Grade 3) skin discomfort, hyperesthesia, and erythema with minimal relief from topical emollients or topical corticosteroids but were self-limited and resolved after discontinuation of UTTR1147A treatment, yielding and MTD of 60 μg/kg IV Q2W.

In UC patients, two doses of UTTR1147A at 90 μg/kg IV q2wk caused moderate (Grade 2) erythema that were managed with topical emollients and resolved within 4–10 weeks after onset but UTTR1147A was better tolerated and no MTD was reached. Overall, dermatologic events (e.g., dry skin, erythema, skin exfoliation, and skin discomfort) appeared within the first month of dosing, were manageable with topical emollients, and reversible within 4 weeks to 3 months after onset. The drug has been well tolerated in an ongoing Phase II study (GA39925) to evaluate the efficacy, safety, and pharmacokinetics of UTTR1147A at 30 μg/kg Q4W, 60 μg/kg Q4W, or 90 μg/kg IV Q4W compared with vedolizumab or placebo in patients with moderate to severe UC. Based on preliminary blinded data, with a data cutoff of 6 March 2020, the overall skin adverse event rate is low at 8.2% (8/98 patients).

Guidelines for management of patients who develop dermatologic reactions are provided in Section 5.1.3.3.

5.1.2.2 Potential Risks

5.1.2.2.1 Administration Site Reactions and Infusion Related Reactions

As with introduction of any foreign biological molecule, the potential risks of UTTR1147A include systemic IRRs and local injection/administration site reactions. IRRs may include true acute allergic/hypersensitivity (e.g., anaphylaxis) reactions and acute pseudoallergic/hypersensitivity-like (e.g., anaphylactoid) reactions. Anaphylaxis and anaphylactoid reactions are the more severe forms of allergic and pseudoallergic reactions, respectively and may have similar or overlapping clinical symptoms. Anaphylaxis is associated with prior exposure to the drug, leading to sensitization and the development of IgE antibodies, and needs to be distinguished from anaphylactoid reactions as the correct diagnosis impacts the decision to re-dose the patient (e.g., patients with anaphylaxis should not be re-challenged). Refer to the UTTR1147A Investigator's Brochure for details about reports of adverse events of infusion related reactions. As UTTR1147A is not administered subcutaneously in this protocol, the potential risk for administration site reactions is not relevant.

5.1.2.2.2 Development of Cross Reacting Anti-Drug Antibodies and Increased Risk for Opportunistic Bacterial and Fungal Infections

Though not seen in human studies to date, there is a possibility that UTTR1147A may induce antibodies that neutralize endogenous IL-22 and, thus, be associated with an increased risk for opportunistic bacterial and fungal infections. Since IL-22 plays a role

in maintaining the integrity of epithelia by promoting its healing and regeneration, neutralizing IL-22 can impact the innate immunity of epithelial tissues (Wolk et al. 2004; Eidenschenk et al. 2014). Mice deficient in IL-22 are more susceptible to certain bacterial and fungal infections when inoculated with a bacterial or fungal challenge (Zheng et al. 2008; De Luca et al. 2010). Similar risks for increased incidence of opportunistic infections are seen with human inborn errors resulting in multiple deficiencies that include IL-22 (Liu et al. 2011; van de Veerdonk et al. 2011; Eidenschenk et al. 2014; Lehman 2014) and in syndromes associated with autoantibodies against multiple cytokines that include IL-22 (Puel et al. 2010).

Refer to the UTTR1147A Investigator's Brochure for details about immunogenicity rates and associated adverse events.

5.1.2.2.3 Enhanced Growth of Existing Epithelial Tumors

There exists a theoretical potential risk for UTTR1147A to promote epithelial tumor progression, likely due to the ability of IL-22 to activate STAT3 in epithelial cells. The cytokine has been known to induce epithelial hyperplasia (Sa et al. 2007; Kirchberger et al. 2013) in vitro and in human tumor cell lines as well as in vivo (Lim and Savan 2014; Bi et al. 2016).

Refer to the UTTR1147A Investigator's Brochure for nonclinical and clinical information regarding neoplasia or epithelial tumors.

5.1.2.3 Laboratory Abnormalities Associated with UTTR1147A (IL-22Fc)

CRP and fibrinogen are acute-phase reactants made in response to hepatocyte stimulation. On-target dose-dependent elevations of CRP and mild elevations of fibrinogen were observed following UTTR1147A administration in nonclinical studies and in clinical studies in healthy volunteers (Studies GA29468 [redacted] The information collected to date does not indicate that UTTR1147A-mediated CRP and fibrinogen elevations are associated with a safety risk.

Refer to the UTTR1147A Investigator's Brochure for detailed information on laboratory abnormalities.

5.1.2.3.1 C-Reactive Protein Elevation

[redacted] CRP elevations have not been associated with signs or symptoms of inflammation, including changes in vital signs such as fever, laboratory values including leukocytosis, or inflammatory cytokines (Rothenberg et al. 2019).

5.1.2.3.2 Fibrinogen Elevation

In healthy volunteers receiving a single dose of UTTR1147A (Study GA29468), mildly increased levels of fibrinogen peaked on approximately Day 8 and returned to near baseline level by Day 29 across all dose levels tested (60 to 120 μg/kg). Overall, increased levels of fibrinogen were less than 2-fold higher than baseline values and were within the normal range of the assay. [redacted]

Reversible increases in fibrinogen were not deemed clinically significant, and were likely due to direct stimulation of fibrinogen production by hepatocytes. Fibrinogen elevations have not been associated with blood clotting abnormalities or adverse events.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Dose Modifications

Dose modifications are not permitted in this study.

5.1.3.2 Treatment Interruption

Treatment interruptions are not applicable in this study, as there are only two doses (see Section 4.6.1).

5.1.3.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 3. Additional guidelines are provided in the subsections below.

Table 3 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
Dermatologic *reactions* [a]	
Grade 1 or 2	• Report details on the *dermatologic reactions* eCRF • Administer treatment for symptomatic relief, including topical emollients
Grade 3 or 4	• Report as an AESI. • Report details on the *dermatologic reactions* eCRF • Administer treatment for symptomatic relief, including topical emollients, topical corticosteroids, and/or oral antihistamines. • If an event is Grade 3, and patient experiences severe discomfort and limitation of self-care activities, consider discontinuing study treatment. • If an event is Grade 4, discontinue study treatment.

ADA=anti-drug antibody; AESI=adverse event of special interest; IRR=infusion-related reaction; ULN=upper limit of normal.

[a] Refer to Section *5.1.2.1.1 for description of dermatologic reactions.*

Table 3 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Infusion-related reactions	
General	• If infusion is stopped, the approximate volume administered should be recorded, as well as all start and stop times.
Grade 1	• Continue infusion. • Reduce infusion rate to 50% of original infusion rate.
Grade 2	• Interrupt infusion. • Administer supportive treatment if indicated per local or institutional standard operating procedures. • Upon symptom resolution, resume infusion at 50% of original infusion rate. • If infusion reaction reoccurs, discontinue study treatment.
Grade 3 or 4	• Stop infusion immediately and administer supportive treatment per local or institutional standard operating procedures (see Appendix 3 for guidance on anaphylaxis). • Discontinue study treatment. • Consider obtaining additional supportive data, if available, to inform the diagnosis of allergic versus pseudoallergic reaction (e.g., serum histamine, serial tryptase measurements).
Cardiac toxicity	
High-sensitivity troponin I or T in the "intermediate" or "indeterminate" range, or > ULN to < 5 × ULN (and above baseline)	• An echocardiogram to assess for cardiac function is recommended. • If echocardiogram shows reduced ejection fraction or new hypokinesis or there is clinical evidence of myocarditis and/or pericarditis, discontinue study treatment and report as an AESI. • Report as an AESI if it meets criteria for major adverse cardiovascular event. [a]
High-sensitivity troponin I or T at a level indicative of myocardial ischemia, ≥ 5 × ULN, or category above "intermediate" or "indeterminate"	• Discontinue study treatment. • An echocardiogram to assess for cardiac function is recommended. • Report as an AESI if it meets criteria for major adverse cardiovascular event. [a]
Conventional cardiac troponin I or T > ULN, if high-sensitivity immunoassay is not available locally	• Discontinue study treatment. • An echocardiogram to assess for cardiac function is recommended. • Report as an AESI if it meets criteria for major adverse cardiovascular event. [a]
Major adverse cardiovascular event [b]	• Discontinue study treatment. • Report as an AESI.

ADA = anti-drug antibody; AESI = adverse event of special interest; IRR = infusion-related reaction; ULN = upper limit of normal.

[b] Refer to Section 5.2.3 for examples of events that qualify as major adverse cardiovascular events.

5.1.3.4 Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value
- Sustained absolute QTcF that is > 515 ms (or > 530 ms for patients with a ventricularly paced rhythm)
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval, including other drugs used to treat severe COVID-19 pneumonia, such as chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir, etc.). Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients.

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.1.3.5 Anaphylaxis

Refer to Appendix 3 for guidelines on anaphylactic precautions. These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

In accordance with local guidelines, the measurement of tryptase (serum or plasma) and histamine (plasma) levels should be considered to support a diagnosis of anaphylaxis, although clinicians should treat anaphylaxis regardless of the availability of the results of these tests.

During the study, all anaphylaxis events should be accurately reported on the appropriate eCRF.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- 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 considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Suspected infusion related reactions or hypersensitivity reactions, including anaphylaxis, within 24 hours of infusion
- MACE, including:
  - Death due to primary cardiovascular causes (cardiac arrest secondary to progression of disease is excluded)

- Non-fatal myocardial infarction or acute coronary syndrome
- New or worsening heart failure (new globally decreased left ventricular ejection fraction on transthoracic ECHO)

- Grade ≥3 *dermatologic reactions (as described in Section 5.1.3.3)*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until the study completion/discontinuation visit.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (also see Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

Causality will be assessed individually for MSTT1041A and UTTR1147A.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction or anaphylactic reaction).

5.3.5.2 *Dermatologic Reactions*

For *dermatologic* adverse events *(as described in Section 5.1.2.1.1)*, details on involved body surface area and appearance should be recorded on the *Dermatologic Reactions* eCRF.

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events

based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.6 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment, including a comparison to baseline values, should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. Abnormal laboratory values that were abnormal at baseline should only be reported as adverse events if they meet one of the following criteria:

- The abnormality represents a deterioration from baseline
- The abnormality had resolved in the intervening period and became newly abnormal
- The abnormality persisted when in the investigators judgment it should have normalized

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment, including a comparison to baseline abnormalities, should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event. Abnormal vital signs that were abnormal at baseline should only be reported as adverse events if they meet one of the following criteria:

- The abnormality represents a deterioration from baseline
- The abnormality had resolved in the intervening period and became newly abnormal
- The abnormality persisted when in the investigators judgment it should have normalized

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ ULN or $> 3 \times$ baseline, if abnormal at baseline) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3 \times$ baseline, if abnormal at baseline) in combination with total bilirubin $> 2 \times$ ULN
- Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3 \times$ baseline, if abnormal at baseline) in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of COVID-19 pneumonia.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of COVID-19 Pneumonia

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events (with the exception of death due to COVID-19 pneumonia progression as described in Section 8). These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.12 Re-Hospitalization or Prolonged Hospitalization

Any adverse event that results in re-hospitalization (i.e., inpatient admission to a hospital following discharge) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.13 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For MSTT1041A or UTTR1147A (or matching placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated MSTT1041A or UTTR1147A (or matching placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more

than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

PPD Medical Monitor contact information:

Telephone Nos.: +1 (888) 483 7729 (North America)
+44 1223 374 240 (EMEA/APAC)
+55 11 4504 4801 (Latin America)

Genentech Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D., Ph.D.
Telephone Nos.: [redacted] (mobile)

Genentech Alternate Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D., Ph.D., MRCP (UK)
Telephone Nos.: [redacted] (mobile)

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the completion/discontinuation visit (Study Day 60, unless the patient has an early discontinuation). Investigators should record all case details

that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the completion/discontinuation visit are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 95 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 95 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for

Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as the study completion/discontinuation visit), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
MSTT1041A	RO7187807 Investigator's Brochure
UTTR1147A	RO7021610 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

A DMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Efficacy analyses will be conducted on the modified intent-to-treat (mITT) population. The mITT population is defined as all patients randomized in the study who received at least one dose of study drug, with patients grouped according to the treatment assigned at randomization.

Safety analyses will be conducted for the safety population, which consists of patients who received at least one dose of study drug, with patients grouped according to the treatment received.

6.1 DETERMINATION OF SAMPLE SIZE

A total of approximately *390* patients will be randomly allocated in a 2:2:1:1 ratio to receive MSTT1041A, UTTR1147A, or their matching placebos. The sample size provides approximately 80% power using a log-rank Chi-square test to detect a *7*-day difference between treatment groups in time to *recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first),* under the following assumptions: median time to improvement in the placebo group is *21* days, with 28 days follow-up, and using a one-sided 5% alpha. The minimal detectable difference is expected to be approximately *5.3 days.*

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized by treatment group. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and summarized.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including, but not limited to, age, sex, days from illness onset to randomization, geographic region, ordinal scale for clinical status, invasive mechanical ventilation) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group for the mITT and safety population.

6.4 EFFICACY ANALYSES

Efficacy analyses will be conducted on the mITT population, consisting of all patients randomized in the study who received at least one dose of study drug, with patients grouped according to the treatment assigned at randomization.

MSTT1041A placebo and UTTR1147A placebo will be pooled in efficacy analyses. Comparison of efficacy will be performed between each of the two treatment groups and the pooled placebo. That is, there are two comparisons:

- MSTT1041A with pooled placebo
- UTTR1147A with pooled placebo

Sensitivity analyses to evaluate the robustness of results will be conducted with comparison of primary efficacy endpoint between MSTT1041A and MSTT1041A placebo, and between UTTR1147A and UTTR1147A placebo.

Details on analysis methods, sensitivity analyses, hypothesis testing, and type I error control across treatment groups will be specified in the Data Analysis Plan (DAP).

Unless otherwise noted, analyses of efficacy outcome measures will be adjusted by stratification factors (the need for invasive mechanical ventilation [yes vs. no] and region).

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of MSTT1041A compared with placebo and of UTTR1147A compared with placebo, in combination with SOC, on the basis of the following endpoint:

- *Time to recovery, defined as time to score of 1 or 2 on the 7-category ordinal scale (whichever occurs first)*

The ordinal scale categories are as follows:

1. Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$2 L supplemental oxygen)
2. Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

Time to recovery will be analyzed using the stratified log-rank test, adjusting for stratification factors. The Kaplan-Meier plot, median time to event, and their 95% CI and p-value from the stratified log-rank test will be presented. A Cox proportional hazards regression model will be used to estimate the hazard ratio comparing MSTT1041A or UTTR1147A with placebo, respectively, adjusting for stratification

factors. Hazard ratios and 95% CIs will be presented. In addition, the p-value from unstratified log-rank test, unadjusted hazard ratio, and 95% CI will also be presented. Further details on the primary endpoint analysis will be included in the DAP.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen)
- Duration of supplemental oxygen
- Proportion of patients alive and free of respiratory failure (requiring non-invasive ventilation, high-flow oxygen, invasive mechanical ventilation, or ECMO) at Day 28
- *Clinical status assessed using a 7-category ordinal scale at Days 14 and 28*
- Incidence of invasive mechanical ventilation *or* ECMO
- Ventilator-free days to Day 28
- Incidence of ICU stay
- Duration of ICU stay
- Time to clinical failure, defined as the time to death, invasive mechanical ventilation, ICU admission, or withdrawal of care (whichever occurs first). For patients entering the study already in ICU or on invasive mechanical ventilation, clinical failure is defined as a one category worsening on the ordinal scale, withdrawal, or death.
- Mortality rate at Days 14 *and* 28
- *Time to clinical improvement, defined as a NEWS2 of ≤2 maintained for 24 hours*

The secondary endpoints will be analyzed in the mITT population. Statistical models will be adjusted for the covariates as described in Section 6.4.

Full details of hypothesis testing, analysis methods, type I error control, and missing data handling will be documented in the DAP.

6.4.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be analyzed using the same methods as described for the secondary endpoints in Section 6.4.2, where appropriate.

6.5 SAFETY ANALYSES

Safety analyses will be conducted on all patients who received at least one dose of study drug, with patients grouped according to the treatment received.

Safety will be assessed through summaries of exposure to study treatment, adverse events, laboratory test results, vital signs, and ECGs.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 scale. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, adverse events leading to discontinuation from study treatment, adverse events leading to discontinuation from study, and treatment-emergent adverse events will be summarized by treatment groups. A treatment-emergent adverse event is defined as any new adverse event reported or worsening of an existing condition on or after the first dose of study drug during. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign, and ECGs will be summarized by appropriate descriptive statistics by treatment groups.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients who received at least one dose of MSTT1041A or UTTR1147A and have sufficient data to enable estimation of key parameters (e.g., C_{max}), with patients grouped according to treatment received.

Estimates for the PK parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum), as appropriate. Individual and mean serum MSTT1041A or UTTR1147A concentration versus time data will be tabulated by dose level. Additional PK analyses will be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received, or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive subjects and ADA-negative subjects at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, subjects are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Subjects are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

No formal statistical analysis of exploratory biomarkers will be performed. Data may be analyzed in the context of this study and in aggregate with data from other studies.

6.9 OPTIONAL INTERIM ANALYSES

Other than the cumulative data review by the DMC for benefit/risk assessment, no formal efficacy interim analyses are planned at this time. The DMC, after reviewing unblinded data, may recommend that a formal efficacy interim analysis be performed. Furthermore, to adapt to information that may emerge during the course of this study, the Sponsor may choose to add a formal interim analysis at the recommendation of the DMC.

The interim analysis will be conducted by DMC. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The DMC Charter will be updated to document potential recommendations the DMC can make as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Due to the pandemic situation and resulting restrictions to hospital access, data monitoring may be performed remotely or on-site. Study monitors will perform ongoing data review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate and complete. Sites will be asked to implement a QC step of a second person reviewing the data entry in the eCRF where possible.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes (PROs), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of

the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study.

Due to the pandemic situation and restricted hospital access, the patient’s legally authorized representative may consent remotely with appropriate documentation by the investigator or the authorized designee in accordance with applicable regulatory guidance. Where informed consent from the patient or the legally authorized representative is not feasible, exception from regulatory informed consent requirements may be permitted under certain circumstances in accordance with applicable law and IRB/EC policies.

The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.
The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will

be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted remotely or on site by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

Genentech, a member of the Roche group, is the Sponsor of this study. A contract research organization (CRO) may provide clinical operations oversight, including, but not limited to, project management, medical monitoring, site management, data quality support, safety reporting, and regulatory activities as specified in the study management plans. Genentech will provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. A DMC will provide safety monitoring for the study in addition to the ongoing review of safety by the Medical Monitor and safety scientist. EDC will be utilized for this study. An IxRS will be used to assign patient numbers, randomize patients into the study and manage site drug supply. A central laboratory will be used for sample management and storage until shipment to specialty laboratories or Genentech for analysis. Local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities (Inpatients Only)

	SCR[cc]	Baseline	Primary Phase																											Follow up		SC[a]
Study day	−2 to RAND	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	35	45	60 or ED
Visit window		0	b	b				b			*b*					c		*b*				b							b	±2 D	±2 D	±3 D
SCREENING ONLY ASSESSMENTS																																
Informed consent [d]	X																															
Inclusion/exclusion criteria	X																															
COVID-19 diagnosis [e]	X																															
Influenza A and B virology [e]	X																															
Demographic data	X																															
Medical history [f]	X																															
Complete physical examination [g]	X																															
Randomization		X																														
LOCAL LABS & ASSESSMENTS																																
Height [h]		X																														
Weight [h]		X													X [i]																	
Pregnancy test (urine or serum) [j]	X														X																	X
Chest X-ray/CT scan [k]	X	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	X

Appendix 1: Schedule of Activities (Inpatients Only)

	SCR[cc]	Baseline	Primary Phase																											Follow up		SC[a]
Study day	−2 to RAND	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	35	45	60 or ED
Visit window		0	b	b				b			*b*					c		*b*				b							b	±2 D	±2 D	±3 D
ECG	X	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	X	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	X	(x)	(x)	X
Limited physical examination [l]		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Vital signs (including SpO_2 & FiO_2) and NEWS2 [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Arterial blood gases [n]	X	X [o]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Ordinal scoring [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [q]	X	X [o]	X	X				X			X				X			X				X							X	X	X	X
Chemistry [r]	X	X [o]	X	X				X			X				X			X				X							X	X	X	X
Coagulation *(incl. d-dimer)* [s]		X [o]		X				X			X				X			X				X							X			X
NT-proBNP or BNP	X														X [i]																	
Troponin I or T [t]	X														X [i]																	
CRP		X [o]		(x)				(x)			(x)				X			(x)				(x)							X			X
Lactate	(x)	(x)																														
SARS-CoV-2 virology		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)

Appendix 1: Schedule of Activities (Inpatients Only)

	SCR[cc]	Baseline	Primary Phase																											Follow up		SC[a]
Study day	−2 to RAND	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	35	45	60 or ED
Visit window		0	b	b				b			*b*					c		*b*				b							b	±2 D	±2 D	±3 D
Adverse events [u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration		X														X [w]																
CENTRAL LABS																																
Serum PK sample(s) [x]		X	X	X				X								X						X [y]							X			X
Serum ADA sample [z]		X														X													X			X
Serum sample for biomarkers [z]		X	X	X				X								X						X [y]							X			X
Blood in PAXgene® tubes for biomarkers [z]		X		X				X																					X			
SARS-CoV-2 viral load [aa]		X														X						X [y]							X			
Blood sample for WGS (optional) [bb]		X																														

ADA = anti-drug antibodies; BNP = brain natriuretic peptide; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CT = computed tomography; D = days; eCRF = electronic Case Report Form; ED = early discontinuation visit; FiO_2 = fraction of inspired oxygen; h = hours; NEWS2 = National Early Warning Score 2; NT-proBNP = N-terminal pro-brain natriuretic peptide; PaO_2 = partial pressure of oxygen; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; RAND = randomization; SC = study completion; SCR = screening; SpO_2 = peripheral capillary oxygen saturation; ULN = upper limit of normal; WGS = whole genome sequencing; **X = mandatory assessment; (x) = Will be recorded on appropriate eCRF if the assessment is clinically indicated per standard of care.**

Notes: On treatment days, all assessments including collection of laboratory samples should be performed prior to dosing, unless otherwise specified. Once patient is ready for discharge from the hospital (or will be transferred to a different care facility), please refer to Appendix 2. Screening period will be up to 2 days. All screening assessments will be completed, including review of screening test results (except for the influenza virology test) and confirming eligibility, prior to randomizing the patient.

[a] Patients who complete a study will perform a study completion visit. Patients who discontinue the study prematurely should perform a study discontinuation visit, if possible.

[b] *The window for central laboratory sample collection is as follows:* On Day 2, collection is 24 ±2 hours after the end of study drug infusion on Day 1, on Day 3, the window is +2 days, and on Days 7, 21, and 28, the window is ±2 days. *For local labs (hematology, chemistry, and coagulation), the following window applies for Days 7, 10, 17, 21, and 28: Results from standard-of-care labs can be used if drawn within 1 day prior to the specified timepoint.*

[c] It is preferred that the second dose of study drug be administered on Day 15. In cases where this is not possible, study drug administration can occur on Day 14, Day 16, or Day 17, provided a pregnancy test (women of childbearing potential), ECG, vital signs, hematology, chemistry, coagulation, NT-proBNP or BNP, troponin I or T, and CRP are performed and evaluated within 2 days prior to study drug administration. Samples for central laboratory tests must also be collected prior to study drug administration, with the exception of the post-dose PK sample.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] For screening, historic results of influenza and SARS-CoV-2 virology, performed within 14 days prior to Day 1 are acceptable.

[f] Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and home oxygen use will be recorded at screening.

[g] Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

[h] If weight or height cannot be assessed on the indicated study day, the most recent documented value is acceptable (e.g., from hospital admission).

[i] Assessment is optional (to be performed at the investigator's discretion) for patients who will not receive a second dose.

[j] For women of childbearing potential, including those who have had a tubal ligation. Positive urine test results will be confirmed with a serum pregnancy test. Study drug can be administered only if the initial urine or serum pregnancy test result is negative or if a positive urine pregnancy test is followed by a negative serum pregnancy test.

[k] Chest CT scan will be performed at Screening and Study completion/Discontinuation visit. For Screening, historic test results within 7 days prior to Day 1 are acceptable. If chest CT scan is not available for Screening, a chest X-ray is acceptable.

[l] Perform a limited, symptom-directed examination as clinically indicated.

[m] Site personnel should record *one* representative set of vital signs (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation measurements, as well as NEWS2-specific assessments (i.e., consciousness and presence or absence of oxygen support), from a single timepoint, ideally within 1 hour prior to treatment administration at the baseline visit (Day 1) and between 8 a.m. and 12 p.m. at subsequent visits during patient hospitalization. When possible, the patient should be assessed at approximately the same time each day.

[n] Arterial blood gases (oxygen,, partial pressure of carbon dioxide, PaO_2, pH, FiO_2, bicarbonate) will be collected at screening and Day 1 only for patients who are mechanically ventilated and have an existing arterial line. On subsequent visits, arterial blood gases will be recorded only if the patient has an existing arterial line and arterial blood gas measurement is clinically indicated per standard of care.

[o] Local laboratory assessments do not need to be repeated if screening or standard of care labs were drawn *the day prior to Day 1*.

[p] Assessment of patient status using the ordinal scale should be recorded *prior to dosing* at baseline on Day 1 and then again *once daily* every morning *(ideally* between 8 a.m. and 12 p.m.*) at subsequent visits during patient hospitalization*. When possible, the patient should be assessed at approximately the same time of day.

[q] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[r] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, LDH, and ferritin.

[s] Coagulation panel includes INR, PT, aPTT, fibrinogen, and D-dimer.

[t] Troponin should be determined via high-sensitivity immunoassay, if possible. If the high-sensitivity immunoassay is not available locally, troponin can be determined via conventional assay. For troponin values >ULN, an echocardiogram may be recommended as described in Sections 4.1.2 and 5.1.3.3.

[u] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until the Study completion/Discontinuation visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[v] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal remedies) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the Study completion/Discontinuation visit. For concomitant therapy used by a patient >7 days prior to initiation, only concomitant therapy for treatment of COVID-19 will be recorded.

[w] A second dose of study drug will be given on Day 15 if the patient remains hospitalized with a requirement for supplemental oxygen therapy, unless patient meets the study drug discontinuation criteria (see Section 4.6.1).

[x] On dosing days (Day 1 and, if applicable, Day 15), predose and postdose (30 [±10] minutes after end of infusion) PK samples will be collected. Single PK samples will be collected at other specified visits, including Day 15 if the second dose is not administered. Leftover PK samples may be used for immunogenicity assessment and biomarker measurements.

[y] Samples should be collected for patients who received a second dose. Sampling is optional for patients who did not receive a second dose.

[z] On dosing days, ADA and biomarker samples will be collected predose.

[aa] If it is possible to only access one nostril for sampling, the same nostril should be used at each sampling time point, if possible (see the appropriate laboratory manual for details).

[bb] Patients must provide consent to participate. Not applicable for a site that has not been granted approval for WGS sampling. If the sample is not collected at the baseline visit for any reason, it may be collected at any later timepoint.

[cc] *Historic standard-of-care assessments are acceptable if performed within 2 days prior to Day 1, unless otherwise specified.*

Appendix 2
Schedule of Activities (Post-Discharge)

	Discharge Day	Remote Visits (Telephone or Video Visit)				In-Clinic Visit [a]	Remote Visits (Telephone or Video Visit)		SC [a]
Study day		3	7	14	21	28	35	45	60 or ED
Visit window		±1 D	±2 D	±2 D	±2 D	±2 D	±2 D	±2 D	±3 D
LOCAL LABS/ASSESSMENTS									
Pregnancy test (urine or serum) [b]	X [p]								X
Chest X-ray/CT scan [c]	(x)					(x)			X
ECG	X [p]					(x)			X
Limited physical examination [d]	(x)					(x)			X
Vital signs (including SpO_2 & FiO_2) and NEWS2 [e]	X					X			X
Ordinal scoring [f]	X	X	X	X	X	X	X	X	X
Hematology [g]	X [p]					X			X
Chemistry [h]	X [p]					X			X
Coagulation [i]	X [p]					X			X
CRP	X [p]					X			X
Limited vital signs [j]		X	X	X	X		X	X	
Adverse events [k]	X	X	X	X	X	X	X	X	X
Concomitant medications [l]	X	X	X	X	X	X	X	X	X

Appendix 2: Schedule of Activities (Post-Discharge)

	Discharge Day	Remote Visits (Telephone or Video Visit)				In-Clinic Visit [a]	Remote Visits (Telephone or Video Visit)		SC [a]
Study day		3	7	14	21	28	35	45	60 or ED
Visit window		±1 D	±2 D	±2 D	±2 D	±2 D	±2 D	±2 D	±3 D
CENTRAL LABS									
Serum PK sample [m]	X [p]					X			X
Serum ADA sample	X [p]					X			X
Serum sample for biomarkers	X [p]					X			X
Blood in PAXgene tubes for biomarkers	X [p]								
SARS-CoV-2 viral load [n]	X [o]					X			

ADA = anti-drug antibodies; CRP = C-reactive protein; CT = computed tomography; ED = early discontinuation visit; D = Day; FiO_2 = *fraction of inspired oxygen;* NEWS2 = National Early Warning Score 2; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = study completion; SCR = screening; SpO_2 = peripheral capillary oxygen saturation; ULN = upper limit of normal; **X = mandatory assessments; (x) = will be recorded on appropriate eCRF if the assessment is clinically indicated per standard of care**.

Notes: ***Study day refers to days on study (e.g., study Day 3 is 2 days after the randomization day) and not to the number of days post-discharge.*** **As discharge dates will vary across patients, this schedule of activities is effective starting on initial discharge day of the patient, subsequent visits should align with the patient's day on study, for a maximum total study duration of 60 days, for each patient.**

[a] If possible, an in-clinic visit should be performed. Otherwise, a remote visit (via telephone or video visit) will be performed and the following assessments will be recorded: Ordinal scoring, limited vital signs, adverse events, and concomitant medications.

[b] For women of childbearing potential, including those who have had a tubal ligation, positive urine test results will be confirmed with a serum pregnancy test.

[c] On Day 60, a chest CT should be performed if possible.

[d] Perform a limited, symptom-directed examination as clinically indicated.

[e] Vital sign measurement (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature), oxygen saturation and NEWS2-specific assessments (i.e., consciousness and presence or absence of oxygen support) should be recorded together in the morning (ideally between 8 a.m. and 12 p.m.), if possible.

[f] Assessment of patient status using the ordinal scale should be performed in the morning (ideally between 8 a.m. and 12 p.m.), if possible.

[g] Hematology includes (WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate.

[i] Coagulation panel includes INR, PT, aPTT, fibrinogen, and D-dimer.

[j] Following hospital discharge, limited vital signs should be reported, if possible. Limited vital signs include pulse rate, oxygen saturation, and details on supplemental oxygen use/mechanical ventilation, if applicable.

[k] All adverse events will be reported until the Study completion/Discontinuation visit. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, or *herbal remedies*) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until the Study completion/Discontinuation visit.

[m] Leftover PK samples may be used for immunogenicity assessment.

[n] If it is possible to only access one nostril for sampling, the same nostril should be used at each sampling time point, if possible (see the appropriate laboratory manual for details).

[o] Collect if patient is discharged on or before Day 15.

[p] *Assessments do not need to be repeated if protocol or standard-of-care assessments were performed on the day prior to discharge day.*

Appendix 3
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Consider the measurement of tryptase (serum or plasma) and histamine (plasma) levels to support a diagnosis of anaphylaxis

Appendix 4
National Early Warning Score 2 (NEWS2)

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

CVPU = confusion, voice, pain, unresponsive; SpO_2 = peripheral capillary oxygen saturation.

The oxygen saturation should be scored according to either the SpO_2 Scale 1 or 2 presented in the table above. The SpO_2 Scale 2 is for patients with a target oxygen saturation requirement of 88%–92% (e.g., in patients with hypercapnic respiratory failure related to advanced lung diseases, such as chronic obstructive pulmonary disease [COPD]). This should only be used in patients confirmed to have hypercapnic respiratory failure by blood gas analysis on either a prior or their current hospital admission.

The decision to use the SpO_2 Scale 2 should be made by the treating physician and should be recorded in the eCRF. In all other circumstances, the SpO_2 Scale 1 should be used.

For physiological parameter “Air or Oxygen?”: Any patients requiring the use of oxygen or other forms of ventilation to maintain oxygen saturations and support respiration should be assigned a score of 2.

The consciousness level should be recorded according to the best clinical condition of the patient during the assessment. Patients who are assessed as “Alert” (A) should be assigned a score of 0. Patients assessed as “New Confusion” (C), “Responsive to Voice” (V), “Responsive to Pain” (P), or “Unconscious” should be assigned a score of 3.

Scores should be assigned for respiratory rate, systolic blood pressure, pulse, and temperature according to the table above.

NEWS2 values will be calculated electronically throughout the study by the Sponsor based upon entry of vital sign parameters by the investigator in the appropriate electronic Case Report Form (eCRF).

Example Case Calculation:

An 82-year-old lady was admitted, tested positive to coronavirus disease 2019 (COVID-19) and admitted to high dependency unit for non-invasive ventilation. Her taken observations and corresponding NEWS2 score are as follows:

Physiological Parameter	Observation	Component Score
Respiratory rate (per min)	26	3
Oxygen saturation (SpO_2 %)	95%	1
Supplemental Oxygen	Yes	2
Systolic blood pressure (mmHg)	95	2
Pulse Rate (bpm)	109	1
Conscious level	New confusion	3
Temperature (°C)	39	1
	Total NEWS2 Score	**13**

REFERENCE

Royal College of Physicians. National early warning score (NEWS) 2. Standardizing the assessment of acute-illness severity in the NHS. London: RCP, 2017.