Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2015301

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original statistical analysis plan, final statistical analysis plan, summary of changes

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	147753
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Available
Indication:	COVID-19
Protocol ID:	GS-US-540-5773
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 24 February 2020

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312); however, sites located in the European Economic Area and Switzerland are not included under the IND and are considered non-IND sites.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734TM) in Participants with Severe COVID-19
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	147753 Not Applicable Not Available
Study Centers Planned:	Up to 50 centers globally, primarily in Asia
Objectives:	The purpose of this study is to provide remdesivir (RDV) to participants with severe COVID-19. The primary objective of this study is as follows: • To evaluate the efficacy of 2 RDV regimens with respect to the normalization of temperature and oxygen saturation through Day 14 The secondary objective of this study is as follows: • To evaluate the safety and tolerability of RDV
Study Design:	This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in adult participants with severe COVID-19. Approximately 400 participants who meet all eligibility criteria may be randomized in a 1:1 ratio into one of the following treatment groups: **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Number of Subjects Planned:	Approximately 400
Target Population:	Adults with severe COVID-19
Duration of Treatment:	The duration of treatment with RDV will be up to 10 days
Diagnosis and Main Eligibility Criteria:	Adult participants with COVID-19 confirmed by polymerase chain reaction (PCR) who meet the following criteria: • Willing and able to provide written informed consent prior to performing study procedures • Hospitalized • Fever of ≥ 36.6 °C armpit, ≥ 37.2 °C oral, or ≥ 37.8 °C rectal • SpO_2 ≤94% on room air • Radiographic evidence of pulmonary infiltrates
Study Procedures/ Frequency:	At screening after the participant has provided informed consent, demographic and baseline characteristics, medical history, and concomitant medications will be documented. Vital signs including temperature, respiratory rate, and SpO_2 will be recorded. Radiographic imaging will be performed if not already available. SARS-CoV-2 testing by PCR testing will be performed; if this testing has been performed within the previous 4 days, no repeat testing is required. If safety laboratory results from the screening day are not already available, laboratory testing including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and creatinine clearance will be performed according to local practice. After screening procedures, eligible participants will be randomized into 1 of the 2 treatment groups in a 1:1 ratio to receive: **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV RDV200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

	The date of randomization will be considered Day 1 and all participants randomized to receive RDV should receive their initial dose on Day 1. On study Days 1 through 14 or until discharge, whichever is earlier, vital signs including respiratory status will be measured and adverse events (AEs) and concomitant medications will be documented. Laboratory testing will be performed according to SOC practice with results for white blood cell count, hemoglobin, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing being reported to the Sponsor. In addition, even if not performed as standard of care, white blood cell count, hemoglobin, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST will be performed at Days 1, 3, 5, 8, 10, and 14 or until discharge, whichever is earlier. Pharmacokinetic (PK) assessments may be conducted at selected sites for local analysis. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-dose and end of infusion), and Day 7 (pre-dose and end of infusion). Up to 20 participants (10/group) may have intensive PK samples collected at Day 1, and Day 5 (treatment group 1), or Day 10 (treatment group 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV.
Test Product, Dose, and Mode of Administration:	Remdesivir (GS-5734) for injection, 100 mg, for IV administration
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Incidence of treatment-emergent AEs and treatment-emergent clinical laboratory abnormalities
Efficacy:	The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: fever; temperature < 36.6 C armpit, < 37.2 C oral, < 37.8 C rectal; and Sp02 > 94%, sustained for at least 24 hours] through Day 14

Statistical Methods:	The proportions of participants in the Full Analysis Set with normalization of fever and oxygen saturation through Day 14 will be compared between the 2 groups using a chi-square test, and point estimates of the treatment difference and the associated 95% confidence interval will be provided. Treatment-emergent AEs and laboratory abnormalities will be summarized using descriptive statistics and listed by subject. Plasma concentrations and PK parameters for RDV and the GS-441524 metabolite may be listed and summarized using descriptive statistics by group. **Sample Size**: A total of approximately 400 participants will be randomized in a 1:1 ratio to 2 groups (200 participants per group) A sample size of 400 participants (200 participants in each group) achieves approximately 85% power to detect a difference of 15% between the 5-day treatment group and the 10-day treatment group, assuming a response rate of 45% in the 5-day treatment group and 60% in the 10-day treatment group. The test statistic used is a chi-square test with a two-sided significance level of 0.05.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°F	Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
CDC	Centers for Disease Control and Prevention
CoV	coronavirus
CRF	case report form
CRO	contract/clinical research organization
CSR	clinical study report
d	deciliter
DAIDS	Division of AIDS
DMC	data monitoring committee
EBOV	Ebola virus
eCCGs	eCRF Completion Guidelines
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
eSAE	Electronic Serious Adverse Event
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
g	grams
GCP	Good Clinical Practice
Gilead	Gilead Sciences
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IB	investigator's brochure
ICH	International Conference on Harmonization (of Technical Requirements for Pharmaceuticals for Human Use)
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
IV	intravenous

IWRS	interactive web response system
J	joule
kg	kilogram
LAM	lactational amenorrhea method
LLOQ	lower limit of quantitation
LLT	lower-level term
LPV	lopinavir
LPV/RTV-IFNb	LPV/RTV + interferon-beta
MARV	Marburg virus
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
min	minute
NHPs	nonhuman primates
OAT	organic anion transporter
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PT	preferred term
PVE	Pharmacovigilance and Epidemiology
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
RDV	remdesivir
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTV	ritonavir
SADR	serious adverse drug reaction
SAE	serious adverse event
SARS	Severe Acute Respiratory Syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
SDV	source data verification
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TM	test method
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China. Sequencing analysis from the patients' respiratory tract samples indicated a novel coronavirus (CoV), which was named COVID-19. As of 23 February 2020, more than 78,000 confirmed cases have been identified in Wuhan, other provinces in China, and in multiple countries outside China {World Health Organisation (WHO) 2020}. More than 2400 deaths associated with COVID-19 have been reported, making COVID-19 a major health emergency.

Antiviral drugs that are being evaluated as potential treatments for COVID-19 include lopinavir/ritonavir (LPV/RTV; used in the treatment of HIV infection) and remdesivir (RDV, GS-5734™). In a study of Severe Acute Respiratory Syndrome (SARS), a significant reduction in acute respiratory distress syndrome/mortality was observed in 41 patients treated with the combination of LPV/RTV, compared with 111 patients receiving monotherapy ribavirin (2.4 % vs 28.8%, p 0.001). However, the use of historical control data does not allow for a reliable estimation of efficacy. Additionally, LPV/RTV has multiple known adverse reactions such as prolonged QT interval, severe gastrointestinal reactions, abnormal blood glucose, pancreatitis, hepatic impairment, and elevated blood lipids. It has multiple drug-to-drug interactions with many commonly used drugs in clinical practice; thus, its clinical safety is not determined. Remdesivir shows potent in vitro activity against the human pathogenic CoVs Middle East Respiratory Syndrome (MERS)-CoV and SARS-CoV in multiple relevant human cell types. In a mouse model of MERS-CoV infection, both prophylactic and therapeutic RDV significantly improved pulmonary function and reduce lung viral loads and severe lung pathology compared with vehicle control animals. In contrast, prophylactic LPV/RTV + interferon-beta (LPV/RTV-IFNb) slightly reduced viral loads without impacting other disease parameters. Therapeutic LPV/RTV-IFNb improves pulmonary function but did not reduce virus replication or severe lung pathology {Sheahan 2020}.

The evaluation of the safety and potential efficacy of RDV in people with COVID-19 is urgently needed.

1.2. Remdesivir (RDV, GS-5734)

Remdesivir is being developed by Gilead Sciences, Inc. (Gilead) and is formulated for intravenous (IV) administration.

1.2.1. General Information

Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, Ebola virus [EBOV], Marburg virus [MARV]), CoVs (eg, SARS-CoV, MERS-CoV), and paramyxoviruses (eg, respiratory syncytial virus [RSV],

Nipah virus, and Hendra virus). For further information on RDV, refer to the current investigator's brochure (IB) for RDV. Information in the IB includes:

- Nonclinical pharmacokinetic (PK) and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

Additional relevant information regarding RDV are described below.

1.2.2. Preclinical Pharmacology and Toxicology

Recent results from initial in vitro testing performed at the China CDC in collaboration with Gilead showed that RDV has potent antiviral activity against SARS-CoV-2 in Vero cells (EC_{50} 0.137 μM). In another study conducted by the Wuhan Institute of Virology, RDV also showed in vitro activity against SARS-CoV-2 in Vero cells (EC_{50} 0.77 μM){Wang 2020}. Gilead notes that the study from the Wuhan Institute of Virology was conducted externally with drug not supplied by Gilead. Researchers in the United States (US) and China are continuing to test RDV against clinical isolates of SARS-CoV-2 using drug supplied by Gilead in multiple relevant cell types that are known to more efficiently metabolize RDV into its active triphosphate form compared with Vero cells.

1.3. Rationale for This Study

There is currently no approved treatment available for COVID-19 infection. The recommendation for using RDV as treatment of COVID-19 is based on the in vitro and in vivo activity of RDV against SARS-CoV-2 and other human highly pathogenic CoVs, MERS-CoV and SARS-CoV.

Remdesivir has acceptable nonclinical tolerability and safety profiles and exhibits in vivo prophylactic and therapeutic efficacy against SARS-CoV and MERS-CoV infection in mice and MERS-CoV infection in rhesus monkeys. In addition, RDV has been shown to be safe and tolerable; with a safety database of over 500 individuals who have received RDV to date. Key attributes of the RDV nonclinical and clinical profile supporting its use for treatment of COVID-19 are as follows:

- Initial in vitro testing performed at the China CDC in collaboration with Gilead showed that RDV has potent antiviral activity against SARS-CoV-2 in Vero cells (EC_{50} 0.137 μM). Remdesivir has also shown potent in vitro activity against the human pathogenic CoVs MERS-CoV and SARS-CoV in multiple relevant human cell types.
- The PK profile of RDV in nonhuman primates (NHPs) and other relevant animal species indicates high and persistent levels of pharmacologically active nucleoside triphosphate metabolite in peripheral blood mononuclear cells (PBMCs), supporting once daily IV administration as a 30-minute infusion.

- Remdesivir demonstrated prophylactic and therapeutic efficacy in a mouse model of SARS- CoV pathogenesis. Administration of 25 mg/kg RDV subcutaneously twice daily beginning 1 day before or 1 day after SARS-CoV inoculation resulted in significantly reduced lung viral load and improved clinical signs of disease as well as lung function {Sheahan 2017}.

- In a mouse model of MERS-CoV pathogenesis, both prophylactic and therapeutic administration of 25 mg/kg RDV subcutaneously twice daily improved pulmonary function and reduced lung viral loads and severe lung pathology. In contrast, prophylactic LPV/RTV IFNb slightly reduced viral loads without impacting other disease parameters. Therapeutic LPV/RTV-IFNb improved pulmonary function but did not reduce virus replication or severe lung pathology {Sheahan 2020}.

- Remdesivir also showed prophylactic and therapeutic efficacy in MERS-CoV-infected rhesus monkeys of Indian origin. Administration of RDV at 10 mg/kg (see RDV IB) or 5 mg/kg once daily for 7 days using IV bolus injection beginning 1 day prior to MERS-CoV inoculation resulted in a significant reduction of clinical scores, clinical signs of respiratory disease, and viral RNA levels compared to vehicle-treated animals. Therapeutic RDV treatment of 5 mg/kg once daily using IV bolus injection initiated 12 hours post- inoculation also resulted in reduced clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions {De Wit 2020}.

Remdesivir has a favorable clinical safety profile based on approximately 500 individuals who received RDV primarily as healthy volunteers in Phase 1 studies and individuals with acute EBOV infection.

1.4. Rationale for Dose Selection of Remdesivir

The proposed regimen for the treatment of established CoV infection, including SARS-CoV and MERS-CoV, is as follows: single RDV 200 mg IV loading dose on Day 1 of treatment followed by 100 mg IV once-daily maintenance doses for a total of up to 10 days of dosing. The proposed dosing regimen is based on efficacy studies in MERS-infected rhesus monkeys treated with RDV (Studies PC-399-2037 and PC-399-2038) and based on clinical safety data in approximately 500 patients including healthy volunteers and individuals with acute EBOV infection.

In the nonclinical studies, RDV was administered at 10 mg/kg (Study PC-399-2038) or 5 mg/kg (Study PC-399-2037) once daily for 7 days using IV bolus injection beginning either 1 day prior to or 12 hours after (5 mg/kg only) MERS-CoV inoculation. Remdesivir treatment was efficacious at reducing viral titers in the lung and alleviating clinical disease signs (RDV IB; {De Wit 2020}). Toxicology studies in cynomolgus monkeys and rats and safety and PK studies in healthy volunteers support the safety of the proposed dose. Overall, RDV has a favorable PK and safety profile that supports evaluation of a 200 mg loading and a 100 mg daily dose that has potential to be efficacious in adult patients with COVID-19.

1.5. Risk/Benefit Assessment for the Study

A pertinent specific risk for participants in this study is the potential for transient, Grade ≤ 2, treatment-emergent elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were observed after multiple daily RDV administrations in Studies GS-US-399-1954 and GS-US-399-5505.

To date in human studies, no serious adverse events (SAEs) have occurred in healthy individuals who have received at least 1 dose of RDV. Remdesivir has been tested in healthy volunteers as a single ascending dose over a dose range of 3 to 225 mg and in a multi-dose study of 150mg for up to 14 days and at 200 mg loading dose followed by 100mg for a total of 10 days.

In nonclinical animal studies, toxicity findings were consistent with dose-dependent and reversible kidney injury and dysfunction. The clinical significance of the nephrotoxicity noted in animal species is unknown. The etiology of reversible kidney injury observed in rats is consistent with the ability of rat renal organic anion transporters (OATs), but not human OATs, to efficiently interact with blood metabolites of RDV, particularly GS-704277. This effect may lead to proportionally higher intracellular accumulation of drug metabolites in renal rat tubules, leading to kidney injury.

The 200 mg loading dose with 8 g of sulfobutylether β-cyclodextrin sodium (SBECD) on Day 1 will be followed by 100 mg of RDV each day for 4 or 9 days with 4 g of SBECD, which is within the range of daily SBECD administration considered safe in humans. A total of 250 mg/kg/day of SBECD is considered safe by the European Medicines Agency and is therefore safe for all adults with weight over 32 kg. The 100 mg dose prepared in 0.9% saline will be hypertonic relative to human serum osmolality but approaches the normal physiological osmolar range for humans. The RDV regimen consisting of a loading dose of 200 mg followed by RDV 100 mg daily for up to 9 days is not anticipated to pose a safety risk to participants enrolled in this study.

There are currently no data available on the interaction of RDV and other investigational agents. Administering RDV concurrent with other investigational anti-CoV agents may lead to antagonism or synergy or have no effect.

The risk mitigation strategy for this study includes restriction of the study population to those without a history of significant renal or hepatic disease:

- Exclusion of participants with ALT > 5 × ULN
- Exclusion of participants with an estimated glomerular filtration rate (eGFR) < 50 mL/min
- Exclusion of coadministration of other investigational agents against COVID-19
- Serum chemistry assessments, including liver function testing, will be closely monitored during the study period.

There are currently no investigational agents with demonstrated clinical efficacy or approved treatments for COVID-19. The timely evaluation of a safe and effective antiviral agent that works by directly and selectively blocking the virus replication and is broadly efficacious against COVID-19 addresses a serious unmet medical need. In consideration of the information included in this protocol, the overall risks to participants are outweighed by the potential benefits of RDV experimental therapy for the treatment of COVID-19. The benefit-risk balance for this study is considered positive.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The purpose of this study is to provide RDV to participants with severe COVID-19.

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens with respect to the normalization of temperature and oxygen saturation through Day 14

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV

3. STUDY DESIGN

This study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19 infection. All participants will continue to receive SOC therapy according to local guidelines.

3.1. Endpoints

The primary endpoint of this study is:

- The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: temperature < 36.6°C armpit, < 37.2°C oral, < 37.8°C rectal; and SpO_2 > 94%, sustained for at least 24 hours] through Day 14

The secondary endpoint of this study is:

- The proportion of participants with treatment emergent adverse events leading to study drug discontinuation

Other endpoints of interest are:

- Time to SpO2 > 94% on room air
- Time to first fever normalization (criteria for normalization: temperature < 36.6°C armpit, < 37.2°C oral, < 37.8°C rectal)
- Time to first negative SARS-CoV-2 polymerase chain reaction (PCR)
- Duration of oxygen therapy
- Duration of hospitalization (days)
- All cause mortality at Day 28
- Time to clinical improvement (days): Clinical improvement is defined using a 6-point ordinal scale at Day 1 status dropped by 2 points or discharge
- Plasma concentrations of RDV and GS-441524

3.2. Study Design

This study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19. Eligible participants will be randomized in equal proportions to 1 of 2 treatment groups. No stratification will be performed.

3.3. Study Treatments

Approximately 400 participants who meet all eligibility criteria may be randomized in a 1:1 ratio into 1 of the following treatment groups:

Treatment Group 1: continued standard of care therapy together with IV RDV200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

Treatment Group 2: continued standard of care therapy together with IV RDV200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

3.4. Duration of Treatment

Participants will receive study treatment with RDV for 5 days (treatment group 1) or 10 days (treatment group 2). If the participant is discharged, RDV treatment will stop at that time.

3.5. Discontinuation Criteria

Study drug dosing in an individual subject will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if a participant experiences:

- Any SAE or ≥ Grade 3 AE suspected to be related to RDV.
- Any elevations in ALT > 5 × ULN; or ALT > 3 × ULN and total bilirubin > 2 ×ULN, confirmed by immediate repeat testing.
- Creatinine clearance < 30mL/min

3.6. End of Study

The end of the study will be the last participant's last observation (or visit).

3.7. Post Study Care

The long-term care of the participant will remain the responsibility of their primary treating physician. Remdesivir is being supplied with curative intent. There is no provision for post-study availability.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 400 participants will be randomized in a 1:1 ratio into 1 of 2 treatment groups.

4.1.1. Subject Replacement

Subjects who discontinue prior to the end of study will not be replaced.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Willing and able to provide written informed consent prior to performing study procedures

2) Aged ≥ 18 years

3) SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization

4) Currently hospitalized with fever defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, ≥ 37.8 °C rectal

5) SpO_2 ≤ 94% on room air at screening

6) Radiographic evidence of pulmonary infiltrates

7) Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Participation in any other clinical trial of an experimental treatment for COVID-19

2) Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 is prohibited < 24 hours prior to study drug dosing

3) Evidence of multiorgan failure

4) Requiring mechanical ventilation at screening

5) ALT or AST > 5 × ULN

6) Creatinine clearance < 50 mL/min

7) Positive pregnancy test (Appendix 3)

8) Breastfeeding woman

9) Known hypersensitivity to the study drug, the metabolites, or formulation excipient

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to 1 of 2 treatment groups on Day 1 using an IWRS and assigned a subject number. Randomization will not be stratified.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Remdesivir

5.2.1. Formulation

Remdesivir for injection, 100 mg, is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 mg of GS-5734 that is to be reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion.

In addition to the active ingredient, RDV for injection, 100 mg, contains the following inactive ingredients: betadex sulfobutyl ether sodium (SBECD), water for injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0.

5.2.2. Packaging and Labeling

Remdesivir for injection, 100 mg, is supplied as a sterile product in a single-use, 30 mL Type I clear glass vial. Each vial is sealed with a fluoro-resin laminated rubber stopper and an aluminum overseal with a red, plastic flip-off cap.

Remdesivir for injection, 100 mg, shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), the J-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs), as applicable, and/or other local regulations.

5.2.3. Storage and Handling

Remdesivir for injection, 100 mg, should be stored below 30 °C (86 °F) prior to use. Storage conditions are specified on the label. Until dispensed for dosing, all vials of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the sterility, stability, and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

Remdesivir for injection, 100 mg, is recommended to be reconstituted and diluted on the same day as administration. Remdesivir for injection, 100 mg, does not contain any preservative and is intended for single-use. Any unused RDV material should be discarded.

5.3. Dosage and Administration of Remdesivir

Remdesivir for injection, 100 mg, will be provided by Gilead. Participants in treatment groups 1 and 2 will receive RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5. Participants in treatment group 2 will also receive RDV 100 mg on Days 6, 7, 8, 9, and 10.

5.4. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition).

Each study site must keep accountability records that capture:

- The date received and quantity of study drug kits
- The date, subject number, and the study drug kit number dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.4.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for eTMF. If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

5.5. Prior and Concomitant Medications

Concomitant use of the following is prohibited in participants receiving RDV and needs to be discontinued at minimum 24 hours prior to receiving first dose of study treatment:

- Investigational agents for COVID-19 including approved HIV protease inhibitors such as lopinavir/ritonavir.

If the local standard of care per written policies or guidelines (ie, not just an individual clinician decision) includes lopinavir/ritonavir or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site. Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for RDV dose modification above. Otherwise, concomitant use of lopinavir/ritonavir and RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications will be captured in this trial. The list of medications will be assessed only from Day 1 prior to enrollment to Day 14 or discharge whichever is earlier.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify the Gilead or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 2 days before randomization and dosing to determine eligibility for participation in the study.

- Obtain written informed consent.

After the informed consent the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Focused medical history including the following information (eg, date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics), allergies and medical history
- Review and record medications and therapies for this current illness
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy
- Targeted physical examination including, vital signs (heart rate, temperature, blood pressure), body weight, and height
- Documentation of respiratory status:
  - Respiratory Rate
  - Oxygen supplementation: room air, nasal canula, face mask, mechanical ventilation
  - SpO_2 at rest or PaO_2
  - Radiographic findings

- Obtain blood samples if not done in the preceding 48 hours for creatinine clearance, ALT and AST
- Pregnancy test (for women of childbearing potential)
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent form.

Study subjects who qualify should be immediately randomized. Randomization and dosing should occur on the same day if possible.

6.2.2. Baseline/Day 1 Assessments

The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility before proceeding with randomization on the Day 1 visit. If the screening and Day 1 visits occur within one day, no procedures need to be repeated. Participants must complete the following assessments before being administered study drug:

- Physical examination including vital signs (heart rate, temperature, blood pressure, and body weight)
- Documentation of respiratory status:

  Respiratory rate

  Oxygen supplementation: room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO Oxygenation: (SpO_2 or PaO_2)

  Radiographic findings (if available)
- Review AEs and document concomitant medications
- Obtain blood samples for white blood cell count, hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST
- Obtain blood sample for sparse *or* intensive pharmacokinetic assessments (optional for subjects/sites participating in this portion of the study)
- Review the Ordinal Scale (see Section 6.9)

6.3. Daily Study Assessments (Days 2-14)

The following evaluations are to be completed daily from Days 2 14 or until discharge whichever comes earlier:

- Vital signs (heart rate, temperature, blood pressure), body weight (if available).
- A symptom-directed (targeted) physical examination will be performed to evaluate for any possible adverse event
- Documentation of respiratory status:

  Respiratory rate

  Oxygen supplementation: room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO Oxygenation: (SpO_2 or PaO_2)

  Radiographic findings (if available)
- SARS-CoV-2 testing results if available should be reported
- Review of AEs and document concomitant medications
- Review Ordinal Scale

6.4. Additional Assessments (Days 3, 5, 8, 10, and 14)

The following evaluations are to be completed at Days 3, 5, 8, 10, and 14 or until discharge whichever comes earlier:

- Safety laboratory tests (white blood cell count, hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST)
- Pharmacokinetic Assessments (sparse *or* intensive) are to be completed at Day 2, 4, 5, 7, and 10 (optional for subjects/sites participating in this portion of the study) or until discharge whichever comes earlier

6.5. Day 28 Follow up Assessment

The following evaluations are to be completed if this visit is conducted in person. For participants who have been discharged from hospital, the final evaluation can be made by phone. Only AE and concomitant medication review is to be completed if visit is conducted by phone.

- Physical examination and vital signs (heart rate, temperature, blood pressure)

- Documentation of respiratory status:

  Respiratory rate

  — Oxygen supplementation: room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO

  Oxygenation: (SpO_2 or PaO_2)

  Radiographic findings (if available)

- Review AEs and document concomitant medications

- Review the Ordinal Scale

6.6. Clinical Laboratory Assessments

Clinical laboratory assessments are required at screening, Days 1, 3, 5, 8, 10 and 14 or until discharge whichever comes earlier. Clinical laboratory assessments at other days may be conducted if required by clinical need or local practice. All laboratory testing will be completed by local laboratories. From Day 1 to Day 14, at specified timepoints, the sponsor will be provided with results for the following analytes: white blood cell count, hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing.

SARS-CoV-2 testing may include RT-qPCR to detect or quantify SARS-CoV-2 or virus sequencing results. If feasible, oropharyngeal, saliva, sputum, stool, and/or blood samples may be collected and assayed using RT-qPCR to quantify SARS-CoV-2 viral load. Pretreatment and posttreatment samples with detectable SARS-CoV-2 may be sequenced for resistance monitoring of the viral polymerase gene if possible.

For all clinical laboratory tests, except those at Day 1, when more than 1 result is available in a calendar day, the highest result should be reported in the eCRF except for creatinine clearance where the lowest result should be recorded. For Day 1 tests, the most recent result before dosing should be used. All SARS-CoV-2 results should be provided

6.7. Physical Examination

A targeted physical examination and vital signs (heart rate, respiratory rate, temperature, blood pressure, SpO_2 at rest or PaO_2) should be performed at least daily.

6.8. Pharmacokinetic Assessments

Pharmacokinetic (PK) assessments may be conducted at selected sites for local analysis. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-dose and end of infusion), and Day 7 (pre-dose and end of infusion). Up to 20 participants

(10/group) may have intensive PK samples collected at Day 1, and Day 5 (treatment group 1), or Day 10 (treatment group 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV. Further details will be provided in the PK assessment manual.

6.9. Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worst (i.e. lowest ordinal) score from the previous day will be recorded. i.e. on Day 3, the lowest ordinal score from Day 2 is obtained and recorded for Day 2. The scale is as follows:

1. Death

2. Hospitalized, on invasive mechanical ventilation or ECMO

3. Hospitalized, on non-invasive ventilation or high flow oxygen devices

4. Hospitalized, requiring supplemental oxygen

5. Hospitalized, not requiring supplemental oxygen

6. Discharged

6.10. Post-treatment Assessments

No assessments are required after Day 28.

6.11. Assessments for Early Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE or clinically significant laboratory abnormality), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 3.5, Discontinuation Criteria). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.11.1. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Discharge from the hospital/institution
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)

6.12. End of Study

The end of the study will occur when the last participant's last observation (or visit).

6.13. Post Study Care

The long-term care of the participant will remain the responsibility of their primary treating physician. Remdesivir is being supplied with curative intent. There is no provision for post-study availability.

6.14. Sample Disposition and Storage

Samples will be processed and retained according to local practice and the regulations pertaining to each institution. No samples will be obtained or retained by Gilead.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. AEs may also include pretreatment or posttreatment complications that occur as a result of protocol specified procedures or special situations (Section 7.6).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented as medical history.
- Preexisting events or conditions that increase in severity or change in nature after the consent form is signed or as a consequence of participation in the clinical study will be considered AEs

7.1.2. Serious Adverse Events

A SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode,

the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AE related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, throughout the duration of the study, including the protocol-required post treatment follow-up period must be reported on the eCRFs as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period must be reported on the applicable eCRFs and Pharmacovigilance an Epidemiology (PVE) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post-treatment follow-up visit but within 30-days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PVE.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guidelines.

7.3.3.1. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If it is not possible to record and submit the SAE information electronically, because the eCRF database cannot be accessed or is not available (including at study-start), record the SAE on the paper SAE reporting form and submit within 24 hours to:

  Gilead PVE
  Email: PPD
  or
  Fax: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed on the applicable eCRFs according to instructions and within the timelines outlined in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Union (EU) Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an investigational product while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an investigational product by a subject.

Misuse is defined as any intentional and inappropriate use of an investigational product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of an investigational product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to an investigational product as a result of one's professional or non-professional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead investigational product.

Counterfeit or falsified medicine: Any investigational product with a false representation of: a) its identity, b) its source, or c) its history.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug and throughout the study, including the post study drug follow-up period, to the Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Gilead PVE
Email: PPD
or
Fax: PPD

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.3.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
email: PPD and fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to the Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Gilead PVE
Email: PPD
or
Fax: PPD

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for instructions on special situation reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

The purpose of this study is to provide RDV to participants with severe COVID-19.

8.1.1. Analysis Objectives

The analysis objectives of this study are as follows:

- To evaluate the efficacy of 2 RDV regimens with respect to the normalization of temperature and Spo_2 through Day 14
- To evaluate the safety and tolerability of RDV

8.1.2. Primary Endpoint

The primary endpoint of this study is:

- The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: T < 36.6 C armpit, < 37.2 C oral, < 37.8C rectal; and Sp02 > 94%, sustained for at least 24 hours] through Day 14

8.1.3. Secondary Endpoint

The secondary endpoint of this study is:

- The proportion of participants with treatment emergent adverse events leading to study drug discontinuation.

8.1.4. Other Endpoints of Interest

Other endpoints of interest are:

- Time to SpO2 > 94% on room air
- Time to first fever normalization
- Time to first negative SARS-CoV-2 PCR
- Duration of oxygen therapy (day)
- Duration of hospitalization (day)
- All cause mortality at day 28

- Time to clinical improvement (day): Clinical improvement defined as 6-point scale of admission status dropped by 2-point or discharge
- Plasma concentrations of RDV and GS-441524

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program or for other purposes.

8.2.1.1. DMC Analysis

The DMC will review safety and efficacy data on a regular basis. There will be one planned DMC analysis conducted after approximately 50% of participants have been randomized.

8.2.2. Final Analysis

The final analysis will be performed after all participants have completed the study or prematurely terminated from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The analysis of the primary endpoint (normalization of fever and oxygen saturation at Day 14) will be conducted at the time of the final analysis.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analysis is defined as the full analysis set (FAS), which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment which they received.

8.3.2. Data Handling Conventions

Natural logarithm transformation for PK parameters will be applied for PK analysis.

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at pre-dose and one-half of the lower limit of quantitation (LLOQ) for post dose time points

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation, will be imputed to the value of the lower or upper limit plus or minus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed. However, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

All available data for participants that do not complete the study will be included in data listings

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age. For categorical demographic and baseline characteristics, a Cochran Mantel Haenszel test will be used to compare treatment groups. For continuous demographic and baseline characteristics, a Wilcoxon rank sum test will be used to compare treatment groups.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The proportions of participants in the FAS with normalization of fever and oxygen saturation through Day 14 will be compared between the 2 groups using a chi-square test. The point estimate of the treatment difference and the associated 95% confidence interval will be provided. Participants who are discharged prior to Day 14 will be considered as achieving normalization. Participants who die or drop out of the study prior to Day 14 without normalization will be considered as not achieving normalization.

8.5.2. Secondary Analyses

The secondary endpoint of proportion of participants with treatment emergent AEs leading to study drug discontinuation will be compared between the 2 groups using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. Secondary or other endpoints of interest related to proportion of participants will be compared between treatment groups using a chi-square test or Fisher's Exact test. Endpoints that are measured as time from randomization or start of dosing will be compared between treatment groups using the Log-Rank test and continuous endpoints will be compared between treatment groups using a Wilcoxon rank sum test or analysis of variance model.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed through the Day 28 follow-up visit will be summarized by treatment group (according to the study drug received). Data for the period will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days.

Summaries (number and percentage of participants) of treatment-emergent AEs (by SOC, and PT) will be provided by treatment group.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 dated July 2017.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment will be included in a data listing.

8.7. Pharmacokinetic Analysis:

Plasma concentrations and PK parameters for RDV and GS-441524 metabolite may be listed and summarized using descriptive statistics by group.

8.8. Adjustments for Multiplicity

The DMC charter will include stopping rules for safety, along with alpha spending considerations. No other adjustments for multiple comparisons are planned.

8.9. Sample Size

A sample size of 400 participants (200 in each group) achieves approximately 85% power to detect a difference of 15% between the 5-day treatment group and the 10-day treatment group, assuming a response rate of 45% in the 5-day treatment group and 60% in the 10-day treatment group and a two-sided significance level of 0.05.

8.10. Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) includes independent experts that do not have direct involvement in the conduct of the study. The IDMC will review the progress of the study and perform interim reviews of safety data, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.
The IDMC's specific activities will be defined by a mutually agreed charter, which will define the IDMC's membership, conduct and meeting schedule.

While the IDMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations including the principles of the Declaration of Helsinki.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB or IEC. No biological samples will be provided to Gilead or any central laboratory during this study. NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator's brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, paper or electronic completed subject CRFs, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification;
- Documentation that subject meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);
- Study discussed and date of informed consent;

- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE;
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF Completion Guidelines (eCCGs) provided by the Sponsor. Subsequent to data entry, a study monitor will perform source data verification (SDV) within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator or other

designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authorities, IRB/IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

De Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and Therapeutic Remdesivir (GS-5734) Treatment in the Rhesus Macaque Model of MERS-CoV Infection. PNAS Latest Articles 2020.

Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-Spectrum Antiviral GS-5734 Inhibits Both Epidemic and Zoonotic Coronaviruses. Science translational medicine 2017:1-20.

Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative Therapeutic Efficacy of Remdesivir and Combination Lopinavir, Ritonavir, and Interferon Beta Against MERS-CoV. Nature communications 2020;11:222.

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus (2019-nCoV) In Vitro. Cell research 2020:1-3.

World Health Organisation (WHO). Coronavirus Disease 2019 (COVID-19) Situation Report - 34. 2020.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19

Original protocol 24 February 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD PPD

Name (Printed)
[Responsible Person's Title]

24 Feb 2020
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) Signature

Date Site Number

Appendix 2. Study Procedures Table

	Screening	Baseline / Day 1[b]	Day 2	Day 3	Day 4	Day 5	Days 6 and 7	Day 8	Day 9	Day 10	Days 12 and 13	Day 14	Day 28[c] Follow-up
Written Informed Consent	X												
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Laboratory Testing	X	X		X		X		X		X		X	
Respiratory Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X											X	
PK Assessments[d]		X	X		X	X	X			X			
RDV Dosing for Group 1		X	X	X	X	X							
RDV Dosing for Group 2		X	X	X	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

a Includes heart rate, respiratory rate, temperature, blood pressure, SpO_2 at rest, and body weight. Body weight collected on screening and Day 1 and otherwise if available.
b Assessments need not be repeated if performed the same calendar day as screening procedures.; data collection other than adverse events should stop Day 14 or discharge whichever is earlier.
c Day 28 evaluations completed if the visit is conducted in person. Only AEs, ordinal scale, and concomitant medication review completed if visit conducted by phone.
d PK assessments sparse *or* intensive (optional for subjects/sites participating in this portion of the study) on Day 1, 2, 4, 5, 7, and 10.

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. No documentation of Tanner stage will be required for people unless deemed prepubescent.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age. Tubal ligation is not considered a method of permanent sterilization for the purposes of this study.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from nonclinical studies of RDV have demonstrated no adverse effect on fertility or embryo-fetal development. Remdesivir has not yet been studied in pregnant women. Before enrolling into studies with RDV, women of childbearing potential must have pregnancy testing performed at screening.

Available data indicate that RDV potentially causes an interaction with hormonal contraception that is considered of limited significance. Hormonal methods must be used with a barrier method.

Please refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at screening. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for women of childbearing potential with infrequent or irregular periods. They must also agree to 1 of the following from Screening until the last dose of the study drug:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  Non-hormonal intrauterine device (IUD)

  Hormonal IUD (must be used with a barrier method)

  Tubal sterilization

  Essure® micro-insert system (provided confirmation of success 3 months after procedure)

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  Barrier methods

  - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
  - Male barriers: Male condom (with or without spermicide)

  Hormonal methods are restricted to drugs associated with the inhibition of ovulation. Each method must be used with a barrier method, preferably male condom. Hormonally-based contraceptives permitted for use in this protocol are as follows:

  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Contraceptive methods must be locally approved to be permitted.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until the last study drug dose.

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

3) Contraception Requirements for Male Subjects

During the study male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg. calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). A Female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	147753
EudraCT Number:	2020-000841-15
Clinical Trials.gov Identifier:	NCT04292899
Indication:	COVID-19
Protocol ID:	GS-US-540-5773
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 24 February 2020 Amendment 1.0: 15 March 2020 Amendment 2.0: 20 March 2020

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312); however, sites located in the European Economic Area and Switzerland are not included under the IND and are considered non-IND sites.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	147753 2020-000841-15 NCT04292899
Study Centers Planned:	Up to approximately 100 centers globally
Objectives:	The purpose of this study is to provide remdesivir (RDV) to participants with severe COVID-19. The primary objective of this study is as follows: • To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14 The secondary objective of this study is as follows: • To evaluate the safety and tolerability of RDV
Study Design:	This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in participants with severe COVID-19. The study will be conducted in two parts. In Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated may be randomized in a 1:1 ratio into one of the following treatment groups: **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

	Part B will enroll participants on mechanical ventilation and, after enrollment to Part A is complete, any additional participants. In Part B, up to an additional approximately 2000 participants who meet all of the eligibility criteria will be enrolled, based on whether they are mechanically ventilated at enrollment, to receive: **Mechanically Ventilated Treatment Group*:*** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 **Extension Treatment Group:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Enrollment in the mechanically ventilated treatment group will be capped at approximately 500 participants. If the 5-day dosing regimen used in Treatment Group 1 of Part A is selected for Part B, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days. National and local regulatory authorities will be informed. Participants in Part A of the study will be the primary efficacy population. Participants enrolled in Part B will have data reported descriptively at study completion.
Number of Subjects Planned:	Approximately 2400
Target Population:	Participants with severe COVID-19
Duration of Treatment:	The duration of treatment with RDV will be up to 10 days
Diagnosis and Main Eligibility Criteria:	Participants with COVID-19 confirmed by polymerase chain reaction (PCR) who meet the following criteria: • Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (age ≥18), or willing and able to provide assent (age ≥12 to <18, where locally and nationally approved) prior to performing study procedures • Hospitalized

- $SpO_2 \leq 94$ % on room air or requiring supplemental oxygen at screening
- Radiographic evidence of pulmonary infiltrates

Study Procedures/ Frequency:

At screening, after the participant has provided informed consent or assent, demographic and baseline characteristics, medical history, and concomitant medications will be documented. Vital signs including temperature, respiratory rate, and SpO_2 will be recorded. Radiographic imaging will be performed if not already available. SARS-CoV-2 testing by PCR testing will be performed; if this testing has been performed within the previous 4 days, no repeat testing is required.

If safety laboratory results from the screening day are not already available, laboratory testing including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum creatinine, and creatinine clearance will be performed according to local practice.

In Part A, after screening procedures, eligible participants will be randomized into 1 of the 2 treatment groups in a 1:1 ratio to receive:

Treatment Group 1: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

Treatment Group 2: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

In Part B, after screening procedures, eligible participants will be assigned to receive:

Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Extension Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 as determined by review of the data. Treatment may be reduced to a total of 5 days following analysis of the data from Part A.

The date of randomization will be considered Day 1 and all participants randomized to receive RDV should receive their initial dose on Day 1.

	On study Days 1 through 14 or until discharge, whichever is earlier, 7-point ordinal scale of clinical status, vital signs including respiratory status will be measured and adverse events (AEs) and concomitant medications will be documented. Laboratory testing will be performed according to SOC practice with results for white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing being reported to the Sponsor. In addition, even if not performed as standard of care, white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST will be performed at Days 1, 3, 5, 8, 10, and 14 or until discharge, whichever is earlier. Pharmacokinetic (PK) assessments may be conducted at selected sites. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-infusion and end of infusion), and Day 7 (pre-infusion and end of infusion). Up to 20 participants (10/group) may have intensive PK samples collected at Day 1, and Day 5 (Treatment Group 1), or Day 10 (Treatment Group 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV.
Test Product, Dose, and Mode of Administration:	Remdesivir (GS-5734) for injection, 100 mg, for IV administration
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	Incidence of treatment-emergent AEs and treatment-emergent clinical laboratory abnormalities
Efficacy:	Clinical status assessed by a 7-point ordinal scale on Day 14
Statistical Methods:	The primary endpoint will be analyzed using a proportional odds model. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the two treatment groups (i.e., whether the common odds ratio is equal to 1). The odds ratio and 95% confidence interval will be provided.

Treatment-emergent AEs and laboratory abnormalities will be summarized using descriptive statistics and listed by subject.

Plasma concentrations and PK parameters (if applicable) for RDV and the GS-441524 metabolite may be listed and summarized using descriptive statistics by group.

Sample Size:

In Part A, a total of approximately 400 participants will be randomized in a 1:1 ratio to 2 groups (200 participants per group)

A sample size of 400 participants (200 participants in each group) achieves > 85 % power to detect an odds ratio of 1.75 using a two-sided significance level of 0.05.

The sample size for Part B is based on the anticipated need for RDV and current trends in the COVID-19 epidemic.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°F	Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{tau}	area under plasma concentration-time curve over dosing interval
BLQ	below the limit of quantitation
CDC	Centers for Disease Control and Prevention
CoV	Coronavirus
CRF	case report form
CRO	contract/clinical research organization
CSR	clinical study report
d	deciliter
DAIDS	Division of AIDS
DMC	data monitoring committee
EBOV	Ebola virus
eCCGs	eCRF Completion Guidelines
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
eSAE	Electronic Serious Adverse Event
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
g	grams
GCP	Good Clinical Practice
Gilead	Gilead Sciences
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IB	investigator's brochure
ICH	International Conference on Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device

IV	intravenous
IWRS	interactive web response system
J	Joule
kg	kilogram
LAM	lactational amenorrhea method
LLOQ	lower limit of quantitation
LLT	lower-level term
LPV	lopinavir
LPV/RTV-IFNb	LPV/RTV + interferon-beta
MARV	Marburg virus
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
min	minute
NHPs	nonhuman primates
OAT	organic anion transporter
PBMC	peripheral blood mononuclear cell
PBPK	physiologically-based pharmacokinetic
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PT	preferred term
PVE	Pharmacovigilance and Epidemiology
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
RDV	remdesivir
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTV	ritonavir
SADR	serious adverse drug reaction
SAE	serious adverse event
SARS	Severe Acute Respiratory Syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
SDV	source data verification
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TM	test method
ULN	upper limit of normal
US	United States
V-A ECMO	Veno-arterial extracorporeal membrane oxygenation

V-V ECMO	Veno-venous extracorporeal membrane oxygenation
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China. Sequencing analysis from the patients' respiratory tract samples indicated a novel coronavirus (CoV), which was named COVID-19. As of 23 February 2020, more than 78,000 confirmed cases have been identified in Wuhan, other provinces in China, and in multiple countries outside China {World Health Organisation (WHO) 2020}. More than 2400 deaths associated with COVID-19 have been reported, making COVID-19 a major health emergency.

Antiviral drugs that are being evaluated as potential treatments for COVID-19 include lopinavir/ritonavir (LPV/RTV; used in the treatment of HIV infection) and remdesivir (RDV, GS-5734™). In a study of Severe Acute Respiratory Syndrome (SARS), a significant reduction in acute respiratory distress syndrome/mortality was observed in 41 patients treated with the combination of LPV/RTV, compared with 111 patients receiving monotherapy ribavirin (2.4 % vs 28.8%, p 0.001). However, the use of historical control data does not allow for a reliable estimation of efficacy. Additionally, LPV/RTV has multiple known adverse reactions such as prolonged QT interval, severe gastrointestinal reactions, abnormal blood glucose, pancreatitis, hepatic impairment, and elevated blood lipids. It has multiple drug-to-drug interactions with many commonly used drugs in clinical practice; thus, its clinical safety is not determined. Remdesivir shows potent in vitro activity against the human pathogenic CoVs Middle East Respiratory Syndrome (MERS)-CoV and SARS-CoV in multiple relevant human cell types. In a mouse model of MERS-CoV infection, both prophylactic and therapeutic RDV significantly improved pulmonary function and reduce lung viral loads and severe lung pathology compared with vehicle control animals. In contrast, prophylactic LPV/RTV + interferon-beta (LPV/RTV-IFNb) slightly reduced viral loads without impacting other disease parameters. Therapeutic LPV/RTV-IFNb improves pulmonary function but did not reduce virus replication or severe lung pathology {Sheahan 2020}.

The evaluation of the safety and potential efficacy of RDV in people with COVID-19 is urgently needed.

1.2. Remdesivir (RDV, GS-5734)

Remdesivir is being developed by Gilead Sciences, Inc. (Gilead) and is formulated for intravenous (IV) administration.

1.2.1. General Information

Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, Ebola virus [EBOV], Marburg virus [MARV]), CoVs (eg, SARS-CoV, MERS-CoV), and paramyxoviruses (eg, respiratory syncytial virus [RSV], Nipah virus, and Hendra virus). For further information on RDV, refer to the current investigator's brochure (IB) for RDV. Information in the IB includes:

- Nonclinical pharmacokinetic (PK) and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

Additional relevant information regarding RDV are described below.

1.2.2. Preclinical Pharmacology and Toxicology

Recent results from initial in vitro testing performed at the China CDC in collaboration with Gilead showed that RDV has potent antiviral activity against SARS-CoV-2 in Vero cells (EC_{50} 0.137 μM). In another study conducted by the Wuhan Institute of Virology, RDV also showed in vitro activity against SARS-CoV-2 in Vero cells (EC_{50} 0.77 μM){Wang 2020}. Gilead notes that the study from the Wuhan Institute of Virology was conducted externally with drug not supplied by Gilead. Researchers in the United States (US) and China are continuing to test RDV against clinical isolates of SARS-CoV-2 using drug supplied by Gilead in multiple relevant cell types that are known to more efficiently metabolize RDV into its active triphosphate form compared with Vero cells.

1.3. Rationale for This Study

There is currently no approved treatment available for COVID-19 infection. The recommendation for using RDV as treatment of COVID-19 is based on the in vitro and in vivo activity of RDV against SARS-CoV-2 and other highly pathogenic human CoVs, MERS-CoV and SARS-CoV.

Remdesivir has acceptable nonclinical tolerability and safety profiles and exhibits in vivo prophylactic and therapeutic efficacy against SARS-CoV and MERS-CoV infection in mice and MERS-CoV infection in rhesus monkeys. In addition, RDV has been shown to be safe and tolerable; with a safety database of over 500 individuals who have received RDV to date. Key attributes of the RDV nonclinical and clinical profile supporting its use for treatment of COVID-19 are as follows:

- Initial in vitro testing performed at the China CDC in collaboration with Gilead showed that RDV has potent antiviral activity against SARS-CoV-2 in Vero cells (EC_{50} 0.137 μM). Remdesivir has also shown potent in vitro activity against the human pathogenic CoVs MERS-CoV and SARS-CoV in multiple relevant human cell types.

- The PK profile of RDV in nonhuman primates (NHPs) and other relevant animal species indicates high and persistent levels of pharmacologically active nucleoside triphosphate metabolite in peripheral blood mononuclear cells (PBMCs), supporting once daily IV administration as a 30-minute infusion.
- Remdesivir demonstrated prophylactic and therapeutic efficacy in a mouse model of SARS- CoV pathogenesis. Administration of 25 mg/kg RDV subcutaneously twice daily beginning 1 day before or 1 day after SARS-CoV inoculation resulted in significantly reduced lung viral load and improved clinical signs of disease as well as lung function {Sheahan 2017}.
- In a mouse model of MERS-CoV pathogenesis, both prophylactic and therapeutic administration of 25 mg/kg RDV subcutaneously twice daily improved pulmonary function and reduced lung viral loads and severe lung pathology. In contrast, prophylactic LPV/RTV IFNb slightly reduced viral loads without impacting other disease parameters. Therapeutic LPV/RTV-IFNb improved pulmonary function but did not reduce virus replication or severe lung pathology {Sheahan 2020}.
- Remdesivir also showed prophylactic and therapeutic efficacy in MERS-CoV-infected rhesus monkeys of Indian origin. Administration of RDV at 10 mg/kg (see RDV IB) or 5 mg/kg once daily for 7 days using IV bolus injection beginning 1 day prior to MERS-CoV inoculation resulted in a significant reduction of clinical scores, clinical signs of respiratory disease, and viral RNA levels compared to vehicle-treated animals. Therapeutic RDV treatment of 5 mg/kg once daily using IV bolus injection initiated 12 hours post- inoculation also resulted in reduced clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions {De Wit 2020}.

Remdesivir has a favorable clinical safety profile based on approximately 500 individuals who received RDV primarily as healthy volunteers in Phase 1 studies and individuals with acute EBOV infection.

The design of enrollment in two parts will allow the selection of a preferred duration of treatment to be determined and then allow continued access to RDV and data collection for eligible participants. In addition, further safety data will be obtained.

1.4. Rationale for Dose Selection of Remdesivir

The proposed regimen for the treatment of established CoV infection, including SARS-CoV and MERS-CoV, is as follows: single RDV 200 mg IV loading dose on Day 1 of treatment followed by 100 mg IV once-daily maintenance doses for a total of up to 10 days of dosing. The proposed dosing regimen is based on efficacy studies in MERS-infected rhesus monkeys treated with RDV (Studies PC-399-2037 and PC-399-2038) and based on clinical safety data in approximately 500 patients including healthy volunteers and individuals with acute EBOV infection.

In the nonclinical studies, RDV was administered at 10 mg/kg (Study PC-399-2038) or 5 mg/kg (Study PC-399-2037) once daily for 7 days using IV bolus injection beginning either 1 day prior to or 12 hours after (5 mg/kg only) MERS-CoV inoculation. Remdesivir treatment was

efficacious at reducing viral titers in the lung and alleviating clinical disease signs (RDV IB; {De Wit 2020}). Toxicology studies in cynomolgus monkeys and rats and safety and PK studies in healthy volunteers support the safety of the proposed dose. Overall, RDV has a favorable PK and safety profile that supports evaluation of a 200 mg loading and a 100 mg daily dose that has potential to be efficacious in adult patients with COVID-19.

The optimal duration of therapy with RDV remains unknown. However, other agents for acute antiviral infection, for example oseltamivir phosphate{TAMIFLU® 2019}, have treatment courses ranging from 5 days duration. There is considerable potential patient benefit and societal benefit in identifying the minimum duration that will be effective.

1.4.1. Pediatric Dosing

As with adult dose, the efficacious dose of RDV against SARS-CoV-2 remains to be established.

Dose selection of remdesivir (RDV) in EBOV infected pediatric patients was informed by a physiologically-based pharmacokinetic (PBPK) model implemented in SimCYP (v.17, Certara). Briefly, a PBPK model was developed to characterize the PK of RDV and the inactive primary circulating nucleoside metabolite, GS-441524, in adults. The model was verified based on its ability to describe the mean and variability of the adult exposures using data from the RDV Phase 1 program (GS-US-399-1812). The adult PBPK model was subsequently used to simulate steady-state pediatric (age range 0 to 18 years) exposures (AUC_{tau}), accounting for age-dependent changes in organ volume/size (liver and kidney), esterase expression, plasma protein binding, and organ blood flow.

These simulations do not account for diminished liver or kidney function due to SARS-CoV-2 infection and/or COVID-19 progression because the impact of infection/disease progression on the PK of remdesivir and GS-441524 is currently unknown.

The results of these simulations indicate:

For pediatric patients with body weight ≥ 40 kg, a 200 mg loading dose followed by 100 mg once-daily maintenance doses of remdesivir (ie, the adult dosage regimen) should be administered. Use of the adult dose in these pediatric patients is expected to maintain exposures of both remdesivir and GS-441524 at or below that which was previously observed to be well tolerated in healthy volunteers (N 24, GS-US-399-1954).

1.5. Risk/Benefit Assessment for the Study

Potential risks associated with the study include unknown adverse events (AEs) and laboratory abnormalities. Although not specifically evaluated yet, adolescents with COVID-19 who receive RDV are expected to have a similar safety profile as adults; no additional safety monitoring is required for adolescent participants and no dose adjustments are required. No differing safety profile has been reported for the adolescents with EBOV who received RDV in clinical trials. Accordingly, the risk:benefit profile, described below, is the same for adolescents and adults.

A pertinent specific risk for participants in this study is the potential for transient, Grade ≤ 2, treatment-emergent elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were observed after multiple daily RDV administrations in Studies GS-US-399-1954 and GS-US-399-5505.

To date in human studies, no serious adverse events (SAEs) have occurred in healthy individuals who have received at least 1 dose of RDV. Remdesivir has been tested in healthy volunteers as a single ascending dose over a dose range of 3 to 225 mg and in a multi-dose study of 150 mg for up to 14 days and at 200 mg loading dose followed by 100 mg for a total of 10 days.

In nonclinical animal studies, toxicity findings were consistent with dose-dependent and reversible kidney injury and dysfunction. The clinical significance of the nephrotoxicity noted in animal species is unknown. The etiology of reversible kidney injury observed in rats is consistent with the ability of rat renal organic anion transporters (OATs), but not human OATs, to efficiently interact with blood metabolites of RDV, particularly GS-704277. This effect may lead to proportionally higher intracellular accumulation of drug metabolites in renal rat tubules, leading to kidney injury.

The 200 mg loading dose with 8 g of sulfobutylether β-cyclodextrin sodium (SBECD) on Day 1 will be followed by 100 mg of RDV each day for 4 or 9 days with 4 g of SBECD, which is within the range of daily SBECD administration considered safe in humans. A total of 250 mg/kg/day of SBECD is considered safe by the European Medicines Agency and is therefore safe for people with weight over 32 kg. The 100 mg dose prepared in 0.9% saline will be hypertonic relative to human serum osmolality but approaches the normal physiological osmolar range for humans. The RDV regimen consisting of a loading dose of 200 mg followed by RDV 100 mg daily for up to 9 days is not anticipated to pose a safety risk to participants enrolled in this study.

There are currently no data available on the interaction of RDV and other investigational agents. Administering RDV concurrent with other investigational anti-CoV agents may lead to antagonism or synergy or have no effect.

The risk mitigation strategy for this study includes restriction of the study population to those without a history of significant renal or hepatic disease:

- Exclusion of participants with ALT > 5 × ULN
- Exclusion of participants with an estimated glomerular filtration rate (eGFR) < 50 mL/min
- Exclusion of coadministration of other investigational agents against COVID-19
- Serum chemistry assessments, including liver function testing, will be closely monitored during the study period.

There are currently no investigational agents with demonstrated clinical efficacy or approved treatments for COVID-19. The timely evaluation of a safe and effective antiviral agent that works by directly and selectively blocking the virus replication and is broadly efficacious against COVID-19 addresses a serious unmet medical need. In consideration of the information included in this protocol, the overall risks to participants are outweighed by the potential benefits of RDV experimental therapy for the treatment of COVID-19. The benefit-risk balance for this study is considered positive.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The purpose of this study is to provide RDV to participants with severe COVID-19.

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV

3. STUDY DESIGN

Part A of this study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19 infection. Part B is a two treatment group multicenter study of RDV in participants with severe COVID-19 infection. Treatment group assignment is based on whether the participant is on mechanical ventilation at treatment assignment. All participants will continue to receive SOC therapy according to local guidelines.

3.1. Endpoints

The primary endpoint of this study is:

- Clinical status assessed by a 7-point ordinal scale on Day 14

The secondary endpoint of this study is:

- The proportion of participants with treatment emergent adverse events

Other endpoints of interest are:

- Time to SpO_2 > 94% on room air
- Time to first negative SARS-CoV-2 polymerase chain reaction (PCR)
- Duration of oxygen therapy (days)
- Duration of hospitalization (days)
- All cause mortality at Day 28
- Time to clinical improvement (days): Clinical improvement is defined as a ≥ 2-point improvement from Day 1 on a 7-point ordinal scale
- Plasma concentrations of RDV and GS-441524

3.2. Study Design

Part A of this study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19 infection. Eligible participants will be randomized in equal proportions to 1 of 2 treatment groups. No stratification will be performed. Part B is a two treatment group multicenter study of RDV in participants with severe COVID-19 infection.

3.3. Study Treatments

In Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated may be randomized in a 1:1 ratio into 1 of the following treatment groups:

Treatment Group 1: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

Treatment Group 2: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

In Part B, an additional approximately 2000 participants who meet all of the eligibility criteria may receive:

Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Extension Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected. If treatment for 5 days is selected, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days. National and local regulatory authorities will be informed.

Enrollment in the mechanically ventilated treatment group will be capped at approximately 500 participants.

Participants in Part A of the study will be the primary efficacy population. Participants enrolled in Part B will have data reported descriptively at study completion.

3.4. Duration of Treatment

Participants will receive study treatment with RDV for 5 days (Treatment Group 1), 10 days (Treatment Group 2), 10 days (Mechanically Ventilated Treatment Group), or either 5 or 10 days (Extension Treatment Group). If the participant is discharged, RDV treatment will stop at that time.

3.5. Discontinuation Criteria

Study drug dosing in an individual subject will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if any of the following occurs:

- Any SAE or ≥ Grade 3 AE suspected to be related to RDV.

- Any elevations in ALT > 5 × ULN; or ALT > 3 × ULN and total bilirubin > 2 ×ULN, confirmed by immediate repeat testing.
- Creatinine clearance < 30mL/min

3.6. End of Study

The end of the study will be the last participant's last observation (or visit).

3.7. Post Study Care

The long-term care of the participant will remain the responsibility of their primary treating physician. Remdesivir is being supplied with curative intent. There is no provision for post-study availability.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

In Part A, approximately 400 participants will be randomized in a 1:1 ratio into 1 of 2 treatment groups. In Part B, up to approximately 2000 participants may be assigned to 1 of 2 treatment groups. Rescreening may occur at the investigator's discretion.

4.1.1. Subject Replacement

Subjects who discontinue prior to the end of study will not be replaced.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age), or willing and able to provide assent (participants ≥ 12 and < 18 years of age, where locally and nationally approved) prior to performing study procedures. For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures

2) Aged ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant institutional review board [IRB] or independent ethics committee [IEC])

3) SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization

4) Currently hospitalized

5) SpO_2 ≤ 94% on room air or requiring supplemental oxygen at screening

6) Radiographic evidence of pulmonary infiltrates

7) Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) Participation in any other clinical trial of an experimental treatment for COVID-19

2) Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing

3) Evidence of multiorgan failure

4) Mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO

5) ALT or AST > 5 × ULN

6) Creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age {Cockcroft 1976} and Schwartz Formula for participants < 18 years of age

7) Positive pregnancy test (Appendix 3)

8) Breastfeeding woman

9) Known hypersensitivity to the study drug, the metabolites, or formulation excipient

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Subjects who meet eligibility criteria will be randomized in a 1:1 ratio to 1 of 2 treatment groups on Day 1 using an IWRS and assigned a subject number. Randomization will not be stratified.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Remdesivir

5.2.1. Formulation

Remdesivir for injection, 100 mg, is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 mg of GS-5734 that is to be reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion.

In addition to the active ingredient, RDV for injection, 100 mg, contains the following inactive ingredients: betadex sulfobutyl ether sodium (SBECD), water for injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0.

5.2.2. Packaging and Labeling

Remdesivir for injection, 100 mg, is supplied as a sterile product in a single-use, 30 mL Type I clear glass vial. Each vial is sealed with a fluoro-resin laminated rubber stopper and an aluminum overseal with a red, plastic flip-off cap.

Remdesivir for injection, 100 mg, shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), the J-GCP (Ministerial Ordinance on Good Clinical Practice for Drugs), as applicable, and/or other local regulations.

5.2.3. Storage and Handling

Remdesivir for injection, 100 mg, should be stored below 30 °C (86 °F) prior to use. Storage conditions are specified on the label. Until dispensed for dosing, all vials of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the sterility, stability, and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

Remdesivir for injection, 100 mg, is recommended to be reconstituted and diluted on the same day as administration. Remdesivir for injection, 100 mg, does not contain any preservative and is intended for single-use. Any unused RDV material should be discarded.

5.3. Dosage and Administration of Remdesivir

Remdesivir for injection, 100 mg, will be provided by Gilead. In Part A, participants in Treatment Groups 1 and 2 will receive RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5. Participants in Treatment Group 2 will also receive RDV 100 mg on Days 6, 7, 8, 9, and 10. In Part B, participants in the Mechanically Ventilated Treatment Group will receive IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10. Participants in the Extension Treatment Group will also receive IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected. If treatment for 5 days is selected, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days. Remdesivir treatment will be stopped at discharge regardless of the scheduled duration of therapy. Remdesivir will be administered over 30 minutes where possible.

5.4. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition).

Each study site must keep accountability records that capture:

- The date received and quantity of study drug kits
- The date, subject number, and the study drug kit number dispensed
- The date, quantity of used and unused study drug returned, along with the initials of the person recording the information

5.4.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate SOP for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for eTMF. If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

5.5. Prior and Concomitant Medications

Concomitant use of the following is prohibited in participants receiving RDV and needs to be discontinued at minimum 24 hours prior to receiving first dose of RDV:

- Traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
- Investigational agents for COVID-19 including approved HIV protease inhibitors such as lopinavir/ritonavir, chloroquine, interferon, etc.

Concomitant use of investigational agents such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc while receiving RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

Medications will be assessed only from Day 1 prior to enrollment to Day 14 or discharge, whichever is earlier.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify the Gilead or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 2 days before randomization and dosing to determine eligibility for participation in the study.

- Obtain written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age), or obtain assent (participants age ≥12 to <18, where locally and nationally approved)

After the informed consent the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Focused medical history including the following information (eg, date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics), allergies and medical history
- Review and record medications and therapies for this current illness
- Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy
- Targeted physical examination including, vital signs (heart rate, temperature, blood pressure), body weight, and height
- Documentation of respiratory status:

  Respiratory Rate

— Oxygen supplementation: room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO

Oxygenation: SpO_2 or PaO_2

Radiographic findings

- Obtain blood samples if not done in the preceding 48 hours for creatinine, creatinine clearance, ALT and AST
- Pregnancy test (for women of childbearing potential)
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent (or assent) form.

Study subjects who qualify should be immediately randomized. Randomization and dosing should occur on the same day if possible.

6.2.2. Baseline/Day 1 Assessments

The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility before proceeding with randomization (Part A) or treatment assignment (Part B) on the Day 1 visit. If the screening and Day 1 visits occur within one day, no procedures need to be repeated. Participants must complete the following assessments before being administered study drug:

- Physical examination including vital signs (heart rate, temperature, blood pressure, and body weight)
- Documentation of respiratory status:

  Respiratory rate

  Oxygen supplementation: room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO

  Oxygenation: SpO_2 or PaO_2

  Radiographic findings (if available)
- Review AEs and document concomitant medications
- Obtain blood samples for white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST
- Obtain blood sample for sparse *or* intensive pharmacokinetic assessments (optional for subjects/sites participating in this portion of the study)
- Review the Ordinal Scale (see Section 6.9)

6.3. Daily Study Assessments (Days 2-14)

The following evaluations are to be completed daily from Days 2 14 or until discharge whichever comes earlier:

- Vital signs (heart rate, temperature, blood pressure), body weight (if available).
- A symptom-directed (targeted) physical examination will be performed to evaluate for any possible adverse event
- Documentation of respiratory status:

  Respiratory rate

  Oxygen supplementation: room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO

  Oxygenation: SpO_2 or PaO_2

  Radiographic findings (if available)
- SARS-CoV-2 testing results if available should be reported
- Review of AEs and document concomitant medications
- Review Ordinal Scale (Section 6.9)

6.4. Additional Assessments (Days 3, 5, 8, 10, and 14)

The following evaluations are to be completed at Days 3, 5, 8, 10, and 14 or until discharge whichever comes earlier:

- Safety laboratory tests (white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST)
- Pharmacokinetic Assessments (sparse *or* intensive) are to be completed at Day 2, 4, 5, 7, and 10 (optional for subjects/sites participating in this portion of the study)

6.5. Day 28 Follow up Assessment (±5 Days)

The following evaluations are to be completed if this visit is conducted in person. For participants who have been discharged from hospital, the final evaluation can be made by phone. Only AE and concomitant medication and ordinal scale (if discharged on or after Day 14) review are to be completed if visit is conducted by phone.

- Physical examination and vital signs (heart rate, temperature, blood pressure)

- Documentation of respiratory status:

  Respiratory rate

  — Oxygen supplementation: room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO

  Oxygenation: SpO_2 or PaO_2

  Radiographic findings (if available)

- Review AEs and document concomitant medications

- Review the Ordinal Scale (Section 6.9). If subject was not discharged by Day 14, any change in category and the date of any change in category from Day 14 to discharge (or Day 28) should be recorded

6.6. Clinical Laboratory Assessments

Clinical laboratory assessments are required at screening, Days 1, 3, 5, 8, 10 and 14 or until discharge whichever comes earlier. Clinical laboratory assessments at other days may be conducted if required by clinical need or local practice. All laboratory testing will be completed by local laboratories. From Day 1 to Day 14, at specified timepoints, the sponsor will be provided with results for the following analytes: white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing.

SARS-CoV-2 testing may include RT-qPCR to detect or quantify SARS-CoV-2 or virus sequencing results. If feasible, oropharyngeal, saliva, sputum, stool, and/or blood samples may be collected and assayed using RT-qPCR to quantify SARS-CoV-2 viral load. Pretreatment and posttreatment samples with detectable SARS-CoV-2 may be sequenced for resistance monitoring of the viral polymerase gene if possible.

6.7. Physical Examination

A targeted physical examination and vital signs (heart rate, respiratory rate, temperature, blood pressure, SpO_2 or PaO_2) should be performed at least daily.

6.8. Pharmacokinetic Assessments

Pharmacokinetic (PK) assessments may be conducted at selected sites. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-infusion and end of infusion), and Day 7 (pre-infusion and end of infusion). Up to 20 participants (10/group) may have intensive PK samples collected at Day 1, and Day 5 (Treatment Group 1), or Day 10 (Treatment Group 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV. Further details will be provided in the PK assessment manual.

6.9. Ordinal Scale

The ordinal scale is an assessment of the clinical status at a given study day. Each day, the worst (i.e. lowest ordinal) score from the previous day will be recorded. i.e. on Day 3, the lowest ordinal score from Day 2 is obtained and recorded for Day 2. The scale is as follows:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring low flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration)
7. Not hospitalized

6.10. Post-treatment Assessments

No assessments are required after Day 28.

6.11. Assessments for Early Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE or clinically significant laboratory abnormality), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 3.5, Discontinuation Criteria). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.11.1. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Discharge from the hospital/institution
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB or IEC

6.12. End of Study

The end of the study will occur when the last participant's last observation (or visit).

6.13. Post Study Care

The long-term care of the participant will remain the responsibility of their primary treating physician. Remdesivir is being supplied with curative intent. There is no provision for post-study availability.

6.14. Sample Disposition and Storage (Non-PK Samples)

Samples will be processed and retained according to local practice and the regulations pertaining to each institution. No samples will be obtained or retained by Gilead.

6.15. Sample Disposition and Storage (PK Samples)

The stored PK samples may be used by Gilead or its research partner for the testing of RDV and metabolites during the course of the study or when sample transport is possible. At the conclusion of this study, the PK samples may be retained in storage by Gilead or at its research partner facility for a period up to 15 years.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. AEs may also include pretreatment or posttreatment complications that occur as a result of protocol specified procedures or special situations (Section 7.6).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented as medical history.

Preexisting events or conditions that increase in severity or change in nature after the consent form is signed or as a consequence of participation in the clinical study will be considered AEs

7.1.2. Serious Adverse Events

A SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable eCRFs: all SAEs and AE related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, throughout the duration of the study, including the protocol-required post treatment follow-up period must be reported on the eCRFs as instructed.

All AEs and clinically significant laboratory abnormalities should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period must be reported on the applicable eCRFs and Pharmacovigilance an Epidemiology (PVE) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post-treatment follow-up visit but within 30-days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PVE.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guidelines.

7.3.3.1. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If it is not possible to record and submit the SAE information electronically, because the eCRF database cannot be accessed or is not available (including at study-start), record the SAE on the paper SAE reporting form and submit within 24 hours to:

  Gilead PVE
  Email: PPD
  or
  Fax: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed on the applicable eCRFs according to instructions and within the timelines outlined in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Union (EU) Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of an investigational product while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of an investigational product by a subject.

Misuse is defined as any intentional and inappropriate use of an investigational product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of an investigational product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to an investigational product as a result of one's professional or non-professional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead investigational product.

Counterfeit or falsified medicine: Any investigational product with a false representation of: a) its identity, b) its source, or c) its history.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug and throughout the study, including the post study drug follow-up period, to the Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Gilead PVE
Email: PPD
or
Fax: PPD

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.3.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows:
email: PPD and fax: PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to the Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Gilead PVE
Email: PPD
or
Fax: PPD

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the eCRF completion guidelines for instructions on special situation reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

The purpose of this study is to provide RDV to participants with severe COVID-19.

8.1.1. Analysis Objectives

The analysis objectives of this study are as follows:

- To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14
- To evaluate the safety and tolerability of RDV

8.1.2. Primary Endpoint

The primary endpoint of this study is:

- Clinical status assessed by a 7-point ordinal scale on Day 14

8.1.3. Secondary Endpoint

The secondary endpoint of this study is:

- The proportion of participants with treatment emergent adverse events

8.1.4. Other Endpoints of Interest

Other endpoints of interest are:

- Time to $SpO_2 > 94\%$ on room air
- Time to first negative SARS-CoV-2 PCR
- Duration of oxygen therapy (days)
- Duration of hospitalization (days)
- All cause mortality at Day 28
- Time to clinical improvement (days): Clinical improvement defined a ≥ 2-point improvement from Day 1 on a 7-point ordinal scale
- Plasma concentrations of RDV and GS-441524
- The proportion of participants in the Mechanically Ventilated Treatment Group and Extension Treatment Group with treatment-emergent AEs

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, the primary analysis of the primary endpoint will be conducted, additional interim analyses may be conducted, and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program or for other purposes.

8.2.1.1. DMC Analysis

The DMC will review safety and efficacy data on a regular basis.

8.2.2. Primary Analysis

The primary analysis will be performed after all participants have completed 14 days in Part A of the study or prematurely terminated from Part A of the study prior to 14 days.

8.2.3. Final Analysis

The final analysis will be performed after all participants have completed the study or prematurely terminated from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Efficacy

The primary analysis set for efficacy analysis is defined as the full analysis set (FAS), which will include all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized.

8.3.1.2. Safety

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized for Part A (5-day dosing group or 10-day dosing group) and according to the treatment to which they were assigned for Part B (Mechanically Ventilated Treatment Group or Extension Treatment Group).

8.3.1.3. Expanded RDV-Treated Analysis Set

The Expanded RDV-Treated Analysis Set will include participants who have received at least 1 dose of RDV in either the Mechanically Ventilated Treatment Group or Extension Treatment Group. This analysis set will be used for both the safety and efficacy evaluations for participants enrolled in Part B.

8.3.2. Data Handling Conventions

Natural logarithm transformation for PK parameters will be applied for PK analysis.

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be treated as zero at pre-dose and one-half of the lower limit of quantitation (LLOQ) for post dose time points

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation, will be imputed to the value of the lower or upper limit plus or minus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed. However, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

All available data for participants that do not complete the study will be included in data listings

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age. For categorical demographic and baseline characteristics, a Cochran Mantel Haenszel test will be used to compare treatment groups in Part A. For continuous demographic and baseline characteristics, a Wilcoxon rank sum test will be used to compare treatment groups in Part A.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint will be analyzed using a proportional odds model. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the two treatment groups (ie, whether the common odds ratio is equal to 1). The odds ratio and 95% confidence interval will be provided.

The proportion of subjects in each category will be summarized by treatment group. The validity of the proportionality assumption will be evaluated.

If a participant is discharged prior to Day 14, the Day 14 ordinal scale category is considered to be not hospitalized. Every effort will be made to obtain clinical status data for all subjects prior to discharge. Subjects who have missing clinical status information on Day 14 will be excluded from the primary analysis.

8.5.2. Secondary Analyses

The secondary endpoint of proportion of participants with treatment emergent AEs will be compared between the 2 treatment groups in Part A using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. Secondary or other endpoints of interest related to proportion of participants will be compared between treatment groups in Part A using a chi-square test or Fisher's Exact test. Endpoints that are measured as time to first event will be compared between treatment groups using the Log-Rank test and continuous endpoints will be compared between treatment groups using a Wilcoxon rank sum test or analysis of variance model.

For Part B, summaries of the 7-point scale ordinal scale and other efficacy endpoints of interest will be provided by group (Mechanically Ventilated Treatment Group or Extension Treatment Group).

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed through the Day 28 follow-up visit will be summarized by treatment group (according to the study drug received). Data for the pretreatment period will be included in data listings.

Summaries will be provided by group: 5-day dosing group or 10-day dosing group for Part A and Mechanically Ventilated Treatment Group or Extension Treatment Group for Part B.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized by group.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days, or up to Day 28, whichever is the later date.

Summaries (number and percentage of participants) of treatment-emergent AEs (by SOC, and PT) will be provided by group.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 dated July 2017.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for more than 30 days will be included in a data listing.

8.7. Pharmacokinetic Analysis:

Plasma concentrations and PK parameters for RDV and GS-441524 metabolite may be listed and summarized using descriptive statistics by group.

8.8. Adjustments for Multiplicity

No adjustments for multiple comparisons are planned.

8.9. Sample Size

The sample size computation is based on an assumed distribution of the 7-point ordinal scale on Day 14 for Part A Treatment Group 1. The odds ratio represents the odds of improvement in the ordinal scale for Treatment Group 2 relative to Treatment Group 1. The sample size needed to detect a given odds ratio for a 1:1 randomization using a 2-tailed test at level α is given by:

$$12\,(z_{\propto/2} + z_{\beta})^2 \,/\, \theta^2 (1 - \sum_{i=1}^{7} \rho_i^3)$$

Where θ is the log odds ratio, ρ_i is the overall probability (combined over both treatment groups) of being in the ith category of the ordinal outcome, and $z_{\alpha/2}$ and z_{β} are the 1- α /2 and β quantiles of the standard normal distribution {Whitehead 1993}.

A sample size of 400 participants (200 in each group) achieves > 85% power to detect an odds ratio of 1.75 using a two-sided significance level of 0.05. In this sample size calculation, it is assumed that the probability distribution of the ordinal scale at Day 14 for Group 1 is as follows:

1. Death, 2%

2. Hospitalized, on invasive mechanical ventilation or ECMO, 4%

3. Hospitalized, on non-invasive ventilation or high flow oxygen devices, 7%

4. Hospitalized, requiring low flow supplemental oxygen, 13%

5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 16%

6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration), 20%

7. Not hospitalized, 38%

The sample size calculation was done using software PASS (Version 14.0).

8.10. Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) includes independent experts that do not have direct involvement in the conduct of the study. The IDMC will review the progress of the study and perform interim reviews of safety data, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.
The IDMC's specific activities will be defined by a mutually agreed charter, which will define the IDMC's membership, conduct and meeting schedule.

While the IDMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with ICH E6(R2) addendum to its guideline for GCP and applicable laws and regulations including the principles of the Declaration of Helsinki.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent (or Assent)

The investigator is responsible for obtaining written informed consent from the participant, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age), or obtaining or assent (age ≥12 to <18, where locally and nationally approved) from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately

signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

9.1.5. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB or IEC. No biological samples will be provided to Gilead or any central laboratory during this study. NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator's brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, paper or electronic completed subject CRFs, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification;
- Documentation that subject meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);

- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE;
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF Completion Guidelines (eCCGs) provided by the Sponsor. Subsequent to data entry, a study monitor will perform source data verification (SDV) within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator or other

designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authorities, IRB/IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

De Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, et al. Prophylactic and Therapeutic Remdesivir (GS-5734) Treatment in the Rhesus Macaque Model of MERS-CoV Infection. PNAS Latest Articles 2020.

Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-Spectrum Antiviral GS-5734 Inhibits Both Epidemic and Zoonotic Coronaviruses. Science translational medicine 2017:1-20.

Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, et al. Comparative Therapeutic Efficacy of Remdesivir and Combination Lopinavir, Ritonavir, and Interferon Beta Against MERS-CoV. Nature communications 2020;11:222.

TAMIFLU®, Genentech Inc. TAMIFLU® (oseltamivir phosphate) capsules for oral use, TAMIFLU® (oseltamivir phosphate) for oral suspension. U.S. Prescribing Information. South San Francisco, CA. Revised August. 2019:

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus (2019-nCoV) In Vitro. Cell research 2020;30:269-71.

Whitehead J. Sample size calculations for ordered categorical data. Stat Med 1993;12 (24):2257-71.

World Health Organisation (WHO). Coronavirus Disease 2019 (COVID-19) Situation Report - 34. 2020.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19

Protocol Amendment 2.0 20 March 2020

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

Name (Printed) Senior Director	Signature
Date	

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Study Procedures Table

	Screening	Baseline / Day 1[b]	Day 2	Day 3	Day 4	Day 5	Days 6 and 7	Day 8	Day 9	Day 10	Days 11, 12 and 13	Day 14	Day 28[c] Follow-up (±5 days)
Written Informed Consent	X												
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Laboratory Testing	X	X		X		X		X		X		X	
Respiratory Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X												
PK Assessments[d]		X	X		X	X	X			X			
RDV Dosing for Group 1		X	X	X	X	X							
RDV Dosing for Group 2		X	X	X	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

a Includes heart rate, respiratory rate, temperature, blood pressure, SpO_2, and body weight. Body weight collected on screening and Day 1 and otherwise if available.
b Assessments need not be repeated if performed the same calendar day as screening procedures.; data collection other than adverse events should stop Day 14 or discharge whichever is earlier.
c Day 28 evaluations completed if the visit is conducted in person. Only AEs, ordinal scale, and concomitant medication review completed if visit conducted by phone.
d PK assessments sparse *or* intensive (optional for subjects/sites participating in this portion of the study) on Day 1, 2, 4, 5, 7, and 10.

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. No documentation of Tanner stage will be required for people unless deemed prepubescent.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age. Tubal ligation is not considered a method of permanent sterilization for the purposes of this study.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Data from nonclinical studies of RDV have demonstrated no adverse effect on fertility or embryo-fetal development. Remdesivir has not yet been studied in pregnant women. Before enrolling into studies with RDV, women of childbearing potential must have pregnancy testing performed at screening.

Available data indicate that RDV potentially causes an interaction with hormonal contraception that is considered of limited significance. Hormonal methods must be used with a barrier method.

Please refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative pregnancy test at screening. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for women of childbearing potential with infrequent or irregular periods. They must also agree to 1 of the following from Screening until the last dose of the study drug:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  Non-hormonal intrauterine device (IUD)

  Hormonal IUD (must be used with a barrier method)

  Tubal sterilization

  Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

  Barrier methods

  - Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
  - Male barriers: Male condom (with or without spermicide)

  Hormonal methods are restricted to drugs associated with the inhibition of ovulation. Each method must be used with a barrier method, preferably male condom. Hormonally-based contraceptives permitted for use in this protocol are as follows:

  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Contraceptive methods must be locally approved to be permitted.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until the last study drug dose.

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

3) Contraception Requirements for Male Subjects

During the study male subjects with female partners of childbearing potential should use condoms when engaging in intercourse of reproductive potential.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). A Female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

333 Lakeside Drive
Foster City, CA 94404

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #1

STUDY GS-US-540-5773
A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19

Original Protocol Date:	24 February 2020
Amendment 1.0 Date:	15 March 2020

Rationale:	Herein is a summary of the major changes made to the Original protocol dated 24 February 2020 and reflected in Amendment 1.0 dated 15 March 2020. • Revised primary endpoint to allow for more robust analysis • Expanded number of sites and subjects globally to meet urgent needs • Divided enrollment into two Parts: A and B • Included a Mechanically Ventilated Treatment Group and an Extension Treatment Group during enrollment to extend RDV therapy • Inserted EudraCT Number and Clinical Trials.gov identifiers • Provided further clarification to the inclusion and exclusion criteria • Included parameters for adolescent participants and adolescent dosing • Revised statistical methodology and analysis due to changes in endpoints and study design • Clarified requirements for oxygen supplementation • Additional formatting and administrative updates and minor grammatical corrections were made throughout the document but are not explicitly outlined in the changes below. Specific changes are presented herein as ***bold and italicized*** or ~~strikethrough~~.

Global Changes:	The following are changes that appear multiple times in the amended protocol: • Removal of the term "adult" participants to account for inclusion of adolescents • Included the term "assent" for informed consents provided to adolescents • Revised laboratory testing results for hemoglobin and/or hematocrit because either of the two will be acceptable • Clarified requirements for oxygen supplementation

Section:	Cover Page
Original Text:	IND Number: 147753 EudraCT Number: Not Applicable Clinical Trials.gov Identifier: Not Available
Revised Text:	IND Number: 147753 EudraCT Number: ~~Not Applicable~~ ***2020-000841-15*** Clinical Trials.gov Identifier: ~~Not Available~~ ***NCT04292899***
Rationale:	Revised to include EudraCT Number and Clinical Trials.gov identifiers

Section:	Protocol Synopsis
Original Text:	**Study Centers Planned:** Up to 50 centers globally, primarily in Asia
Revised Text:	**Study Centers Planned:** Up to ***approximately*** ~~50~~***100*** centers globally~~, primarily in Asia~~
Rationale:	To expand the number of centers globally

Section:	Protocol Synopsis Section 2
Original Text:	The primary objective of this study is as follows: • To evaluate the efficacy of 2 RDV regimens with respect to the normalization of temperature and oxygen saturation through Day 14
Revised Text:	The primary objective of this study is as follows: • To evaluate the efficacy of 2 RDV regimens with respect to ***clinical status assessed by a 7-point ordinal scale on*** ~~the normalization of temperature and oxygen saturation through~~ Day 14
Rationale:	Revised to make primary objective statistically robust as a registrational study

Section:	Protocol Synopsis
Original Text:	This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in adult participants with severe COVID-19. Approximately 400 participants who meet all eligibility criteria may be randomized in a 1:1 ratio into one of the following treatment groups: **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Subjects Planned: Approximately 400 Target Population: Adults with severe COVID-19
Revised Text:	This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in ~~adult~~ participants with severe COVID-19. ***The study will be conducted in two parts. In Part A,*** ~~A~~ ***a***pproximately 400 participants who meet all eligibility criteria ***and who are not mechanically ventilated*** may be randomized in a 1:1 ratio into one of the following treatment groups: **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 ***Part B will enroll participants on mechanical ventilation and, after enrollment to Part A is complete, any additional participants. In Part B, up to an additional approximately 2000 participants who meet all of the eligibility criteria will be enrolled, based on whether they are mechanically ventilated at enrollment, to receive:*** ***Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10*** ***Extension Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10*** ***Enrollment in the mechanically ventilated treatment group will be capped at approximately 500 participants.***

	If the 5-day dosing regimen used in Treatment Group 1 of Part A is selected for Part B, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days. National and local regulatory authorities will be informed. ***Participants in Part A of the study will be the primary efficacy population. Participants enrolled in Part B will have data reported descriptively at study completion.*** Subjects Planned: Approximately ~~400~~***2400*** Target Population: ~~Adults~~ ***Participants*** with severe COVID-19
Rationale:	Included two parts to allow for optimal duration of treatment to be determined and continued access to RDV and further data collection.

Section:	Protocol Synopsis
Original Text:	Adult participants with COVID-19 confirmed by polymerase chain reaction (PCR) who meet the following criteria: • Willing and able to provide written informed consent prior to performing study procedures • Hospitalized • Fever of ≥ 36.6 °C armpit, ≥ 37.2 °C oral, or ≥ 37.8 °C rectal • SpO_2 ≤94% on room air • Radiographic evidence of pulmonary infiltrates
Revised Text:	~~Adult p~~ ***P***articipants with COVID-19 confirmed by polymerase chain reaction (PCR) who meet the following criteria: • Willing and able to provide written informed consent ***(age ≥18) or assent (age ≥12 to <18, where locally and nationally approved)*** prior to performing study procedures • Hospitalized • ~~Fever of ≥ 36.6 °C armpit, ≥ 37.2 °C oral, or ≥ 37.8 °C rectal~~ • SpO_2 ≤94% on room air ***or requiring supplemental oxygen at screening*** • Radiographic evidence of pulmonary infiltrates
Rationale:	To clarify participant demographics and eligibility criteria

Section:	Protocol Synopsis
Original Text:	If safety laboratory results from the screening day are not already available, laboratory testing including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and creatinine clearance will be performed according to local practice. After screening procedures, eligible participants will be randomized into 1 of the 2 treatment groups in a 1:1 ratio to receive: **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

	Treatment Group 2: continued standard of care therapy together with IV RDV200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10The date of randomization will be considered Day 1 and all participants randomized to receive RDV should receive their initial dose on Day 1. On study Days 1 through 14 or until discharge, whichever is earlier, vital signs including respiratory status will be measured and adverse events (AEs) and concomitant medications will be documented. Laboratory testing will be performed according to SOC practice with results for white blood cell count, hemoglobin, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing being reported to the Sponsor. In addition, even if not performed as standard of care, white blood cell count, hemoglobin, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST will be performed at Days 1, 3, 5, 8, 10, and 14 or until discharge, whichever is earlier. Pharmacokinetic (PK) assessments may be conducted at selected sites, for local analysis. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-dose and end of infusion), and Day 7 (pre-dose and end of infusion). Up to 20 participants (10/group) may have intensive PK samples collected at Day 1, and Day 5 (treatment group 1), or Day 10 (treatment group 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV.
Revised Text:	If safety laboratory results from the screening day are not already available, laboratory testing including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), ***serum creatinine,*** and creatinine clearance will be performed according to local practice. ***In Part A,*** ~~A~~ ***a***fter screening procedures, eligible participants will be randomized into 1 of the 2 treatment groups in a 1:1 ratio to receive: **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV ***RDV 200*** mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 ***In Part B, after screening procedures, eligible participants will be assigned to receive:***

	Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 ***Extension Treatment* Group: *continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 as determined by review of the data. Treatment may be reduced to a total of 5 days following analysis of the data from Part A.*** The date of randomization will be considered Day 1 and all participants randomized to receive RDV should receive their initial dose on Day 1. On study Days 1 through 14 or until discharge, whichever is earlier, ***7-point ordinal scale of clinical status,*** vital signs including respiratory status will be measured and adverse events (AEs) and concomitant medications will be documented. Laboratory testing will be performed according to SOC practice with results for white blood cell count, hemoglobin ***and/or hematocrit***, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing being reported to the Sponsor. In addition, even if not performed as standard of care, white blood cell count, hemoglobin ***and/or hematocrit,*** platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST will be performed at Days 1, 3, 5, 8, 10, and 14 or until discharge, whichever is earlier. Pharmacokinetic (PK) assessments may be conducted at selected sites~~, for local analysis~~. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-~~dose~~ ***infusion*** and end of infusion), and Day 7 (pre-~~dose~~ ***infusion*** and end of infusion). Up to 20 participants (10/group) may have intensive PK samples collected at Day 1, and Day 5 (~~t~~***T***reatment ~~g~~***G***roup 1), or Day 10 (~~t~~***T***reatment ~~g~~***G***roup 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV.
Rationale:	To clarify study procedure requirements

Section:	Protocol Synopsis
Original Text:	The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: fever; temperature < 36.6°C armpit, < 37.2°C oral, < 37.8°C rectal; and Sp02 > 94%, sustained for at least 24 hours] through Day 14 The proportions of participants in the Full Analysis Set with normalization of fever and oxygen saturation through Day 14 will be compared between the 2 groups using a chi-square test, and point estimates of the treatment difference and the associated 95% confidence interval will be provided. Treatment-emergent AEs and laboratory abnormalities will be summarized using descriptive statistics and listed by subject.

	Plasma concentrations and PK parameters for RDV and the GS-441524 metabolite may be listed and summarized using descriptive statistics by group. **Sample Size**: A total of approximately 400 participants will be randomized in a 1:1 ratio to 2 groups (200 participants per group) A sample size of 400 participants (200 participants in each group) achieves approximately 85% power to detect a difference of 15% between the 5-day treatment group and the 10-day treatment group, assuming a response rate of 45% in the 5-day treatment group and 60% in the 10-day treatment group. The test statistic used is a chi-square test with a two-sided significance level of 0.05.
Revised Text:	~~The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: fever; temperature < 36.6 C armpit, < 37.2 C oral, < 37.8 C rectal; and Sp02 > 94%, sustained for at least 24 hours] through Day 14~~ ***Clinical status assessed by a 7-point ordinal scale on Day 13*** ~~The proportions of participants in the Full Analysis Set with normalization of fever and oxygen saturation through Day 14 will be compared between the 2 groups using a chi-square test, and point estimates of the treatment difference and the associated 95% confidence interval will be provided.~~ ***The primary endpoint will be analyzed using a proportional odds model. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the two treatment groups (ie, whether the common odds ratio is equal to 1). The odds ratio and 95% confidence interval will be provided.*** Treatment-emergent AEs and laboratory abnormalities will be summarized using descriptive statistics and listed by subject. Plasma concentrations and PK parameters ***(if applicable)*** for RDV and the GS-441524 metabolite may be listed and summarized using descriptive statistics by group. **Sample Size**: ***In Part A,*** ~~A~~***a*** total of approximately 400 participants will be randomized in a 1:1 ratio to 2 groups (200 participants per group)

	A sample size of 400 participants (200 participants in each group) achieves ~~approximately~~ > 85% power to detect ***on odds ratio of 1.75 using*** ~~a difference of 15% between the 5-day treatment group and the 10-day treatment group, assuming a response rate of 45% in the 5-day treatment group and 60% in the 10-day treatment group. The test statistic used is a chi-square test with~~ a two-sided significance level of 0.05. ***The sample size for Part B is based on the anticipated need for RDV and current trends in the COVID-19 epidemic.***
Rationale:	To clarify endpoint analysis methodology accounting for primary endpoint

Section:	Section 1.3
Original Text:	Remdesivir has a favorable clinical safety profile based on approximately 500 individuals who received RDV primarily as healthy volunteers in Phase 1 studies and individuals with acute EBOV infection.
Revised Text:	Remdesivir has a favorable clinical safety profile based on approximately 500 individuals who received RDV primarily as healthy volunteers in Phase 1 studies and individuals with acute EBOV infection. ***The design of enrollment in two parts will allow the selection of a preferred duration of treatment to be determined and then allow continued access to RDV and data collection for eligible participants. In addition, further safety data will be obtained.***
Rationale:	To provide reasoning for including two parts for enrollment into the protocol

Section:	Section 1.4
Original Text:	In the nonclinical studies, RDV was administered at 10 mg/kg (Study PC-399-2038) or 5 mg/kg (Study PC-399-2037) once daily for 7 days using IV bolus injection beginning either 1 day prior to or 12 hours after (5 mg/kg only) MERS-CoV inoculation. Remdesivir treatment was efficacious at reducing viral titers in the lung and alleviating clinical disease signs (RDV IB; {DeWit 2020}). Toxicology studies in cynomolgus monkeys and rats and safety and PK studies in healthy volunteers support the safety of the proposed dose. Overall, RDV has a favorable PK and safety profile that supports evaluation of a 200 mg loading and a 100 mg daily dose that has potential to be efficacious in adult patients with COVID-19.
Revised Text:	In the nonclinical studies, RDV was administered at 10 mg/kg (Study PC-399-2038) or 5 mg/kg (Study PC-399-2037) once daily for 7 days using IV bolus injection beginning either 1 day prior to or 12 hours after (5 mg/kg only) MERS-CoV inoculation. Remdesivir treatment was efficacious at reducing viral titers in the lung and alleviating clinical disease signs (RDV IB; {DeWit 2020}). Toxicology studies in cynomolgus monkeys and rats and safety and PK studies in healthy volunteers support the safety of the proposed dose. Overall, RDV has a favorable PK and safety profile that supports evaluation of a 200 mg loading and a 100 mg daily dose that has potential to be efficacious in adult patients with COVID-19.

	The optimal duration of therapy with RDV remains unknown. However, other agents for acute antiviral infection, for example oseltamivir phosphate {TAMIFLU® 2019}, have treatment courses ranging from 5 days duration. There is considerable potential patient benefit and societal benefit in identifying the minimum duration that will be effective.
Rationale:	To clarify rationale for selection of a 5-day treatment regimen

Section:	Section 1.4.1
Original Text:	N/A
Revised Text:	*Pediatric Dosing* ***As with adult dose, the efficacious dose of RDV against SARS-CoV-2 remains to be established.*** ***Dose selection of remdesivir (RDV) in EBOV infected pediatric patients was informed by a physiologically-based pharmacokinetic (PBPK) model implemented in SimCYP (v.17, Certara). Briefly, a PBPK model was developed to characterize the PK of RDV and the inactive primary circulating nucleoside metabolite, GS-441524, in adults. The model was verified based on its ability to describe the mean and variability of the adult exposures using data from the RDV Phase 1 program (GS-US-399-1812). The adult PBPK model was subsequently used to simulate steady-state pediatric (age range 0 to 18 years) exposures (AUC_{tau}), accounting for age-dependent changes in organ volume/size (liver and kidney), esterase expression, plasma protein binding, and organ blood flow.*** ***These simulations do not account for diminished liver or kidney function due to SARS-CoV-2 infection and/or COVID-19 progression because the impact of infection/disease progression on the PK of remdesivir and GS-441524 is currently unknown.*** ***The results of these simulations indicate:*** ***For pediatric patients with body weight ≥ 40 kg, a 200 mg loading dose followed by 100 mg once-daily maintenance doses of remdesivir (ie, the adult dosage regimen) should be administered. Use of the adult dose in these pediatric patients is expected to maintain exposures of both remdesivir and GS-441524 at or below that which was previously observed to be well tolerated in healthy volunteers (N=24, GS-US-399-1954).***
Rationale:	To include clinical data on pediatric dosing

Section:	Section 1.5
Original Text:	A pertinent specific risk for participants in this study is the potential for transient, Grade ≤ 2, treatment-emergent elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were observed after multiple daily RDV administrations in Studies GS-US-399-1954 and GS-US-399-5505.
Revised Text:	***Potential risks associated with the study include unknown adverse events (AEs) and laboratory abnormalities. Although not specifically evaluated yet, adolescents with COVID-19 who receive RDV are expected to have similar safety profile as adults; no additional safety monitoring is required for adolescent participants and no dose adjustments are required. No differing safety profile has been reported for the adolescents with EBOV who received RDV in clinical trials. Accordingly, the risk:benefit profile, described below, is the same for adolescents and adults.*** A pertinent specific risk for participants in this study is the potential for transient, Grade ≤ 2, treatment-emergent elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were observed after multiple daily RDV administrations in Studies GS-US-399-1954 and GS-US-399-5505.
Rationale:	To clarify safety profile and monitoring for adolescents

Section:	Section 3
Original Text:	This study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19 infection. All participants will continue to receive SOC therapy according to local guidelines.
Revised Text:	***Part A of*** ~~T~~ ***t***his study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19 infection. ***Part B is a two treatment group multicenter study of RDV in participants with severe COVID-19 infection. Treatment group assignment is based on whether the participant is on mechanical ventilation at treatment assignment.*** All participants will continue to receive SOC therapy according to local guidelines.
Rationale:	To provide distinction between Part A and Part B of the protocol

Section:	Section 3.1
Original Text:	The primary endpoint of this study is: • The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: temperature < 36.6°C armpit, < 37.2°C oral, < 37.8°C rectal; and SpO_2 > 94%, sustained for at least 24 hours] through Day 14 The secondary endpoint of this study is: • The proportion of participants with treatment emergent adverse events leading to study drug discontinuation Other endpoints of interest are:

	• Time to SpO_2 > 94% on room air • Time to first fever normalization (criteria for normalization: temperature < 36.6°C armpit, < 37.2°C oral, < 37.8°C rectal) • Time to first negative SARS-CoV-2 polymerase chain reaction (PCR) • Duration of oxygen therapy • Duration of hospitalization (days) • All cause mortality at Day 28 • Time to clinical improvement (days): Clinical improvement is defined using a 6-point ordinal scale at Day 1 status dropped by 2 points or discharge • Plasma concentrations of RDV and GS-441524
Revised Text:	The primary endpoint of this study is: • ~~The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: temperature < 36.6°C armpit, < 37.2°C oral, < 37.8°C rectal; and SpO2 > 94%, sustained for at least 24 hours] through Day 14~~ ***Clinical status assessed by a 7-point ordinal scale on Day 14*** The secondary endpoint of this study is: • The proportion of participants with treatment emergent adverse events ~~leading to study drug discontinuation~~ Other endpoints of interest are: • Time to SpO_2 > 94% on room air • ~~Time to first fever normalization (criteria for normalization: temperature < 36.6°C armpit, < 37.2°C oral, < 37.8°C rectal)~~ • Time to first negative SARS-CoV-2 polymerase chain reaction (PCR) • Duration of oxygen therapy ***(days)*** • Duration of hospitalization (days) • All cause mortality at Day 28 • Time to clinical improvement (days): Clinical improvement is defined ***as a ≥ 2-point improvement from Day 1 on a*** ~~using a 6~~***7***-point ordinal scale ~~at Day 1 status dropped by 2 points or discharge~~ • Plasma ***concentrations*** of RDV and GS-441524
Rationale:	Revised primary endpoint and clarified other endpoints of interests

Section:	Section 3.2
Original Text:	This study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19. Eligible participants will be randomized in equal proportions to 1 of 2 treatment groups. No stratification will be performed.

Revised Text:	***Part A of this study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19 infection.*** ~~This study is a randomized, open-label, multicenter study of RDV in participants with severe COVID-19.~~ Eligible participants will be randomized in equal proportions to 1 of 2 treatment groups. No stratification will be performed. ***Part B is a two treatment group multicenter study of RDV in participants with severe COVID-19 infection.***
Rationale:	To provide distinction between Part A and Part B

Section:	Section 3.3
Original Text:	Approximately 400 participants who meet all eligibility criteria may be randomized in a 1:1 ratio into 1 of the following treatment groups: **Treatment Group 1:** continued standard of care therapy together with IV RDV200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV RDV200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10
Revised Text:	***In Part A,*** ~~A~~ ***a***pproximately 400 participants who meet all eligibility criteria ***and who are not mechanically ventilated*** may be randomized in a 1:1 ratio into 1 of the following treatment groups: **Treatment Group 1:** continued standard of care therapy together with IV ~~RDV200~~ ***RDV 200*** mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued standard of care therapy together with IV ~~RDV200~~ ***RDV 200*** mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 ***In Part B, an additional approximately 2000 participants who meet all of the eligibility criteria may receive:*** ***Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10*** ***Extension Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected. If treatment for 5 days is selected, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days. National and local regulatory authorities will be informed.*** ***Enrollment in the mechanically ventilated treatment group will be capped at approximately 500 participants.***

	Participants in Part A of the study will be the primary efficacy population. Participants enrolled in Part B will have data reported descriptively at study completion.
Rationale:	To clarify treatment parameters between Part A and Part B

Section:	Section 3.4
Original Text:	Participants will receive study treatment with RDV for 5 days (treatment group 1), or 10 days (treatment group 2). If the participant is discharged, RDV treatment will stop at that time.
Revised Text:	Participants will receive study treatment with RDV for 5 days (~~t~~*T*reatment ~~g~~*G*roup 1), ~~or~~ 10 days (~~t~~*T*reatment ~~g~~*G*roup 2), ***10 days (Mechanically Ventilated Treatment Group), or either 5 or 10 days (Extension Treatment Group).*** If the participant is discharged, RDV treatment will stop at that time.
Rationale:	Revised to include extension group study treatment period

Section:	Section 3.5
Original Text:	Study drug dosing in an individual subject will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if a participant experiences:
Revised Text:	Study drug dosing in an individual subject will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if ***any of the following occurs*** ~~a participant experiences~~:
Rationale:	Paraphrased for clarity

Section:	Section 4.1
Original Text:	Approximately 400 participants will be randomized in a 1:1 ratio into 1 of 2 treatment groups.
Revised Text:	***In Part A,*** ~~A~~ approximately 400 participants will be randomized in a 1:1 ratio into 1 of 2 treatment groups. ***In Part B, up to approximately 2000 participants may be assigned to 1 of the 2 treatment groups. Rescreening may occur at the investigator's discretion.***
Rationale:	To provide distinction of subjects assigned to Part A and Part B

Section:	Section 4.2
Original Text:	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Willing and able to provide written informed consent prior to performing study procedures 2) Aged ≥ 18 years 3) SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization 4) Currently hospitalized with fever defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, ≥ 37.8 °C rectal 5) SpO_2 ≤ 94% on room air at screening 6) Radiographic evidence of pulmonary infiltrates 7) Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.
Revised Text:	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Willing and able to provide written informed consent ***(participants ≥ 18 years of age) or assent (participants ≥ 12 and < 18 years of age, where locally and nationally approved) prior to performing study procedures. For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent*** prior to performing study procedures 2) Aged ≥ 18 years ***(at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant institutional review board [IRB] or independent ethics committee [IEC])*** 3) SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization 4) Currently hospitalized ~~with fever defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, ≥ 37.8 °C rectal~~ 5) SpO_2 ≤ 94% on room air or ***requiring supplemental oxygen*** at screening 6) Radiographic evidence of pulmonary infiltrates 7) Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3.
Rationale:	To further define inclusion criteria requirements and add criteria for adolescents

Section:	Section 4.3
Original Text:	Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study: 1) Participation in any other clinical trial of an experimental treatment for COVID-19 2) Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 is prohibited < 24 hours prior to study drug dosing 3) Evidence of multiorgan failure 4) Requiring mechanical ventilation at screening 5) ALT or AST > 5 x ULN 6) Creatinine clearance < 50 mL/min 7) Positive pregnancy test (Appendix 3) 8) Breastfeeding woman 9) Known hypersensitivity to the study drug, the metabolites, or formulation excipient
Revised Text:	Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study: 1) Participation in any other clinical trial of an experimental treatment for COVID-19 2) Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 ~~is prohibited~~ < 24 hours prior to study drug dosing 3) Evidence of multiorgan failure 4) ***Mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO.*** ~~Requiring mechanical ventilation at screening~~ 5) ALT or AST > 5 x ULN 6) Creatinine clearance < 50 mL/min ***using the Cockcroft-Gault formula for participants ≥ 18 years of age {Cockcroft 1976} and Schwartz Formula for participants < 18 years of age*** 7) Positive pregnancy test (Appendix 3) 8) Breastfeeding woman 9) Known hypersensitivity to the study drug, the metabolites, or formulation excipient
Rationale:	To further define exclusion criteria requirements

Section:	Section 5.3
Original Text:	Remdesivir for injection, 100 mg, will be provided by Gilead. Participants in treatment groups 1 and 2 will receive RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5. Participants in treatment group 2 will also receive RDV 100 mg on Days 6, 7, 8, 9, and 10.

Revised Text:	Remdesivir for injection, 100 mg, will be provided by Gilead. *In Part A,* ~~P~~*p*articipants in ~~t~~***T***reatment ~~g~~*G*roups 1 and 2 will receive RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5. Participants in ~~t~~***T***reatment ~~g~~***G***roup 2 will also receive RDV 100 mg on Days 6, 7, 8, 9, and 10. ***In Part B, participants in the Mechanically Ventilated Treatment Group will receive IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and10. Participants in the Extension Treatment Group will also receive IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected. If treatment for 5 days is selected, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days. Remdesivir treatment will be stopped at discharge regardless of the scheduled duration of therapy. Remdesivir will be administered over 30 minutes where possible.***
Rationale:	To provide further guidance on RDV administration for each of the Treatment Groups

Section:	Section 5.5
Original Text:	Concomitant use of the following is prohibited in participants receiving RDV and needs to be discontinued at minimum 24 hours prior to receiving first dose of RDV: • Investigational agents for COVID-19 including approved HIV protease inhibitors such as lopinavir/ritonavir. If the local standard of care per written policies or guidelines (ie, not just an individual clinician decision) includes lopinavir/ritonavir or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site. Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for RDV dose modification above. Otherwise, concomitant use of lopinavir/ritonavir and RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations. Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications will be captured in this trial. The list of medications will be assessed only from Day 1 prior to enrollment to Day 14 or discharge whichever is earlier.

Revised Text:	Concomitant use of the following is prohibited in participants receiving RDV and needs to be discontinued at minimum 24 hours prior to receiving first dose of RDV: • ***Traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang)*** • Investigational agents for COVID-19 including approved HIV protease inhibitors such as lopinavir/ritonavir, ***chloroquine, interferon, etc.*** ***Concomitant use of investigational agents such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc while receiving RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.*** ~~If the local standard of care per written policies or guidelines (ie, not just an individual clinician decision) includes lopinavir/ritonavir or other agents, then continuing these during the study is permitted, but may require additional safety monitoring by the site. Additionally, there should be plans on how the concomitant drugs are stopped for transaminase elevations, and prior to the thresholds for RDV dose modification above. Otherwise, concomitant use of lopinavir/ritonavir and RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.~~ ~~Concomitant medications in a hospitalized population change daily and are difficult to collect and attribute to success and failure of therapy and impact on safety. Therefore, only select concomitant medications will be captured in this trial. The list of m~~ ***M***edications will be assessed only from Day 1 prior to enrollment to Day 14 or discharge**,** whichever is earlier.
Rationale:	To provide further guidance on prohibited medications during study

Section:	Section 6.2.1
Original Text:	Subjects will be screened within 2 days before randomization and dosing to determine eligibility for participation in the study. • Obtain written informed consent After the informed consent the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria: • Focused medical history including the following information (eg, date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics), allergies and medical history • Review and record medications and therapies for this current illness • Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy

	• Targeted physical examination including, vital signs (heart rate, temperature, blood pressure), body weight, and height • Documentation of respiratory status: — Respiratory Rate — Oxygen supplementation: room air, nasal canula,-face mask, mechanical ventilation — SpO_2 at rest or PaO_2 — Radiographic findings • Obtain blood samples if not done in the preceding 48 hours for creatinine, creatinine clearance, ALT and AST • Pregnancy test (for women of childbearing potential) • Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent form.
Revised Text:	Subjects will be screened within 2 days before randomization and dosing to determine eligibility for participation in the study. • Obtain written informed consent ***or assent (age ≥12 to <18, where locally and nationally approved).*** After the informed consent the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria: • Focused medical history including the following information (eg, date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics), allergies and medical history • Review and record medications and therapies for this current illness • Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy • Targeted physical examination including, vital signs (heart rate, temperature, blood pressure), body weight, and height • Documentation of respiratory status: — Respiratory Rate — Oxygen supplementation: room air, ~~nasal canula~~ ***low flow O_2 (L/min and %), high flow O_2 (L/min and %),*** ~~face mask~~, ***CPAP/BIPAP ($_{FiO2}$ or %),*** mechanical ventilation ***(FiO_2 or %), ECMO*** — ***Oxygenation:*** SpO_2 ~~at rest~~ or PaO_2 — Radiographic findings • Obtain blood samples if not done in the preceding 48 hours for ***creatinine,*** creatinine clearance, ALT and AST • Pregnancy test (for women of childbearing potential) • Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent ***(or assent)*** form.
Rationale:	To clarify assessments done at the screening visit

Section:	Section 6.2.2
Original Text:	The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility before proceeding with randomization on the Day 1 visit. If the screening and Day 1 visits occur within one day, no procedures need to be repeated. Participants must complete the following assessments before being administered study drug: • Physical examination including vital signs (heart rate, temperature, blood pressure, and body weight) • Documentation of respiratory status: — Respiratory rate — Oxygen supplementation: room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO — Oxygenation: (SpO_2 or PaO_2) — Radiographic findings (if available) • Review AEs and document concomitant medications • Obtain blood samples for white blood cell count, hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST • Obtain blood sample for sparse or intensive pharmacokinetic assessments (optional for subjects/sites participating in this portion of the study) • Review the Ordinal Scale (see Section 6.9)
Revised Text:	The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility before proceeding with randomization ***(Part A) or treatment assignment (Part B)*** on the Day 1 visit. If the screening and Day 1 visits occur within one day, no procedures need to be repeated. Participants must complete the following assessments before being administered study drug: • Physical examination including vital signs (heart rate, temperature, blood pressure, and body weight) • Documentation of respiratory status: — Respiratory rate — Oxygen supplementation: ***room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO*** ~~room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO~~ — Oxygenation: ~~(~~SpO_2 or PaO_2~~)~~ — Radiographic findings (if available) • Review AEs and document concomitant medications • Obtain blood samples for white blood cell count, ***hemoglobin and/or*** hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST

	• Obtain blood sample for sparse or intensive pharmacokinetic assessments (optional for subjects/sites participating in this portion of the study) • Review the Ordinal Scale (see Section 6.9)
Rationale:	To clarify procedures at the Baseline/Day 1 visit

Section:	Section 6.3
Original Text:	• Documentation of respiratory status: — Respiratory rate — Oxygen supplementation: room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO — Oxygenation: (SpO_2 or PaO_2) — Radiographic findings (if available) • SARS-CoV-2 testing results if available should be reported • Review of AEs and document concomitant medications • Review Ordinal Scale
Revised Text:	• Documentation of respiratory status: — Respiratory rate — Oxygen supplementation: ***room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO*** ~~room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO~~ — Oxygenation: ~~(~~SpO2 or PaO2~~)~~ — Radiographic findings (if available) • SARS-CoV-2 testing results if available should be reported • Review of AEs and document concomitant medications • Review Ordinal Scale ***(Section 6.9)***
Rationale:	To clarify procedures at the Days 2-14 visits

Section:	Section 6.4
Original Text:	• Safety laboratory tests (white blood cell count, hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST) • Pharmacokinetic Assessments (sparse *or* intensive) are to be completed at Day 2, 4, 5, 7, and 10 (optional for subjects/sites participating in this portion of the study) or until discharge whichever comes earlier
Revised Text:	• Safety laboratory tests (white blood cell count, ***hemoglobin and/or*** hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST) • Pharmacokinetic Assessments (sparse *or* intensive) are to be completed at Day 2, 4, 5, 7, and 10 (optional for subjects/sites participating in this portion of the study) ~~or until discharge whichever comes earlier~~
Rationale:	To clarify when additional assessments are to be completed

Section:	Section 6.5
Original Text:	The following evaluations are to be completed if this visit is conducted in person. For participants who have been discharged from hospital, the final evaluation can be made by phone. Only AE and concomitant medication review is to be completed if visit is conducted by phone. • Physical examination and vital signs (heart rate, temperature, blood pressure) • Documentation of respiratory status: — Respiratory rate — Oxygen supplementation: room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO — Oxygenation: (SpO2 or PaO2) — Radiographic findings (if available) • Review AEs and document concomitant medications • Review the Ordinal Scale
Revised Text:	**6.5 Day 28 Follow up Assessment *(± 5 Days)*** The following evaluations are to be completed if this visit is conducted in person. For participants who have been discharged from hospital, the final evaluation can be made by phone. Only AE and concomitant medication *and ordinal scale (if discharged on or after Day 14)* review ~~is~~ *are* to be completed if visit is conducted by phone. • Physical examination and vital signs (heart rate, temperature, blood pressure) • Documentation of respiratory status: — Respiratory rate — Oxygen supplementation: ***room air, low flow O_2 (L/min and %), high flow O_2 (L/min and %), CPAP/BIPAP (FiO2 or %), mechanical ventilation (FiO2 or %), ECMO*** ~~room air, nasal canula, face mask, noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO~~ — Oxygenation: ~~(~~SpO2 or PaO2~~)~~ — Radiographic findings (if available) • Review AEs and document concomitant medications • Review the Ordinal Scale ***(Section 6.9). If subject was not discharged by Day 14, any change in category and the date of any change in category from Day 14 to*** discharge ***(or Day 28) should be recorded***
Rationale:	To clarify the Day 28 follow-up assessment visit

Section:	Section 6.6
Original Text:	Clinical laboratory assessments are required at screening, Days 1, 3, 5, 8, 10 and 14 or until discharge whichever comes earlier. Clinical laboratory assessments at other days may be conducted if required by clinical need or local practice. All laboratory testing will be completed by local laboratories. From Day 1 to Day 14, at specified timepoints, the sponsor will be provided with results for the following analytes: white blood cell count, hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing. SARS-CoV-2 testing may include RT-qPCR to detect or quantify SARS-CoV 2 or virus sequencing results. If feasible, oropharyngeal, saliva, sputum, stool, and/or blood samples may be collected and assayed using RT-qPCR to quantify SARS-CoV-2 viral load. Pretreatment and posttreatment samples with detectable SARS-CoV-2 may be sequenced for resistance monitoring of the viral polymerase gene if possible. For all clinical laboratory tests, except those at Day 1, when more than 1 result is available in a calendar day, the highest result should be reported in the eCRF except for creatinine clearance where the lowest result should be recorded. For Day 1 tests, the most recent result before dosing should be used. All SARS-CoV-2 results should be provided
Revised Text:	Clinical laboratory assessments are required at screening, Days 1, 3, 5, 8, 10 and 14 or until discharge whichever comes earlier. Clinical laboratory assessments at other days may be conducted if required by clinical need or local practice. All laboratory testing will be completed by local laboratories. From Day 1 to Day 14, at specified timepoints, the sponsor will be provided with results for the following analytes: white blood cell count, ***hemoglobin and/or*** hematocrit, platelets, creatinine and creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing. SARS-CoV-2 testing may include RT-qPCR to detect or quantify SARS-CoV 2 or virus sequencing results. If feasible, oropharyngeal, saliva, sputum, stool, and/or blood samples may be collected and assayed using RT-qPCR to quantify SARS-CoV-2 viral load. Pretreatment and posttreatment samples with detectable SARS-CoV-2 may be sequenced for resistance monitoring of the viral polymerase gene if possible. ~~For all clinical laboratory tests, except those at Day 1, when more than 1 result is available in a calendar day, the highest result should be reported in the eCRF except for creatinine clearance where the lowest result should be recorded. For Day 1 tests, the most recent result before dosing should be used. All SARS-CoV-2 results should be provided~~
Rationale:	Clarified clinical laboratory assessments

Section:	Section 6.7
Original Text:	A targeted physical examination and vital signs (heart rate, respiratory rate, temperature, blood pressure, SpO2 at rest or PaO2) should be performed at least daily.
Revised Text:	A targeted physical examination and vital signs (heart rate, respiratory rate, temperature, blood pressure, SpO2 ~~at rest~~ or PaO2) should be performed at least daily.
Rationale:	Removed text to align with changes to study procedures

Section:	Section 6.8
Original Text:	Pharmacokinetic (PK) assessments may be conducted at selected sites for local analysis. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-dose and end of infusion), and Day 7 (pre-dose and end of infusion). Up to 20 participants (10/group) may have intensive PK samples collected at Day 1, and Day 5 (treatment group 1), or Day 10 (treatment group 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV. Further details will be provided in the PK assessment manual.
Revised Text:	Pharmacokinetic (PK) assessments may be conducted at selected sites ~~for local analysis~~. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-~~dose~~ ***infusion*** and end of infusion), and Day 7 (pre-~~dose~~ ***infusion*** and end of infusion). Up to 20 participants (10/group) may have intensive PK samples collected at Day 1, and Day 5 (~~t~~***T***reatment ~~g~~***G***roup 1), or Day 10 (~~t~~***T***reatment ~~g~~***G***roup 2). All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV. Further details will be provided in the PK assessment manual.
Rationale:	Revised for text consistency and alignment with changes in protocol

Section:	Section 6.9
Original Text:	The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worst (i.e. lowest ordinal) score from the previous day will be recorded. i.e. on Day 3, the lowest ordinal score from Day 2 is obtained and recorded for Day 2. The scale is as follows: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices 4. Hospitalized, requiring supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen 6. Discharged

Revised Text:	The ordinal scale is an assessment of the clinical status at ~~the first assessment of~~ a given study day. Each day, the worst (i.e. lowest ordinal) score from the previous day will be recorded. i.e. on Day 3, the lowest ordinal score from Day 2 is obtained and recorded for Day 2. The scale is as follows: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices 4. Hospitalized, requiring ***low flow*** supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen ***- requiring ongoing medical care (COVID-19 related or otherwise)*** ***6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration)*** ~~7. Discharged~~ ***8. Not hospitalized***
Rationale:	Revised to provide clarification to the ordinal scale definition

Section:	Section 6.14 Section 6.15
Original Text:	**6.14 Sample Disposition and Storage** Samples will be processed and retained according to local practice and the regulations pertaining to each institution. No samples will be obtained or retained by Gilead. **6.15** N/A
Revised Text:	**6.14 Sample Disposition and Storage *(Non-PK Samples)*** Samples will be processed and retained according to local practice and the regulations pertaining to each institution. No samples will be obtained or retained by Gilead. ***6.15 Sample Disposition and Storage (PK Samples)*** ***The stored PK samples may be used by Gilead or its research partner for the testing of RDV and metabolites during the course of the study or when sample transport is possible. At the conclusion of this study, the PK samples may be retained in storage by Gilead or at its research partner facility for a period up to 15 years.***
Rationale:	Revised to clarify sample disposition and storage information for non-PK and PK samples

Section:	Section 7.3.2
Original Text:	All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

Revised Text:	All AEs *and clinically significant laboratory abnormalities* should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.
Rationale:	To clarify definitions of safety monitoring

Section:	Section 8.1.1
Original Text:	The analysis objectives of this study are as follows: • To evaluate the efficacy of 2 RDV regimens with respect to the normalization of temperature and SpO_2 through Day 14 • To evaluate the safety and tolerability of RDV
Revised Text:	The analysis objectives of this study are as follows: • To evaluate the efficacy of 2 RDV regimens with respect to ***clinical status assessed by a 7-point ordinal scale on*** ~~the normalization of temperature and SpO_2 through~~ Day ~~14~~*11* • To evaluate the safety and tolerability of RDV
Rationale:	Revised to make primary objective statistically robust and to align with registrational studies

Section:	Section 8.1.3
Original Text:	The secondary endpoint of this study is: • The proportion of participants with treatment emergent adverse events leading to study drug discontinuation.
Revised Text:	The secondary endpoint of this study is: • The proportion of participants with treatment emergent adverse events ~~leading to study drug discontinuation.~~
Rationale:	Revised to clarify scope of data analysis for secondary endpoint

Section:	Section 8.1.2
Original Text:	The primary endpoint of this study is: • The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: T < 36.6 C armpit, < 37.2 C oral, < 37.8C rectal; and $Sp0_2$ > 94%, sustained for at least 24 hours] through Day 14
Revised Text:	The primary endpoint of this study is: • ~~The proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: T < 36.6 C armpit, < 37.2 C oral, < 37.8C rectal; and $Sp0_2$ > 94%, sustained for at least 24 hours] through Day 14~~ ***Clinical status assessed by a 7-point ordinal scale on Day 14***
Rationale:	Revised primary endpoint to allow for more robust analysis

Section:	Section 8.1.3
Original Text:	The secondary endpoint of this study is: • The proportion of participants with treatment emergent adverse events leading to study drug discontinuation.
Revised Text:	The secondary endpoint of this study is: • The proportion of participants with treatment emergent adverse events ~~leading to study drug discontinuation~~
Rationale:	Revised secondary endpoint to allow for more robust analysis

Section:	Section 8.1.4
Original Text:	Other endpoints of interest are: • Time to SpO_2 > 94% on room air • Time to first fever normalization • Time to first negative SARS-CoV-2 PCR • Duration of oxygen therapy (day) • Duration of hospitalization (day) • All cause mortality at day 28 • Time to clinical improvement (day): Clinical improvement defined as 6-point scale of admission status dropped by 2-point or discharge • Plasma concentrations of RDV and GS-441524
Revised Text:	Other endpoints of interest are: • Time to SpO_2 > 94% on room air • ~~Time to first fever normalization~~ • Time to first negative SARS-CoV-2 PCR • Duration of oxygen therapy (day***s***) • Duration of hospitalization (day***s***) • All cause mortality at ~~d~~***D***ay 28 • Time to clinical improvement (day): Clinical improvement defined ~~as~~ ***a ≥ 2-point improvement from Day 1 on a 7~~6~~***-point ***ordinal*** scale ~~of admission status dropped by 2-point or discharge~~ • Plasma concentrations of RDV and GS-441524 • ***The proportion of participants in the Mechanically Ventilated Treatment Group and Extension Treatment Group with treatment emergent adverse events***
Rationale:	Clarified to allow for more robust analysis

Section:	Section 8.2.1
Original Text:	Prior to the final analysis, interim analyses may be conducted and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program or for other purposes.

Revised Text:	Prior to the final analysis, ***the primary analysis of the primary endpoint will be conducted, additional*** interim analyses may be conducted***,*** and the analyses may be submitted to regulatory agencies to seek guidance for the overall clinical development program or for other purposes.
Rationale:	Clarified scope for interim analysis

Section:	Section 8.2.1.1
Original Text:	The DMC will review safety and efficacy data on a regular basis. There will be one planned DMC analysis conducted after approximately 50% of participants have been randomized.
Revised Text:	The DMC will review safety and efficacy data on a regular basis. ~~There will be one planned DMC analysis conducted after approximately 50% of participants have been randomized.~~
Rationale:	Revised language to accommodate current enrollment rate, which makes formal interim efficacy analysis mute

Section:	Section 8.2.2
Original Text:	**8.2.2. Final Analysis**
Revised Text:	~~**8.2.2 Final Analysis**~~ *Primary Analysis* ***The primary analysis will be performed after all participants have completed 14 days in Part A of the study or prematurely terminated from Part A of the study prior to 14 days.***
Rationale:	To include scope for primary analysis activities

Section:	Section 8.2.3
Original Text:	N/A
Revised Text:	***8.2.3 Final Analysis*** The final analysis will be performed after all participants have completed the study or prematurely terminated from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. ~~The analysis of the primary endpoint (normalization of fever and oxygen saturation at Day 14) will be conducted at the time of the final analysis~~
Rationale:	Removed sentence to align with revised primary endpoint

Section:	Section 8.3.1.1
Original Text:	The primary analysis set for efficacy analysis is defined as the full analysis set (FAS), which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized.

Revised Text:	The primary analysis set for efficacy analysis is defined as the full analysis set (FAS), which will include all participants who (1) are randomized ***into Part A*** the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized.
Rationale:	Included reference to scope of analysis for participants enrolled into Part A

Section:	Section 8.3.1.2
Original Text:	The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment which they received**.**
Revised Text:	The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment ~~which they received.~~ ***to which they were randomized for Part A (5-day dosing group or 10-day dosing group) and according to the treatment to which they were assigned for Part B (Mechanically Ventilated Treatment Group or Extension Treatment Group).***
Rationale:	To clarify safety analyses parameters for Part A and Part B

Section:	Section 8.3.1.3
Original Text:	N/A
Revised Text:	***8.3.1.3 Expanded RDV-Treated Analysis Set*** ***The Expanded RDV-Treated Analysis Set will include participants who have received at least 1 dose of RDV in either the Mechanically Ventilated Treatment Group or Extension Treatment Group. This analysis set will be used for both the safety and efficacy evaluations for participants enrolled in Part B.***
Rationale:	To include scope of data analysis for subjects enrolled in Part B

Section:	Section 8.5.1
Original Text:	The proportions of participants in the FAS with normalization of fever and oxygen saturation through Day 14 will be compared between the 2 groups using a chi-square test. The point estimate of the treatment difference and the associated 95% confidence interval will be provided. Participants who are discharged prior to Day 14 will be considered as achieving normalization. Participants who die or drop out of the study prior to Day 14 without normalization will be considered as not achieving normalization.

Revised Text:	***The primary endpoint will be analyzed using a proportional odds model. The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the two treatment groups (ie, whether the common odds ratio is equal to 1). The odds ratio and 95% confidence interval will be provided.*** ***The proportion of subjects in each category will be summarized by treatment group. The validity of the proportionality assumption will be evaluated.*** ***If a participant is discharged prior to Day 14, the Day 14 ordinal scale category is considered to be not hospitalized. Every effort will be made to obtain clinical status data for all subjects prior to discharge. Subjects who have missing clinical status information on Day 14 will be excluded from the primary analysis.*** ~~The proportions of participants in the FAS with normalization of fever and oxygen saturation through Day 14 will be compared between the 2 groups using a chi-square test. The point estimate of the treatment difference and the associated 95% confidence interval will be provided. Participants who are discharged prior to Day 14 will be considered as achieving normalization. Participants who die or drop out of the study prior to Day 14 without normalization will be considered as not achieving normalization.~~
Rationale:	To clarify methodology used for primary endpoint analysis

Section:	Section 8.5.2
Original Text:	The secondary endpoint of proportion of participants with treatment emergent AEs leading to study drug discontinuation will be compared between the 2 groups using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. Secondary or other endpoints of interest related to proportion of participants will be compared between treatment groups using a chi-square test or Fisher's Exact test. Endpoints that are measured as time from randomization or start of dosing will be compared between treatment groups using the Log-Rank test and continuous endpoints will be compared between treatment groups using a Wilcoxon rank sum test or analysis of variance model.

Revised Text:	The secondary endpoint of proportion of participants with treatment emergent AEs ~~leading to study drug discontinuation~~ will be compared between the 2 ***treatment*** groups ***in Part A*** using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. Secondary or other endpoints of interest related to proportion of participants will be compared between treatment groups ***in Part A*** using a chi-square test or Fisher's Exact test. Endpoints that are measured as time ~~from randomization or start of dosing~~ ***to first event*** will be compared between treatment groups using the Log-Rank test and continuous endpoints will be compared between treatment groups using a Wilcoxon rank sum test or analysis of variance model. ***For Part B, summaries of the 7-point scale ordinal scale and other efficacy endpoints of interest will be provided by group (Mechanically Ventilated Treatment Group or Extension Treatment Group).***
Rationale:	To clarify methodology used for secondary endpoint analysis

Section:	Section 8.6
Original Text:	All safety data collected on or after the date that study drug was first dispensed through the Day 28 follow-up visit will be summarized by treatment group (according to the study drug received). Data for the period will be included in data listings.
Revised Text:	All safety data collected on or after the date that study drug was first dispensed through the Day 28 follow-up visit will be summarized by treatment group (according to the study drug received). Data for the ***pretreatment*** period will be included in data listings. ***Summaries will be provided by group: 5-day dosing group or 10-day dosing group for Part A and Mechanically Ventilated Treatment Group or Extension Treatment Group for Part B.***
Rationale:	To clarify safety analysis parameters

Section:	Section 8.6.2
Original Text:	Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the randomization date up to the date of last dose of study drug plus 30 days
Revised Text:	Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the randomization date up to the date of last dose of study drug plus 30 days***, or up to Day 28, whichever is the later date.***
Rationale:	To clarify definition of treatment-emergent AEs

Section:	Section 8.6.3
Original Text:	Selected laboratory data will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized. Graded laboratory abnormalities will be defined using the grading scheme in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 dated July 2017. Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent. Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment will be included in a data listing.
Revised Text:	Selected laboratory data will be summarized using only observed data. Data and change from baseline at all scheduled time points will be summarized. Graded laboratory abnormalities will be defined using the grading scheme in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 dated July 2017. Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent. Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment ***for more than 30 days*** will be included in a data listing.
Rationale:	To further define what laboratory data to be included in the data listings

Section:	Section 8.8
Original Text:	The DMC charter will include stopping rules for safety, along with alpha spending considerations. No other adjustments for multiple comparisons are planned.
Revised Text:	~~The DMC charter will include stopping rules for safety, along with alpha spending considerations.~~ No ~~other~~ adjustments for multiple comparisons are planned.
Rationale:	To clarify that no adjustments are planned for multiplicity

Section:	Section 8.9
Original Text:	A sample size of 400 participants (200 in each group) achieves approximately 85% power to detect a difference of 15% between the 5-day treatment group and the 10-day treatment group, assuming a response rate of 45% in the 5-day treatment group and 60% in the 10-day treatment group and a two-sided significance level of 0.05.
Revised Text:	***The sample size computation is based on an assumed distribution of the 7-point ordinal scale on Day 14 for Part A Treatment Group 1. The odds ratio represents the odds of improvement in the ordinal scale for Treatment Group 2 relative to Treatment Group 1. The sample size needed to detect a given odds ratio for a 1:1 randomization using a 2-tailed test at level α is given by:*** $$\mathbf{12}\ (z_{\propto/2} + z_{\beta})^2 \ / \ \theta^2 (1 - \sum_{i=1}^{7} \rho_i^3)$$ ***Where θ is the log odds ratio, ρ_i is the overall probability (combined over both treatment groups) of being in the ith category of the ordinal outcome, and $z_{\alpha/2}$ and z_{β} are the 1- α /2 and β quantiles of the standard normal distribution (Whitehead, 1993).*** ***A sample size of 400 participants (200 in each group) achieves > 85% power to detect an odds ratio of 1.75 using a two-sided significance level of 0.05. In this sample size calculation, it is assumed that the probability distribution of the ordinal scale at Day 14 for Group 1 is as follows:*** 1. ***Death, 2%*** 2. ***Hospitalized, on invasive mechanical ventilation or ECMO, 4%*** 3. ***Hospitalized, on non-invasive ventilation or high flow oxygen devices, 7%*** 4. ***Hospitalized, requiring low flow supplemental oxygen, 13%*** 5. ***Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 16%*** 6. ***Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration), 20%*** 7. ***Not hospitalized, 38%*** ***The sample size calculation was done using software PASS (Version 14.0).*** ~~A sample size of 400 participants (200 in each group) achieves approximately 85% power to detect a difference of 15% between the 5-day treatment group and the 10-day treatment group, assuming a response rate of 45% in the 5-day treatment group and 60% in the 10-day treatment group and a two-sided significance level of 0.05.~~
Rationale:	To clarify parameters for sample size computation

Section:	Section 9.1.4
Original Text:	**9.1.4 Informed Consent** The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.
Revised Text:	**9.1.4 Informed Consent *(or Assent)*** The investigator is responsible for obtaining written informed consent ***or assent (age ≥12 to <18, where locally and nationally approved)*** from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.
Rationale:	Revised informed consent requirements to account for adolescent assent

Section:	Appendix 2
Original Text:	**Appendix 2. Study Procedures Table**

	Screening	Baseline / Day 1[b]	Day 2	Day 3	Day 4	Day 5	Days 6 and 7	Day 8	Day 9	Day 10	Days 12 and 13	Day 14	Day 28[c] Follow-up
Written Informed Consent	X												
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Laboratory Testing	X	X		X		X		X		X		X	
Respiratory Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X											X	

a Includes heart rate, respiratory rate, temperature, blood pressure, SpO_2, and body weight. Body weight collected on screening and Day 1 and otherwise if available.

Revised Text:

Appendix 2. Study Procedures Table

	Screening	Baseline / Day 1[b]	Day 2	Day 3	Day 4	Day 5	Days 6 and 7	Day 8	Day 9	Day 10	Days *11*, 12 and 13	Day 14	Day 28[c] Follow-up *(±5 days)*
Written Informed Consent	X												
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Laboratory Testing	X	X		X		X		X		X		X	
Respiratory Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X											~~X~~	

a Includes heart rate, respiratory rate, temperature, blood pressure, SpO_2 ~~at rest~~, and body weight. Body weight collected on screening and Day 1 and otherwise if available.

Rationale: Revised to include Day 11, ±5-day window for Day 28 follow up visit, revised footnote, and removed pregnancy test requirement at Day 14 in order to align with rest of protocol.

Section:	Appendix 3
Original Text:	**b. Contraception Requirements for Female Subjects of Childbearing Potential** The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative serum pregnancy test at Screening. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until the last dose of the study drug:
Revised Text:	**b. Contraception Requirements for Female Subjects of Childbearing Potential** The inclusion of female subjects of childbearing potential requires using at least an acceptable effective contraceptive measure. They must have a negative ~~serum~~ pregnancy test at Screening. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is applicable also for women of childbearing potential with infrequent or irregular periods. They must also agree to one of the following from Screening until the last dose of the study drug:
Rationale:	Clarified pregnancy testing requirement at Screening

Section:	Appendix 3
Original Text:	Consistent and correct use of 1 of the following methods of birth control listed below. • Non-hormonal intrauterine device (IUD) • Hormonal IUD (must be used with a barrier method) • Tubal sterilization • Essure® micro-insert system (provided confirmation of success 3 months after procedure)

Revised Text:	Consistent and correct use of 1 of the following methods of birth control listed below. • Non-hormonal intrauterine device (IUD) • Hormonal IUD (must be used with a barrier method) • Tubal sterilization • ~~Essure® micro-insert system (provided confirmation of success 3 months after procedure)~~
Rationale:	Clarified requirements for birth control methods

"I have read and understand the above, and agree to this protocol amendment as written."
Principal Investigator **Date**

333 Lakeside Drive
Foster City, CA 94404

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #2

STUDY GS-US-540-5773
A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19

Original Protocol Date:	24 February 2020
Amendment 1.0 Date:	15 March 2020
Amendment 2.0 Date:	20 March 2020

Rationale:	Herein is a summary of the major changes made to Amendment 1.0 dated 15 March 2020 and reflected in Amendment 2.0 dated 20 March 2020. • Revised informed consent language to include informed consent with a legal representative and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions • Specific changes are presented herein as ***bold and italicized***

Section:	Synopsis
Original Text:	Willing and able to provide written informed consent (age ≥18) or assent (age ≥12 to <18, where locally and nationally approved) prior to performing study procedures
Revised Text:	Willing and able to provide written informed consent***, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator*** (age ≥18)***,*** or ***willing and able to provide*** assent (age ≥12 to <18, where locally and nationally approved) prior to performing study procedures
Rationale:	To include guidance on legal representative providing informed consent and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions

Section:	Section 4.2
Original Text:	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Willing and able to provide written informed consent (participants ≥ 18 years of age) or assent (participants ≥ 12 and < 18 years of age, where locally and nationally approved) prior to performing study procedures. For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures

Revised Text:	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Willing and able to provide written informed consent***, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator*** (participants ≥ 18 years of age)***,*** or ***willing and able to provide*** assent (participants ≥ 12 and < 18 years of age, where locally and nationally approved) prior to performing study procedures. For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures
Rationale:	To include guidance on legal representative providing informed consent and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions

Section:	Section 6.2.1
Original Text:	Subjects will be screened within 2 days before randomization and dosing to determine eligibility for participation in the study. • Obtain written informed consent or assent (age ≥12 to <18, where locally and nationally approved)
Revised Text:	Subjects will be screened within 2 days before randomization and dosing to determine eligibility for participation in the study. • Obtain written informed consent, ***or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age),*** or ***obtain*** assent ***(participants*** age ≥12 to <18, where locally and nationally approved)
Rationale:	To include guidance on legal representative providing informed consent and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions

Section:	Section 9.1.4
Original Text:	The investigator is responsible for obtaining written informed consent or assent (age ≥12 to <18, where locally and nationally approved) from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

Revised Text:	The investigator is responsible for obtaining written informed consent ***from the participant, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age),*** or ***obtaining*** assent (age ≥12 to <18, where locally and nationally approved) from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.
Rationale:	To include guidance on legal representative providing informed consent and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions

"I have read and understand the above, and agree to this protocol amendment as written."	
Principal Investigator	**Date**

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Name of Test Drug:	Remdesivir (RDV; GS-5734™)
Study Number:	GS-US-540-5773
Protocol Version (Date):	Amendment 3.0 (12 April 2020)
Analysis Type:	Part A Analysis
Analysis Plan Version:	Version 1
Analysis Plan Date:	22 April 2020
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
eCRF	Electronic case report form
FAS	Full Analysis Set
HLT	high-level term
LLN	lower limit of normal
LLT	lowest level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PT	preferred term
Q1, Q3	first quartile, third quartile
RDV	remdesivir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal

1. INTRODUCTION

This Phase 3 study is conducted in two parts. In Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated are randomized to one of two treatment groups. Part B starts after Part A is completed and includes up to approximately 5600 participants.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the analysis of Part A of Study GS-US-540-5773. This SAP is based on the study protocol Amendment 3.0 dated 12 April 2020 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The purpose of this study is to provide remdesivir (RDV) to participants with severe COVID-19.

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV.

1.2. Study Design

This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in participants with severe COVID-19.

Treatment Groups

For Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated may be randomized in a 1:1 ratio into one of the following treatment groups:

- **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

- **Treatment Group 2:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Part B will enroll participants on mechanical ventilation and, after enrollment to Part A is complete, any additional participants. In Part B, up to an additional approximately 5600 participants who meet all of the eligibility criteria will be enrolled, based on whether they are mechanically ventilated at enrollment, to receive:

Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Extension Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

If the 5-day dosing regimen used in Treatment Group 1 of Part A is selected for Part B, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days.

Key Eligibility Criteria

Participants with COVID-19 confirmed by polymerase chain reaction (PCR) who meet the following criteria:

- Willing and able to provide written informed consent (age ≥18) or assent (age ≥12 to <18, where locally and nationally approved) prior to performing study procedures
- Hospitalized
- SpO2 ≤ 94% on room air or requiring supplemental oxygen at screening
- Radiographic evidence of pulmonary infiltrates

Schedule of Assessments

The date of randomization is considered Day 1 and it is expected that all randomized participants receive their initial dose of RDV on Day 1.

On Days 1 through 14 or until discharge, whichever is earlier, vital signs including respiratory status will be measured and adverse events (AEs) and concomitant medications will be documented. Laboratory testing will be performed according to standard of care practice with results for white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing being reported to the Sponsor. Clinical status will be recorded on the 7-point ordinal scale for each day.

In addition, even if not performed as standard of care, white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST will be performed at Days 1, 3, 5, 8, 10, and 14 or until discharge, whichever is earlier.

Pharmacokinetic (PK) assessments may be conducted at selected sites. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-dose and end of infusion), and Day 7 (pre-dose and end of infusion). Up to 20 participants may have intensive PK samples collected at Day 1, and Day 5 or Day 10 at pre-dose and end of infusion, and the following times from start of infusion: 1 hour, 3 hours, 6 hours, 8 hours, 12 hours and 24 hours. All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV.

Randomization

Participants who meet eligibility criteria are randomized in a 1:1 ratio to 1 of 2 treatment groups on Day 1 using an IWRS and assigned a subject number. Randomization is not stratified.

Sites

Up to approximately 160 centers globally.

Duration of Treatment

Participants will receive study treatment with RDV for 5 days (Treatment Group 1) or 10 days (Treatment Group 2) in Part A, and 10 days (Mechanically Ventilated Treatment Group), or either 5 or 10 days (Extension Treatment Group) in Part B. If the participant is discharged, RDV treatment will end at that time.

Discontinuation Criteria

Study drug dosing in an individual participant will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if any of the following occurs:

- Any serious adverse event (SAE) or ≥ Grade 3 AE suspected to be related to RDV.
- Any elevations in ALT > 5 × ULN; or ALT > 3 × ULN and total bilirubin > 2 × ULN, confirmed by immediate repeat testing.
- Creatinine clearance < 30mL/min

Discontinuation of study medication is not a seriousness criterion.

End of Study

The end of the study will be the last participant's last observation (or visit).

1.3. Sample Size and Power

In Part A, a total of approximately 400 participants will be randomized in a 1:1 ratio to 2 groups (200 participants per group).

The sample size computation is based on an assumed distribution of the 7-point ordinal scale on Day 14 for Part A Treatment Group 1. The odds ratio represents the odds of improvement in the ordinal scale for Treatment Group 2 relative to Treatment Group 1. The sample size needed to detect a given odds ratio for a 1:1 randomization using a 2-tailed test at level α is given by:

$$12\ (z_{\propto/2} + z_{\beta})^2\ /\ \theta^2(1 - \sum_{i=1}^{7} \rho_i^3)$$

Where θ is the log odds ratio, ρ_i is the overall probability (combined over both treatment groups) of being in the ith category of the ordinal outcome, and $z_{\alpha/2}$ and z_{β} are the 1- α /2 and β quantiles of the standard normal distribution {Whitehead 1993}.

A sample size of 400 participants (200 in each group) achieves > 85% power to detect an odds ratio of 1.75 using a two-sided significance level of 0.05. In this sample size calculation, it is assumed that the probability distribution of the ordinal scale at Day 14 for Treatment Group 1 is as follows:

1. Death, 2%
2. Hospitalized, on invasive mechanical ventilation or ECMO, 4%
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices, 7%
4. Hospitalized, requiring low flow supplemental oxygen, 13%
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 16%
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration), 20%
7. Not hospitalized, 38%

The sample size calculation was performed using software PASS (Version 14.0).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. DMC Analysis

The DMC will review the results from the analysis of the Day 14 snapshot.

2.1.2. Primary Analysis

The primary analysis will be performed after availability of data from participants in Part A of the study who have completed 14 days or prematurely terminated from Part A of the study on or prior to Day 14.

2.1.3. Part A Final Analysis

The final analysis for participants randomized in Part A will be performed after all these participants have completed Part A of the study or prematurely terminated from Part A of the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. This SAP describes the statistical analysis methods and data presentations to be used for the analysis of Part A.

2.2. Final Analysis

The final analysis for this study will be performed after all participants have completed Part B of the study or prematurely terminated from the study (Part A or Part B), outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-subject listings will be presented for all participants in the All Randomized Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a subject. The treatment group to which participants were randomized will be used in the listings.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. Participants included in each analysis set will be determined before database finalization for the primary analysis. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of participants in each analysis set will be provided by treatment group and in total.

3.1.1. All Randomized Analysis Set

The **All Randomized Analysis Set** will include all participants who are randomized into Part A of the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The primary analysis set for efficacy analysis is defined as the **Full Analysis Set (FAS)**, which will include all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized.

3.1.3. Safety Analysis Set

The primary analysis set for safety analyses is defined as the **Safety Analysis Set**, which will include all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized for Part A.

3.2. Subject Grouping

Participants will be grouped by randomized treatment (RDV for 5 Days and RDV for 10 Days), regardless of the actual number of days of treatment.

3.2.1. Subject Subgroups for Efficacy Analyses

The primary endpoint will be analyzed for the following subject subgroups:

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Oxygen support status based on the 7-point ordinal scale: (a) Invasive mechanical ventilation, (b) high flow oxygen, (c) low flow oxygen, and (d) room air (See Appendix 2)
- Country: (a) USA, (b) Italy, and (c) ex-Italy

3.2.2. Subject Subgroups for Safety Analyses

Incidence of all treatment-emergent AEs (TEAEs) will be summarized for the following subject subgroups:

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Country: (a) USA, (b) Italy, and (c) ex-Italy

Survival will be summarized for the following subject subgroups:

- Age (years): (a) < 65, further broken down by (a1) < 50 and (a2) ≥ 50 to < 65, and (b) ≥ 65, further broken down by (b1) ≥ 65 to < 75 and (b2) ≥ 75
- Sex at birth: (a) male and (b) female
- Country: (a) USA, (b) Italy, and (c) ex-Italy

3.3. Multiple Comparisons

No prespecified multiplicity adjustments are planned for confidence intervals or statistical tests.

3.4. Missing Data and Outliers

3.4.1. Missing Data

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

In this study, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary. The handling of missing or incomplete dates for AE onset is described in Section 7.2.5.2, and for prior and concomitant medications in Section 7.5.

3.4.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.5. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the first dose date will be used instead. If a randomized subject was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

3.6. Analysis Visit Windows

3.6.1. Definition of Study Day

Study Day 1 is defined as the first dosing date of study drug.

Study Days are calculated relative to Study Day 1 and derived as follows:

- For postdose study days: Assessment Date First Dosing Date + 1
- For days prior to the first dose: Assessment Date First Dosing Date

Therefore, **Study Day 1**/ **First Dose Date** is the day of first dose of study drug administration, as recorded on the Study Drug Administration eCRF form.

Last Dose Date is defined as the maximum, nonmissing, nonzero dose end date of treatment recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Withdrawn" box checked for participants who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF. Refer to Appendix 2 for missing date imputation, if necessary.

Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 28-day follow-up visit date, for participants who prematurely discontinued study according to the Study Completion eCRF.

Baseline value is defined as the last value obtained on or prior to the first dose date (and time, if available) unless otherwise specified (see Section 3.6.3).

3.6.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purposes of analysis, observations will be assigned to analysis windows. The study day as defined in Section 3.6.2 will be used when data are summarized by visit.

Vital signs, SpO_2 and PaO_2 were to be collected daily; therefore, windows are not assigned and results will be summarized for each Study Day, except for Study Day 28. For Study Day 28, the nominal day is Study Day 28, the lower limit is Study Day 15 and there is no upper limit.

Ordinal scale results were to be recorded prior to dosing on Study Day 1. The worst result for each day from Day 1 through the earliest of discharge date or Day 14 was to be recorded. For subjects who were discharged after Day 14, changes in score category were to be recorded each day from Day 15 to the earliest of discharge date or Day 28. For the ordinal scale, baseline is defined as the value recorded prior to dosing, or the last value obtained prior to the first dose date if the predose value was not recorded on the day of dosing. Results will be summarized for each Study Day without windows.

SARS-CoV-2 PCR results were to be reported (if collected) each day. However, the windows in Table 3-1 will be assigned to account for missing data.

The analysis windows for hematology and chemistry laboratory parameters and PCR are presented in Table 3-1.

Table 3-1. Analysis Windows for PCR and Hematology and Chemistry Laboratory Tests (hemoglobin, hematocrit, platelet count, WBC, ALT, AST, total bilirubin, glucose, serum creatinine, and eGFR)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1		1 (pre dose)*
Day 3	3	1 (post dose)*	3
Day 5	5	4	6
Day 8	8	7	8
Day 10	10	9	11
Day 14	14	12	15
Post Day 14**	28	16	

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time. For Day 3, the lower limit includes values collected after the first dose date/time on Day 1.
** Post Day 14 laboratory values will be considered for treatment emergent laboratory presentations only.

3.6.3. Selection of Data in the Event of Multiple Records for an Analysis Visit Day

Depending on the statistical analysis method, single values may be required for each Study Day or analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis does not require 1 value per Study Day or analysis window.

If multiple valid, nonmissing measurements exist for a Study Day/analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date (and time, if available) of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity for categorical data.
- For postbaseline values:

  For windows spanning multiple days, the record(s) collected on the day closest to the nominal day will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

  For PCR, if there is more than 1 record on the selected day, the latest value will be selected. If there are multiple records with the same time or no time recorded on the same day, the selected value will be the highest severity (ie, highest value or positive result).

  For laboratory values (other than PCR) and SpO_2 and PaO_2, if there is more than 1 record on the selected day, the worst value will be selected. See Appendix 2 for definition of worst value.

  For other parameters, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

The number and percentage of participants randomized at each investigator site will be summarized by treatment group and overall using the Safety Analysis Set. The denominator for this calculation will be the number of participants in the Safety Analysis Set.

The summary of subject disposition will be provided by treatment group and overall for all screened participants. This summary will include the number of participants screened, screen failure participants who were not randomized, participants who met all eligibility criteria and were not randomized, participants randomized, participants randomized but never treated, participants in the Safety Analysis Set, and participants in the FAS.

In addition, the number and percentage of the participants in the following categories will be summarized:

- Completed randomized 5-day or 10-day treatment on study drug as recorded on the Study Drug Completion form
- Prematurely discontinuing study drug prior to completion of 5 days of dosing (Treatment Group 1) or 10 days of dosing (Treatment Group 2) with summary of reasons for discontinuing study drug as recorded on the Study Drug Completion form
- Still on study up to the data cut date (if applicable)
- Completed study
- Prematurely discontinuing from study prior to the data cut date (with summary of reasons for discontinuing study) as recorded on the Study Completion form

The denominator for the percentages of participants in each category will be the number of participants in the Safety Analysis Set.

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure

4.2.1. Exposure to Study Drug

Number of doses received will be summarized by treatment group for the Safety Analysis Set.

4.3. Protocol Deviations

A listing will be provided for all randomized participants who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the FAS. A by-subject listing will be provided for those participants with important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, sex, race/ethnicity, and age) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data. The summaries of demographic data and baseline subject characteristics will be provided for the Safety Analysis Set.

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

Similar summaries will be produced for the following subgroups: USA, Italy and ex-Italy.

A by-subject demographic listing will be provided.

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics:

- Clinical status (7-point ordinal scale)
- Duration of hospitalization prior to first dose of RDV
- Duration of symptoms prior to first dose of RDV
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Oxygen support status based on the 7-point ordinal scale (invasive mechanical ventilation, high flow oxygen, low flow oxygen, room air)

For categorical data, the CMH test (row means scores differ statistic for ordinal data [oxygen support status]) will be used to compare the 2 treatment groups. For clinical status and continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

Similar summaries will be produced for the following subgroups: USA, Italy and ex-Italy.

5.3. Medical History

Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is considered to be preexisting and should be documented as medical history. General medical history data will be collected at screening. It will be coded using the current version of MedDRA. A summary table will present the percentages of participants reporting each medical history preferred term, sorted first in alphabetical order by system organ class (SOC) and then by preferred term (PT) in descending order of total frequency within SOC.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is clinical status assessed by a 7-point ordinal scale on Day 14. The endpoint will be derived by combining the available death, hospital discharge alive and ordinal scale assessment reported by the site, where death supersedes discharge alive and discharge alive supersedes the ordinal scale score reported by the site. The proportion of participants for each ordinal scale category endpoint by treatment group is expressed as percentages for presentation purpose.

Sites were instructed to report the worst ordinal scale category for each day. Therefore, the ordinal scale result on the day the participant was discharged alive does not necessarily reflect Not hospitalized (7). The definition of the 7-point ordinal scale endpoint for the efficacy analyses is defined as follows:

- If a participant dies while hospitalized (as recorded on the Death eCRF and Hospitalization eCRF), the endpoint on the day of death and all subsequent days through Day 28 will be set to Death (1)
- If the participant is discharged alive, the endpoint on the day of discharge alive and all subsequent days through Day 28 will be set to Not hospitalized (7)
- If the participant is discharged alive and dies on the same day or a later day (as recorded on the Death eCRF and Hospitalization eCRF), the endpoint on the day of discharge alive and all subsequent days until the day of death will be set to Not hospitalized (7). On the day of death and all subsequent days through Day 28, the endpoint will be set to Death (1),

Every effort will be made to obtain clinical status data for all participants prior to discharge alive. The last known clinical status will be used for days with missing clinical status (eg , where the reason for Hospital Discharge is not “Discharged Alive” and the subject has not died). All post-baseline days with missing ordinal scale score, from Day 2 to Day 14 and Day 28, will use the previous last known clinical status.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: The odds of improvement for the 5-day treatment group (Treatment Group 1) is the same as the odds of improvement for the 10-day treatment group (Treatment Group 2) with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

Alternative hypothesis: The odds of improvement for the 5-day treatment group (Treatment Group 1) is different from the odds of improvement for the 10-day treatment group (Treatment Group 2) with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The primary endpoint will be analyzed using a proportional odds model including treatment as the independent variable and baseline score as a continuous covariate. The odds ratio and 95% confidence interval will be provided. The corresponding SAS code is as following:

```
proc logistic data  example;
class trt/ param  ref order  data;
model outcome(descending)   trt baseline;
run;
```

The proportion of participants in each category will be summarized by treatment group. The assumption of odds proportionality will be assessed using a score test and reported. It will be concluded that 10-day treatment is superior to 5-day treatment if the lower bound of the 2-sided 95% CI of the odds ratio (10-day / 5-day) on Day 14 is more than 1.

The FAS will be the primary analysis set for efficacy endpoint evaluation.

6.1.4. Secondary Analyses of the Primary Efficacy Endpoint

As supportive analyses of the primary endpoint, the following will be conducted:

- The primary endpoint will be analyzed using a proportional odds model including treatment as the independent variable (dropping baseline score as a covariate).
- The clinical status at Day 14 will be compared between treatment groups using a 2-sided Wilcoxon Rank sum test, stratified on baseline clinical status.

The change from baseline in clinical status category on Days 5, 7, 11 and 14 will be summarized by treatment groups using descriptive statistics. Change from baseline will be compared between the treatment groups using a 2-sided Wilcoxon Rank sum test. This analysis will use the definition specified in Section 6.1.1.

The number and percentage of participants in each clinical status category for each day from Baseline through Day 14 and at Day 28 will be summarized by treatment group. In addition, stacked bar charts by study day (Baseline through Day 14) will be produced by treatment group. These results will be summarized using the clinical status definition in Section 6.1.1 and two methods: (1) with the definition specified in Section 6.1.1 and (2) with the definition specified in Section 6.1.1 but excluding days with missing ordinal scale score not due to death or discharge alive.

The number and percentage of participants in each clinical status category for each day from Baseline through Day 14 and at Day 28 will be summarized within each subgroup defined in Section 3.2.1. These results will use the definition specified in Section 6.1.1.

The above analyses will be conducted using the FAS.

6.2. Other Endpoints of Interest

The other endpoints of interest include:

- Number of subjects with negative PCR on Days 5 and 10
- Number of days of oxygen support through discharge alive, death or Day 14 based on the 7-point ordinal scale reported values. This summary will present results separately for subjects who died on or prior to Day 14 and those who were discharged alive on or prior to Day 14 and will include:

  Days on invasive mechanical ventilation

  Days on high flow oxygen devices

  Days requiring low flow supplemental oxygen
- Shift in oxygen support status from baseline to Days 5, 7, 11, 14, and last assessment
- Duration of hospitalization (days) (duration from hospital admission and duration from Day 1). For the primary analysis, duration of hospitalization through Day 14 is calculated for subjects who were discharged alive on or prior to Day 14. For the final Part A analysis, duration of hospitalization is calculated through the last visit for subjects who were discharged alive prior to the last visit.
- All-cause mortality
- Time to clinical improvement (days): Clinical improvement is defined as a ≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale using the definition specified in Section 6.1.1.
- Proportion of subjects with a ≥ 2-point improvement or discharged alive based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14 and Day 28
- Time to ≥ 1-point improvement (days) from baseline clinical status on the 7-point ordinal scale using the definition specified in Section 6.1.1.
- Proportion of subjects with a ≥ 1-point improvement based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14 and Day 28
- Time to recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1, where recovery is defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Proportion of subjects with recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14 and Day 28

- Time to modified recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1, where modified recovery is defined as an improvement from a baseline score of 2 through 4 to a score of 5, 6 or 7, or an improvement from a baseline score of 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Proportion of subjects with modified recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14 and Day 28
- Time to room air (for subjects not on room air at baseline) based on the 7-point ordinal scale using the definition specified in Section 6.1.1, defined as an improvement from a baseline score of 2 through 4 to a score of 5, 6 or 7
- Proportion of subjects with improvement to room air based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14 and Day 28

6.2.1. Analysis of Other Endpoints of Interest

The number and percent of subjects with negative PCR on Days 5 and 10 will be summarized. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided.

Number of days of oxygen support status modes (invasive mechanical ventilation, high flow oxygen, low flow oxygen) will be compared between the treatment groups using the Wilcoxon Rank sum test. Number of days will be calculated as the number of days oxygen support was reported on the 7-point ordinal scale CRF through death, discharge alive, or Day 14.

A shift table of baseline oxygen support status (death, invasive mechanical ventilation, high flow oxygen, low flow oxygen, room air, discharge alive) to Days 5, 7, 11, 14, and the last available status will be provided. For the primary analysis, the last assessment on or prior to Day 14 will be included.

Duration of hospitalization will be calculated only for participants who are discharged alive and will be compared between the treatment groups using the Wilcoxon Rank sum test.

All-cause mortality will be estimated using the Kaplan-Meier product limit method with all available data. The treatment groups will be compared using the log-rank test, and the hazard ratio and 95% confidence interval will be provided. Participants who did not die will be censored at the last study day.

Days to clinical improvement will be estimated using a competing risk analysis approach, with death as the competing risk. Baseline score will be included in the model as a continuous covariate. The hazard ratio and 95% confidence interval will be provided. Subjects without clinical improvement will be censored on the day of the last non-missing ordinal scale assessment.

Days to recovery, days to modified recovery and days to room air will be estimated using a competing risk analysis approach, with death as the competing risk. Baseline score will be included in the model as a continuous covariate. The hazard ratio and 95% confidence interval

will be provided. Subjects without recovery will be censored on the day of the last non-missing ordinal scale assessment.

The number and percent of subjects with ≥ 1-point improvement, ≥ 2-point improvement, recovery, modified recovery, and improvement to room air will be presented with 95% confidence intervals on Day 5, Day 7, Day 11 and Day 14. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. For the number of subjects on room air, only subjects on room air at baseline will be included.

Analyses will be performed using the FAS.

6.3. Changes from Protocol-Specified Efficacy Analyses

The protocol stated that participants who have missing clinical status information on Day 14 will be excluded from the primary analysis; however death and discharge alive information as well as last known clinical status will be used for Day 14 (see Section 6.1.1).

The protocol stated that endpoints that are measured as time to first event will be compared between treatment groups using the log-rank test; however, a competing risk approach (with death as the competing risk) will be used. Treatment groups will be compared using the hazard ratio with 95% confidence interval.

The endpoint of interest of time to SpO_2 > 94% on room air was changed to time to room air because SpO_2 was not collected routinely for participants on room air.

The endpoint of interest of time to first negative PCR was updated to the number of subjects with negative PCR on Days 5 and 10 because PCR was not collected on a routine basis.

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the safety analysis set. All safety data collected on or after the date that study drug was first dispensed through 30 days after last dose will be summarized by treatment group for the Safety Analysis Set, unless specified otherwise. All safety data will be included in data listings.

7.1. Secondary Endpoint

The secondary endpoint of the proportion of participants with any treatment emergent adverse events will be compared between the 2 groups using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided.

7.2. Adverse Events and Deaths

7.2.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. SOC, high-level group term (HLGT), high-level term (HLT), PT, and lowest-level term (LLT) will be provided in the AE dataset.

7.2.2. Adverse Event Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening) or Grade 5 (fatal) according to toxicity criteria specified in the document above. The severity grade of events for which the investigator did not record severity will be left as "missing" for data listings.

7.2.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.2.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology Department before data finalization.

7.2.5. Treatment-Emergent Adverse Events

7.2.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.2.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The month and year (or year) of the AE onset is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date marked as ongoing or on or after the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.2.6. Summaries of Adverse Events and Deaths

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group using the Safety Analysis Set:

- Grade 3 or higher treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- Grade 3 or higher treatment-emergent study drug-related AEs

- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug
- Treatment-emergent deaths

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of participants who experienced the above AEs. Treatment-emergent deaths observed in the study will be also included in this summary.

For each of the categories, the proportion of participants reporting AEs will be compared between the 2 groups using a Fisher's Exact test. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all treatment-emergent AEs, treatment-emergent AEs with Grade 3 or higher, treatment-emergent study drug-related AEs, treatment-emergent study drug-related AEs with Grade 3 or higher, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency. Treatment-emergent AEs and study-drug related treatment-emergent AEs will also be summarized by highest grade.

Data listings will be provided for the following:

- All AEs
- Study-Drug-Related AEs
- AEs with severity of Grade 3 or higher
- SAEs
- Study-Drug-Related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

7.3. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.2.2.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and PCR separately. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the DAIDS Grading Scale will be flagged in the data listings, as appropriate.

7.3.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date (and time, if applicable) of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1. Baseline and change from baseline will be compared between the treatment groups using the 2-sided Wilcoxon rank sum test.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3.

7.3.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 (July 2017) will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.3.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.3.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by laboratory test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up to 30 days after last dosing date.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.4. Body Weight, and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, and vital signs (including heart rate, respiratory rate, blood pressure, SpO_2 or PaO_2) as follows (due to different methods of measuring temperature, temperature will not be summarized):

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values on one Study Day, data will be selected for analysis as described in Section 3.6.3. No formal statistical testing is planned.

A by-subject listing of body weight, BMI, and vital signs (including heart rate, respiratory rate, temperature, blood pressure, SpO_2 and PaO_2) will be provided by subject ID number and visit in chronological order.

7.5. Prior and Concomitant Medications

Concomitant use of traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang) or investigational agents with putative antiviral activity for COVID-19 including approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc is prohibited in participants receiving RDV.

Concomitant use of investigational agents such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc while receiving RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred name in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries of concomitant medications will be provided for the Safety Analysis Set. Participants with any concomitant medications will be listed. No inferential statistics will be provided.

7.6. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy during the study.

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.2.2 using the safety analysis set.

7.8. Changes from Protocol-Specified Safety Analyses

No change from the protocol-specified safety analysis is planned.

8. REFERENCES

Whitehead J. Sample size calculations for ordered categorical data. Stat Med 1993;12 (24):2257-71.

9. SOFTWARE

SAS® Version 9.4 (SAS Institute Inc., Cary, NC.) is to be used for all programming of tables, listings, and figures.

PASS Version 14 (NCSS, LLC, Kaysville, Utah) was used for planned sample size and power calculation.

10. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

11. APPENDICES

Appendix 1. Study Procedures Table

	Screening	Baseline / Day 1[b]	Day 2	Day 3	Day 4	Day 5	Days 6 and 7	Day 8	Day 9	Day 10	Days 11, 12 and 13	Day 14	Day 28[c] Follow-up (±5 days)
Written Informed Consent	X												
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Laboratory Testing	X	X		X		X		X		X		X	
Respiratory Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X												
PK Assessments[d]		X	X		X	X	X			X			
RDV Dosing for Group 1		X	X	X	X	X							
RDV Dosing for Group 2		X	X	X	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

a Includes heart rate, respiratory rate, temperature, blood pressure, SpO2 at rest, and body weight. Body weight collected on screening and Day 1 and otherwise if available.
b Assessments need not be repeated if performed the same calendar day as screening procedures.; data collection other than adverse events should stop Day 14 or discharge whichever is earlier.
c Day 28 evaluations completed if the visit is conducted in person. Only AEs, ordinal scale, and concomitant medication review completed if visit conducted by phone.
d PK assessments sparse *or* intensive (optional for subjects/sites participating in this portion of the study) on Day 1, 2, 4, 5, 7, and 10.

Appendix 2. Programming Specifications

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

   Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

   a) AGE (years) is calculated from the number of days between the DOB and Study Day 1,

   b) Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

   c) Divide the result in (b) by 12,

   AGE the integer of the result in (c),

   Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened participants refer to all participants who are screened (ie, with non-missing screening date) and have a screening number. For summaries the same subject is counted only once.

3) Screen failure participants are the participants who were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the subject was consent to.

4) Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if subject took at least 1 dose of study drug and assigned as blank if the subject was never dosed.

6) In the disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

7) Body mass index (BMI)

   BMI will be calculated only at baseline as follows:

   BMI (weight [kg]) / (height [meters]^2)

   Baseline height and weight will be used for this calculation if available.

8) Definition of worst values for laboratory and SpO_2 and PaO_2 results.

Test	Result
ALT	Highest result
AST	Highest result
Creatinine	Highest result
Glucose	Highest result if any >ULN and none <LLN Lowest result if any <LLN and none >ULN Otherwise use the average
Total bilirubin	Highest result
GFR/Creatinine Clearance	Lowest result
Hemoglobin	Lowest result
Hematocrit	Lowest result
Platelet count	Lowest result
WBC	Lowest result
SpO_2	Lowest result
PaO_2	Lowest result

If there are 2 values with the same "worst" numerical result on the same day, the later value is chosen.

9) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

CMH test for nominal variable (Y), the p-value from the general association test should be used for nominal variables:

```
proc freq;
tables trt * Y /cmh; /*general association test*/
run;
```

CMH test for ordinal variable (Y), the p-value from the row mean score test should be used for ordinal variables:

```
proc freq;
tables trt * Y / cmh2 ; /*row mean score test*/
run;
```

Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation two-sided test should be used for continuous variables:

```
proc npar1way wilcoxon;
class trt;
var Y;
run;
```

10) Please note, "Not Permitted", "Unknown", or missing categories will be excluded from percentage calculation and also excluded for p-value generation for categorical data analysis (eg, CMH test or Fisher exact test).

11) Proportional Odds

A proportional odds model is used for the primary efficacy endpoint:

```
proc logistic;
class trt/ param  ref order  data;
model outcome(descending)   trt baseline;
run;
```

where outcome is the ordinal scale response at Day 14.

12) Binomial Response

The proportion difference between two treatment groups and its 95% CIs are calculated based on the unconditional exact method using 2 inverted 1-sided tests in SAS v9.3 or above.

The following SAS code will be used to compute cell counts and p-values.

```
data example;
input  grp trt $  outcome $ count ;

datalines;
1      Treat-A      2-Fail      x
1      Treat-A      1-Succ     xxx
1      Treat-B      2-Fail      x
1      Treat-B      1-Succ     xxx
run;

proc freq data    example;
table trt*outcome /riskdiff(CL  (exact)) alpha  0.05;
weight count; exact RISKDIFF(METHOD  SCORE);
output out  ciexact(keep  _RDIF1_ XL_RDIF1 XU_RDIF1 _RSK11_  _RSK21) riskdiff;
run;

data final(keep  A1 B1 Estimate LowerCL UpperCL ocharc1);
set ciexact;
label Estimate   "Percentage Difference"
LowerCL    "95% Lower Confidence Limit"
UpperCL    "95% Upper Confidence Limit"
A1    "Percentage of Success in Treat-A"
B1    "Percentage of Success in Treat-B";
Estimate  100*  RDIF1  ;
LowerCL    100*XL  RDIF1;
UpperCL    100*XU_RDIF1;
A1    100*_RSK11_;
```

```
B1    100*  RSK21  ;
ocharc1    right(compress(put(Estimate,8.1)) || '% (' || compress(put(LowerCL,8.1)) || '%
to ' || compress(put(UpperCL,8.1)) || '%)');
run;
```

The 95% CI for percentage estimate for each treatment is calculated based on the Clopper-Pearson exact method.

```
proc freq;
by trt;
tables event/ binomial;
exact binomial;
run;
```

Fisher's exact test for categorical response, where *trt* is the treatment, and *response* is the categorical response. P-value from 2-sided Fisher's exact test should be used.

```
proc freq data;
tables trt*response/fisher; /*p value from Fisher's exact test*/
run;
```

13) Log-rank test

Log-rank test for time to death between treatment groups:

```
proc lifetest;
strata trt;
time days*censor(0);
run;
```

The binary indicator variable (CENSOR) with a value of 1 indicates the time to the event of interest is complete or 0 indicates the time to the event is censored. DAYS is a time to event variable.

14) Hazard ratio

The following SAS code will be used to compute hazard ratio (HR) and its 95% CI:

```
proc phreg;
model days*censor(0)    trt / rl;
run;
```

15) Competing risk analysis

The following SAS code will be used to generate the cause-specific hazard ratio and 95% confidence intervals for the competing risk analysis:

```
proc phreg;
class trt;
```

```
model days*event(0, 2)    trt base/ rl;
hazardratio "Cause-specific hazard" trt;
run;
```

where EVENT 1 if the participant had the event; EVENT 2 if the participant died prior to having the event, and EVENT 0 if the subject did not have the event and did not die. BASE baseline value.

SAS code to obtain a cumulative incidence function plot and dataset for further processing for time to first event table:

```
proc lifetest outcif  outcif plots  cif;
strata trt;
time days*event(0) / failcode    1; *Note: this produces data for the event of interest only;
run;
```

SAS code to obtain support tables:

```
proc univariate;
 by trt event;
 var days;
 output pctlpre  P_ min  min max  max pctlpts   10, 25, 50, 75, 90;
run;
```

16) SAS code for stratified 2-sided Wilcoxon Rank sum test (stratified on baseline result)

```
proc freq;
   table base*trt*aval/cmh2 scores  modridit;
run;
```

where BASE is the baseline value.

17) TEAE

<u>Events with Missing Onset Day and/or Month</u>

An event is considered treatment emergent if the following 3 criteria are met:

i. The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of study drug, and

ii. The month and year (or year) of the onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug, and

iii. End date is as follows:

The (complete) end date is on or after the first dose date, or

The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or

End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date meets any of the 3 criteria specified above.

18) The number of decimal places in reporting p-values should be as follows:

a) values less than 0.001 → < 0.001

b) values 0.001 to less than 1.000 → 4 decimal places (no rounding)

19) The precision in reporting numerical values should be as follows:

Raw measurements will be reported the same as the data captured electronically or on the CRF.

Standard deviation and standard error will be reported to one more significant decimal place than the raw measurement.

Mean, median, minimum, Q1, Q3, maximum, 95% CIs will be reported to the same number of decimal places of the raw measurements.

Exceptions may be considered; for example, if more than 4 significant digits are provided for the measurement.

20) Last dose date is not expected to be missing. However, if last dose date is missing due to data issues, it will be imputed using the maximum of non-missing, non-zero dose, study drug start and stop dates.

21) Ordinal scale and oxygen support status

The oxygen support status is derived from the ordinal scale:

Ordinal Scale		Oxygen Support Status
1	Death	Death
2	Hospitalized, on invasive mechanical ventilation or ECMO	Invasive Mechanical Ventilation
3	Hospitalized, on non-invasive ventilation or high flow oxygen devices	High Flow Oxygen
4	Hospitalized, requiring low flow supplemental oxygen	Low Flow Oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	Room Air
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration)	Room Air

7	Not hospitalized	Discharge

22) Censoring rules

Time to death: subjects are censored at the last known date alive (last study day)

Time to ≥ 2 point improvement, time to ≥ 1 point improvement, time to recovery; time to modified recovery; time to room air: if a subject does not experience the event of interest and does not die, the subject is censored at the last non-missing ordinal scale assessment date.

GS-US-540-5773_Part_A_SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	22-Apr-2020 23:34:49
PPD	Regulatory Affairs eSigned	23-Apr-2020 01:13:09
PPD	Clinical Research eSigned	23-Apr-2020 05:49:24

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Name of Test Drug:	Remdesivir (RDV; GS-5734™)
Study Number:	GS-US-540-5773
Protocol Version (Date):	Amendment 3.0 (12 April 2020)
Analysis Type:	Part A Final Analysis
Analysis Plan Version:	Version 2
Analysis Plan Date:	18 May 2020
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECMO	extracorporeal membrane oxygenation
eCRF	Electronic case report form
FAS	Full Analysis Set
HLT	high-level term
LLN	lower limit of normal
LLT	lowest level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PCR	polymerase chain reaction
PT	preferred term
Q1, Q3	first quartile, third quartile
RDV	remdesivir
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal

1. INTRODUCTION

This Phase 3 study is conducted in two parts. In Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated are randomized to one of two treatment groups. Part B starts after Part A is completed and includes up to approximately 5600 participants.

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the analysis of Part A of Study GS-US-540-5773. This SAP is based on the study protocol Amendment 3.0 dated 12 April 2020 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

The purpose of this study is to provide remdesivir (RDV) to participants with severe COVID-19.

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV.

1.2. Study Design

This is a Phase 3 randomized, open-labeled, multi-center study of RDV therapy in participants with severe COVID-19.

Treatment Groups

For Part A, approximately 400 participants who meet all eligibility criteria and who are not mechanically ventilated may be randomized in a 1:1 ratio into one of the following treatment groups:

- **Treatment Group 1:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

- **Treatment Group 2:** continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Part B will enroll participants on mechanical ventilation and, after enrollment to Part A is complete, any additional participants. In Part B, up to an additional approximately 5600 participants who meet all of the eligibility criteria will be enrolled, based on whether they are mechanically ventilated at enrollment, to receive:

Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Extension Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

If the 5-day dosing regimen used in Treatment Group 1 of Part A is selected for Part B, all participants in the Extension Treatment Group and all new participants will be reassigned to receive treatment for a total of 5 days.

Key Eligibility Criteria

Participants with COVID-19 confirmed by polymerase chain reaction (PCR) who meet the following criteria:

- Willing and able to provide written informed consent (age ≥18) or assent (age ≥12 to <18, where locally and nationally approved) prior to performing study procedures
- Hospitalized
- SpO2 ≤ 94% on room air or requiring supplemental oxygen at screening
- Radiographic evidence of pulmonary infiltrates

Schedule of Assessments

The date of randomization is considered Day 1 and it is expected that all randomized participants receive their initial dose of RDV on Day 1.

On Days 1 through 14 or until discharge, whichever is earlier, vital signs including respiratory status will be measured and adverse events (AEs) and concomitant medications will be documented. Laboratory testing will be performed according to standard of care practice with results for white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing being reported to the Sponsor. Clinical status will be recorded on the 7-point ordinal scale for each day.

In addition, even if not performed as standard of care, white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST will be performed at Days 1, 3, 5, 8, 10, and 14 or until discharge, whichever is earlier.

Pharmacokinetic (PK) assessments may be conducted at selected sites. At participating sites, sparse PK samples may be collected at Day 2 (end of infusion), and Day 4 (pre-dose and end of infusion), and Day 7 (pre-dose and end of infusion). Up to 20 participants may have intensive PK samples collected at Day 1, and Day 5 or Day 10 at pre-dose and end of infusion, and the following times from start of infusion: 1 hour, 3 hours, 6 hours, 8 hours, 12 hours and 24 hours. All blood samples for PK assessments will be drawn from the opposite arm than that used to administer RDV.

Randomization

Participants who meet eligibility criteria are randomized in a 1:1 ratio to 1 of 2 treatment groups on Day 1 using an IWRS and assigned a subject number. Randomization is not stratified.

Sites

Up to approximately 160 centers globally.

Duration of Treatment

Participants will receive study treatment with RDV for 5 days (Treatment Group 1) or 10 days (Treatment Group 2) in Part A, and 10 days (Mechanically Ventilated Treatment Group), or either 5 or 10 days (Extension Treatment Group) in Part B. If the participant is discharged, RDV treatment will end at that time.

Discontinuation Criteria

Study drug dosing in an individual participant will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if any of the following occurs:

- Any serious adverse event (SAE) or ≥ Grade 3 AE suspected to be related to RDV.
- Any elevations in ALT > 5 × ULN; or ALT > 3 × ULN and total bilirubin > 2 × ULN, confirmed by immediate repeat testing.
- Creatinine clearance < 30mL/min

Discontinuation of study medication is not a seriousness criterion.

End of Study

The end of the study will be the last participant's last observation (or visit).

1.3. Sample Size and Power

In Part A, a total of approximately 400 participants will be randomized in a 1:1 ratio to 2 groups (200 participants per group).

The sample size computation is based on an assumed distribution of the 7-point ordinal scale on Day 14 for Part A Treatment Group 1. The odds ratio represents the odds of improvement in the ordinal scale for Treatment Group 2 relative to Treatment Group 1. The sample size needed to detect a given odds ratio for a 1:1 randomization using a 2-tailed test at level α is given by:

$$12\ (z_{\propto/2} + z_{\beta})^2\ /\ \theta^2(1 - \sum_{i=1}^{7} \rho_i^3)$$

Where θ is the log odds ratio, ρ_i is the overall probability (combined over both treatment groups) of being in the ith category of the ordinal outcome, and $z_{\alpha/2}$ and z_{β} are the 1- α /2 and β quantiles of the standard normal distribution {Whitehead 1993}.

A sample size of 400 participants (200 in each group) achieves > 85% power to detect an odds ratio of 1.75 using a two-sided significance level of 0.05. In this sample size calculation, it is assumed that the probability distribution of the ordinal scale at Day 14 for Treatment Group 1 is as follows:

1. Death, 2%
2. Hospitalized, on invasive mechanical ventilation or ECMO, 4%
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices, 7%
4. Hospitalized, requiring low flow supplemental oxygen, 13%
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise), 16%
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration), 20%
7. Not hospitalized, 38%

The sample size calculation was performed using software PASS (Version 14.0).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. DMC Analysis

The DMC will review the results from the analysis of the Day 14 snapshot.

2.1.2. Primary Analysis

The primary analysis will be performed after availability of data from participants in Part A of the study who have completed 14 days or prematurely terminated from Part A of the study on or prior to Day 14.

2.1.3. Part A Final Analysis

The final analysis for participants randomized in Part A will be performed after all these participants have completed Part A of the study or prematurely terminated from Part A of the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. This SAP describes the statistical analysis methods and data presentations to be used for the analysis of Part A.

2.2. Final Analysis

The final analysis for this study will be performed after all participants have completed Part B of the study or prematurely terminated from the study (Part A or Part B), outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

By-subject listings will be presented for all participants in the All Randomized Analysis Set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a subject. The treatment group to which participants were randomized will be used in the listings.

3.1. Analysis Sets

Analysis sets define the participants to be included in an analysis. Analysis sets and their definitions are provided in this section. Participants included in each analysis set will be determined before database finalization for the primary analysis. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of participants in each analysis set will be provided by treatment group and in total.

3.1.1. All Randomized Analysis Set

The **All Randomized Analysis Set** will include all participants who are randomized into Part A of the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The primary analysis set for efficacy analysis is defined as the **Full Analysis Set (FAS)**, which will include all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized.

3.1.3. Safety Analysis Set

The primary analysis set for safety analyses is defined as the **Safety Analysis Set**, which will include all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of RDV. Participants will be grouped according to the treatment to which they were randomized for Part A.

3.2. Subject Grouping

Participants will be grouped by randomized treatment (RDV for 5 Days and RDV for 10 Days), regardless of the actual number of days of treatment.

3.2.1. Subject Subgroups for Efficacy Analyses

The primary endpoint will be analyzed for the following subject subgroups:

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Oxygen support status based on the 7-point ordinal scale: (a) Invasive mechanical ventilation, (b) high flow oxygen, (c) low flow oxygen, and (d) room air (See Appendix 2)
- Country: (a) USA, (b) Italy, and (c) ex-Italy

3.2.2. Subject Subgroups for Safety Analyses

Incidence of all treatment-emergent AEs (TEAEs) will be summarized for the following subject subgroups:

- Age (years): (a) < 65 and (b) ≥ 65
- Sex at birth: (a) male and (b) female
- Country: (a) USA, (b) Italy, and (c) ex-Italy

Survival will be summarized for the following subject subgroups:

- Age (years): (a) < 65, further broken down by (a1) < 50 and (a2) ≥ 50 to < 65, and (b) ≥ 65, further broken down by (b1) ≥ 65 to < 75 and (b2) ≥ 75
- Sex at birth: (a) male and (b) female
- Country: (a) USA, (b) Italy, and (c) ex-Italy

3.3. Multiple Comparisons

No prespecified multiplicity adjustments are planned for confidence intervals or statistical tests.

3.4. Missing Data and Outliers

3.4.1. Missing Data

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

In this study, a missing pre-treatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary. The handling of missing or incomplete dates for AE onset is described in Section 7.2.5.2, and for prior and concomitant medications in Section 7.5.

3.4.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.5. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the first dose date will be used instead. If a randomized subject was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.
- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

3.6. Analysis Visit Windows

3.6.1. Definition of Study Day

Study Day 1 is defined as the first dosing date of study drug.

Study Days are calculated relative to Study Day 1 and derived as follows:

- For postdose study days: Assessment Date First Dosing Date + 1
- For days prior to the first dose: Assessment Date First Dosing Date

Therefore, **Study Day 1**/ **First Dose Date** is the day of first dose of study drug administration, as recorded on the Study Drug Administration eCRF form.

Last Dose Date is defined as the maximum, nonmissing, nonzero dose end date of treatment recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Withdrawn" box checked for participants who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF. Refer to Appendix 2 for missing date imputation, if necessary.

Last Study Date is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 28-day follow-up visit date, for participants who prematurely discontinued study according to the Study Completion eCRF.

Baseline value is defined as the last value obtained on or prior to the first dose date (and time, if available) unless otherwise specified (see Section 3.6.3).

3.6.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purposes of analysis, observations will be assigned to analysis windows. The study day as defined in Section 3.6.1 will be used when data are summarized by visit.

Vital signs were to be collected daily; therefore, windows are not assigned and results will be summarized for each Study Day, except for Study Day 28. For Study Day 28, the nominal day is Study Day 28, the lower limit is Study Day 15 and there is no upper limit.

Ordinal scale results were to be recorded prior to dosing on Study Day 1. The worst result for each day from Day 1 through the earliest of discharge date or Day 14 was to be recorded. For subjects who were discharged after Day 14, changes in score category were to be recorded each day from Day 15 to the earliest of discharge date or Day 28. For the ordinal scale, baseline is defined as the value recorded prior to dosing, or the last value obtained prior to the first dose date if the predose value was not recorded on the day of dosing. Results will be summarized for each Study Day without windows. If more than one result was reported on the same day, the worst result will be selected.

SARS-CoV-2 PCR results were to be reported (if collected) each day. However, the windows in Table 3-1 will be assigned to account for missing data.

The analysis windows for hematology and chemistry laboratory parameters and PCR are presented in Table 3-1.

Table 3-1. Analysis Windows for PCR and Hematology and Chemistry Laboratory Tests (hemoglobin, hematocrit, platelet count, WBC, ALT, AST, total bilirubin, glucose, serum creatinine, and eGFR)

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline	1		1 (pre dose)*
Day 3	3	1 (post dose)*	3
Day 5	5	4	6
Day 8	8	7	8
Day 10	10	9	11
Day 14	14	12	15
Post Day 14**	28	16	

* For Baseline, the upper limit includes values collected at or prior to the first dose date/time. For Day 3, the lower limit includes values collected after the first dose date/time on Day 1.
** Post Day 14 laboratory values will be considered for treatment emergent laboratory presentations only.

3.6.3. Selection of Data in the Event of Multiple Records for an Analysis Visit Day

Depending on the statistical analysis method, single values may be required for each Study Day or analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis does not require 1 value per Study Day or analysis window.

If multiple valid, nonmissing measurements exist for a Study Day/analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date (and time, if available) of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity for categorical data.
- For postbaseline values:

  For windows spanning multiple days, the record(s) collected on the day closest to the nominal day will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

  - For PCR, if there is more than 1 record on the selected day, the latest value will be selected. If there are multiple records with the same time or no time recorded on the same day, the selected value will be the highest severity (ie, highest value or positive result).
  - For laboratory values (other than PCR) and SpO2 and PaO2, if there is more than 1 record on the selected day, the worst value will be selected. See Appendix 2 for definition of worst value.
  - For other parameters, if there is more than 1 record on the selected day, the average will be taken for continuous data and the worst severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

The number and percentage of participants randomized at each investigator site will be summarized by treatment group and overall using the Safety Analysis Set. The denominator for this calculation will be the number of participants in the Safety Analysis Set.

The summary of subject disposition will be provided by treatment group and overall for all screened participants. This summary will include the number of participants screened, screen failure participants who were not randomized, participants who met all eligibility criteria and were not randomized, participants randomized, participants randomized but never treated, participants in the Safety Analysis Set, and participants in the FAS.

In addition, the number and percentage of the participants in the following categories will be summarized:

- Completed randomized 5-day or 10-day treatment on study drug as recorded on the Study Drug Completion form
- Prematurely discontinuing study drug prior to completion of 5 days of dosing (Treatment Group 1) or 10 days of dosing (Treatment Group 2) with summary of reasons for discontinuing study drug as recorded on the Study Drug Completion form
- Still on study up to the data cut date (if applicable)
- Completed study
- Prematurely discontinuing from study (prior to the data cut date for the primary analysis only) with summary of reasons for discontinuing study as recorded on the Study Completion form

The denominator for the percentages of participants in each category will be the number of participants in the Safety Analysis Set.

No inferential statistics will be generated. A data listing of reasons for study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure

4.2.1. Exposure to Study Drug

Number of doses received will be summarized by treatment group for the Safety Analysis Set.

Time to premature discontinuation of study drug will be analyzed using the Kaplan-Meier method by treatment group. Subjects who completed study drug will be censored at the last dose date.

4.3. Protocol Deviations

A listing will be provided for all randomized participants who violated at least 1 inclusion or exclusion criterion. The listing will include the criteria not met.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation reason and the total number of important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the FAS. A by-subject listing will be provided for those participants with important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, sex, race/ethnicity, and age) and baseline characteristics (eg, body weight, height, and body mass index [BMI]) will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percentage of participants for categorical data. The summaries of demographic data and baseline subject characteristics will be provided for the Safety Analysis Set.

Age groups (< 50, ≥ 50 to < 65, ≥ 65 to < 75 and ≥ 75) will be summarized by treatment group and overall.

For categorical data, the Cochran-Mantel-Haenszel (CMH) test (ie, general association statistic for nominal data and row mean scores for ordinal data [age groups]) will be used to compare the 2 treatment groups. For continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

Similar summaries will be produced for the following subgroups: USA, Italy and ex-Italy.

A by-subject demographic listing will be provided.

5.2. Other Baseline Characteristics

The following baseline disease characteristics will be summarized by treatment group and overall using descriptive statistics:

- Clinical status (7-point ordinal scale)
- Duration of hospitalization prior to first dose of RDV
- Duration of symptoms prior to first dose of RDV
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Oxygen support status based on the 7-point ordinal scale (invasive mechanical ventilation, high flow oxygen, low flow oxygen, room air)

For categorical data, the CMH test (row means scores differ statistic for ordinal data [oxygen support status]) will be used to compare the 2 treatment groups. For clinical status and continuous data, the 2-sided Wilcoxon rank sum test will be used to compare the 2 treatment groups.

Similar summaries will be produced for the following subgroups: USA, Italy and ex-Italy.

5.3. Medical History

Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is considered to be preexisting and should be documented as medical history. General medical history data will be collected at screening. It will be coded using the current version of MedDRA. A summary table will present the percentages of participants reporting each medical history preferred term, sorted first in alphabetical order by system organ class (SOC) and then by preferred term (PT) in descending order of total frequency within SOC.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is clinical status assessed by a 7-point ordinal scale on Day 14. The endpoint will be derived by combining the available death, hospital discharge alive and ordinal scale assessment reported by the site, where death supersedes discharge alive and discharge alive supersedes the ordinal scale score reported by the site. The proportion of participants for each ordinal scale category endpoint by treatment group is expressed as percentages for presentation purpose.

Sites were instructed to report the worst ordinal scale category for each day. Therefore, the ordinal scale result on the day the participant was discharged alive does not necessarily reflect Not hospitalized (7). The definition of the 7-point ordinal scale endpoint for the efficacy analyses is defined as follows:

- If a participant dies while hospitalized (as recorded on the Death eCRF and Hospitalization eCRF), the endpoint on the day of death and all subsequent days through Day 28 will be set to Death (1)
- If the participant is discharged alive, the endpoint on the day of discharge alive and all subsequent days through Day 28 will be set to Not hospitalized (7)
- If the participant is discharged alive and dies on the same day or a later day (as recorded on the Death eCRF and Hospitalization eCRF), the endpoint on the day of discharge alive and all subsequent days until the day of death will be set to Not hospitalized (7). On the day of death and all subsequent days through Day 28, the endpoint will be set to Death (1),

Every effort will be made to obtain clinical status data for all participants prior to discharge alive. The last known clinical status will be used for days with missing clinical status (eg , where the reason for Hospital Discharge is not “Discharged Alive” and the subject has not died). All post-baseline days with missing ordinal scale score, from Day 2 to Day 14 and Day 28, will use the previous last known clinical status.

6.1.2. Statistical Hypothesis for the Primary Efficacy Endpoint

Null hypothesis: The odds of improvement for the 5-day treatment group (Treatment Group 1) is the same as the odds of improvement for the 10-day treatment group (Treatment Group 2) with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

Alternative hypothesis: The odds of improvement for the 5-day treatment group (Treatment Group 1) is different from the odds of improvement for the 10-day treatment group (Treatment Group 2) with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

6.1.3. Primary Analysis of the Primary Efficacy Endpoint

The primary endpoint will be analyzed using a proportional odds model including treatment as the independent variable and baseline score as a continuous covariate. The odds ratio and 95% confidence interval will be provided. The corresponding SAS code is as following:

```
proc logistic data  example;
class trt/ param  ref order  data;
model outcome(descending)   trt baseline;
run;
```

The percentage of participants in each category will be summarized by treatment group. The assumption of odds proportionality will be assessed using a score test and reported. It will be concluded that 10-day treatment is superior to 5-day treatment if the lower bound of the 2-sided 95% CI of the odds ratio (10-day / 5-day) on Day 14 is more than 1.

6.1.4. The FAS will be the primary analysis set for efficacy endpoint evaluation. Secondary Analyses of the Primary Efficacy Endpoint

As supportive analyses of the primary endpoint, the following will be conducted:

- The primary endpoint will be analyzed using a proportional odds model including treatment as the independent variable (dropping baseline score as a covariate).
- The clinical status at Day 14 will be compared between treatment groups using a 2-sided Wilcoxon Rank sum test, stratified on baseline clinical status.

The change from baseline in clinical status category on Days 5, 7, 11, 14, 28 and last available assessment will be summarized by treatment groups using descriptive statistics. Change from baseline will be compared between the treatment groups using a 2-sided Wilcoxon Rank sum test. This analysis will use the definition specified in Section 6.1.1.

The number and percentage of participants in each clinical status category for each day from Baseline through Day 14 and at Day 28 and using the last available assessment will be summarized by treatment group. These results will be summarized using the clinical status definition in Section 6.1.1 and two methods: (1) with the definition specified in Section 6.1.1 and (2) with the definition specified in Section 6.1.1 but excluding days with missing ordinal scale score not due to death or discharge alive. In addition, stacked bar charts by study day (Baseline through Day 14 and at Day 28) will be produced by treatment group using the definition specified in Section 6.1.1.

The number and percentage of participants in each clinical status category for each day from Baseline through Day 14 and at Day 28 and last available assessment will be summarized within each subgroup defined in Section 3.2.1. These results will use the definition specified in Section 6.1.1.

The above analyses will be conducted using the FAS.

6.2. Other Endpoints of Interest

The other endpoints of interest include:

- Number of subjects with negative PCR on Days 5 and 10
- Number of days of oxygen support while hospitalized through discharge alive, death or Day 14 based on the 7-point ordinal scale reported values (See Appendix 2). This summary will present results separately for subjects who died on or prior to Day 14 and those who were discharged alive on or prior to Day 14 and will include:

  Days on invasive mechanical ventilation

  Days on high flow oxygen devices

  Days requiring low flow supplemental oxygen

  Because oxygen support status was collected only while the subject was in the hospital, if a subject was discharged alive and died afterwards, the subject will be included only in the summary for subjects discharged alive.

- Shift in oxygen support status from baseline to Days 5, 7, 11, 14, 28 and last available assessment
- Duration of hospitalization (days) (duration from hospital admission and duration from Day 1). For the primary analysis, duration of hospitalization through Day 14 is calculated for subjects who were discharged alive on or prior to Day 14. For the final Part A analysis, duration of hospitalization is calculated through Day 28 for subjects who were discharged alive prior to Day 28. If subjects were rehospitalized for COVID-19 related reasons, the hospitalization discharge information is entered in the eCRF database using the latest hospitalization admission.
- All-cause mortality
- Time to clinical improvement (days): Clinical improvement is defined as a ≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale using the definition specified in Section 6.1.1.
- Percentage of subjects with a ≥ 2-point improvement or discharged alive based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28, and last available assessment
- Time to ≥ 1-point improvement (days) from baseline clinical status on the 7-point ordinal scale using the definition specified in Section 6.1.1.
- Percentage of subjects with a ≥ 1-point improvement based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment

- Time to recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1, where recovery is defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Percentage of subjects with recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to modified recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1, where modified recovery is defined as an improvement from a baseline score of 2 through 4 to a score of 5, 6 or 7, or an improvement from a baseline score of 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Percentage of subjects with modified recovery based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to room air (for subjects not on room air at baseline) based on the 7-point ordinal scale using the definition specified in Section 6.1.1, defined as an improvement from a baseline score of 2 through 4 to a score of 5, 6 or 7
- Percentage of subjects with improvement to room air based on the 7-point ordinal scale using the definition specified in Section 6.1.1 on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment

6.2.1. Analysis of Other Endpoints of Interest

The number and percent of subjects with negative PCR on Days 5 and 10 will be summarized. The point estimate of the treatment difference and the associated 95% confidence intervals will be constructed based on an unconditional exact method using 2 inverted 1-sided tests.

Number of days of oxygen support status modes (invasive mechanical ventilation, high flow oxygen, low flow oxygen) will be compared between the treatment groups using the Wilcoxon Rank sum test. Number of days will be calculated as the number of days oxygen support was reported on the 7-point ordinal scale eCRF through death, discharge alive, or Day 14.

A shift table of baseline oxygen support status (death, invasive mechanical ventilation, high flow oxygen, low flow oxygen, room air, discharge alive) to Days 5, 7, 11, 14, 28 and the last available status will be provided. For the primary analysis, the last available assessment on or prior to Day 14 will be included.

Duration of hospitalization will be calculated only for participants who are discharged alive on or prior to Day 28 and will be compared between the treatment groups using the Wilcoxon Rank sum test.

All-cause mortality will be estimated using the Kaplan-Meier product limit method with all available data. The treatment groups will be compared using the log-rank test stratified by baseline clinical status. The hazard ratio and 95% confidence interval will be provided based on a stratified proportional hazards model. Participants who did not die will be censored at the last study day.

Days to clinical improvement will be estimated using a competing risk analysis approach, with death as the competing risk. Baseline score will be included in the model as a continuous covariate. The hazard ratio and 95% confidence interval will be provided. Subjects without clinical improvement will be censored on the day of the last non-missing ordinal scale assessment.

Days to recovery, days to modified recovery and days to room air will be estimated using a competing risk analysis approach, with death as the competing risk. Baseline score will be included in the model as a continuous covariate. The hazard ratio and 95% confidence interval will be provided. Subjects without recovery will be censored on the day of the last non-missing ordinal scale assessment.

The number and percent of subjects with ≥ 1-point improvement, ≥ 2-point improvement, recovery, modified recovery, and improvement to room air will be presented with 95% confidence intervals on Day 5, Day 7, Day 11 and Day 14. The point estimate of the treatment difference and the associated 95% confidence intervals will be provided. For the number of subjects on room air, only subjects on room air at baseline will be included.

Point estimates of treatment differences in percentages and 95% confidence intervals will be calculated based on stratum-adjusted Mantel-Haenszel proportion where the stratum is baseline clinical status {Koch 1989} (see Appendix 2). Comparisons between treatment groups will be performed using the CMH test stratified on baseline clinical status.

Analyses will be performed using the FAS.

6.3. Changes from Protocol-Specified Efficacy Analyses

The protocol stated that participants who have missing clinical status information on Day 14 will be excluded from the primary analysis; however death and discharge alive information as well as last known clinical status will be used for Day 14 (see Section 6.1.1).

The protocol stated that endpoints that are measured as time to first event will be compared between treatment groups using the log-rank test; however, a competing risk approach (with death as the competing risk) will be used. Treatment groups will be compared using the hazard ratio with 95% confidence interval.

The endpoint of interest of time to SpO_2 > 94% on room air was changed to time to room air because SpO_2 was not collected routinely for participants on room air.

The endpoint of interest of time to first negative PCR was updated to the number of subjects with negative PCR on Days 5 and 10 because PCR was not collected on a routine basis.

7. SAFETY ANALYSES

Safety data will be summarized for the participants in the safety analysis set. All safety data collected on or after the date that study drug was first dispensed through 30 days after last dose will be summarized by treatment group for the Safety Analysis Set, unless specified otherwise. All safety data will be included in data listings.

7.1. Secondary Endpoint

The secondary endpoint of the percentage of participants with any treatment emergent adverse events will be compared between the 2 groups using the CMH test stratified on baseline clinical status. The point estimate of the treatment difference and the associated 95% confidence intervals will be calculated based on stratum-adjusted Mantel-Haenszel proportion where the stratum is baseline clinical status (see Appendix 2).

7.2. Adverse Events and Deaths

7.2.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. SOC, high-level group term (HLGT), high-level term (HLT), PT, and lowest-level term (LLT) will be provided in the AE dataset.

7.2.2. Adverse Event Severity

The severity of AEs will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017. For each episode, the highest grade attained should be reported as defined in the grading scale. The DAIDS scale is available at the following location:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening) or Grade 5 (fatal) according to toxicity criteria specified in the document above. The severity grade of events for which the investigator did not record severity will be left as “missing” for data listings.

7.2.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected “Related” on the AE eCRF to the question of “Related to Study Treatment.” Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.2.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology Department before data finalization.

7.2.5. Treatment-Emergent Adverse Events

7.2.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.2.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The month and year (or year) of the AE onset is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date marked as ongoing or on or after the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.2.6. Summaries of Adverse Events and Deaths

The number and percentage of participants who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group using the Safety Analysis Set:

- Grade 3 or higher treatment-emergent AEs
- All treatment-emergent study drug-related AEs
- Grade 3 or higher treatment-emergent study drug-related AEs

- All treatment-emergent SAEs
- All treatment-emergent study drug-related SAEs
- All treatment-emergent AEs that caused premature discontinuation from study drug
- Treatment-emergent deaths

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of participants who experienced the above AEs. Treatment-emergent deaths observed in the study will be also included in this summary.

For each of the categories, the percentage of participants reporting AEs will be compared between the 2 groups using the CMH test stratified on baseline clinical status. The point estimate of the treatment difference and the associated 95% confidence intervals will be calculated based on stratum-adjusted Mantel-Haenszel proportion where the stratum is baseline clinical status (see Appendix 2).

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all treatment-emergent AEs, treatment-emergent AEs with Grade 3 or higher, treatment-emergent study drug-related AEs, treatment-emergent study drug-related AEs with Grade 3 or higher, and treatment-emergent SAEs will be summarized by PT only, in descending order of total frequency. Treatment-emergent AEs and study-drug related treatment-emergent AEs will also be summarized by highest grade.

Data listings will be provided for the following:

- All AEs
- Study-Drug-Related AEs
- AEs with severity of Grade 3 or higher
- SAEs
- Study-Drug-Related SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

7.3. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.2.2.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and PCR separately. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the DAIDS Grading Scale will be flagged in the data listings, as appropriate.

7.3.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window
- Percentage change from baseline to each postbaseline analysis window (if specified)

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date (and time, if applicable) of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1. Baseline and change from baseline will be compared between the treatment groups using the 2-sided Wilcoxon rank sum test.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.6.3.

7.3.2. Graded Laboratory Values

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1 (July 2017) will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.3.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.3.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by laboratory test and treatment group; participants will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Treatment-emergent laboratory abnormalities
- Treatment-emergent Grade 3 and 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with nonmissing postbaseline values up to 30 days after last dosing date.

A by-subject listing of laboratory abnormalities and Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order.

7.3.3. Liver-Related Laboratory Evaluations

Subjects with AST or ALT > 3 × ULN will be listed.

7.4. Body Weight, and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, and vital signs (including heart rate, respiratory rate, blood pressure) as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values on one Study Day, data will be selected for analysis as described in Section 3.6.3. No formal statistical testing is planned.

Temperature will not be summarized due to different methods of measuring temperature. SpO_2 and PaO_2 will not be summarized due to multiple measures through varying oxygen supplementation methods.

A by-subject listing of body weight, BMI, and vital signs (including heart rate, respiratory rate, temperature, blood pressure, SpO_2 and PaO_2) will be provided by subject ID number and visit in chronological order.

7.5. Prior and Concomitant Medications

Concomitant use of traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang) or investigational agents with putative antiviral activity for COVID-19 including approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc is prohibited in participants receiving RDV.

Concomitant use of investigational agents such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc while receiving RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of participants for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered by preferred name in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries of concomitant medications will be provided for the Safety Analysis Set. Participants with any concomitant medications will be listed. No inferential statistics will be provided.

7.6. Other Safety Measures

A data listing will be provided for participants experiencing pregnancy during the study.

7.7. Subject Subgroup for Safety Endpoints

Incidence of all treatment-emergent AEs will be repeated within each subgroup defined in Section 3.2.2 using the safety analysis set.

7.8. Changes from Protocol-Specified Safety Analyses

The protocol stated that the secondary endpoint of particpants with treatment emergent AEs would be compared between the treatment groups using a Fisher's Exact test. However, a CMH test stratified on baseline clinical status will be used to account for differences in baseline clinical status.

8. REFERENCES

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

Whitehead J. Sample size calculations for ordered categorical data. Stat Med 1993;12 (24):2257-71.

9. SOFTWARE

SAS® Version 9.4 (SAS Institute Inc., Cary, NC.) is to be used for all programming of tables, listings, and figures.

PASS Version 14 (NCSS, LLC, Kaysville, Utah) was used for planned sample size and power calculation.

10. SAP REVISION

Revision Date	Section	Summary of Revision	Reason for Revision
15 May 2020	3.6.2, 7.4	SpO_2 and PaO_2 summaries removed	Removed because they were collected under various oxygen support statuses
	3.6.3, 4.1, 6.1.3	Minor updates to wording and formats	Clarity and consistency
	5,1	Age groups added to list of baseline variables to be summarized	Clarity and consistency
	6.1.4	Day 28 and last available assessment were added to summaries	Omission
	6.2	Other endpoints of interest were clarified	Clarity and consistency
	6.2.1, 7.1, 7.8, Appendix 2	Analyses adjusting for baseline clinical status were added	Clarity and consistency
	7.3.2.2	Description of listing was updated	Clarity and consistency
	7.3.3	Listing added	Omission

11. APPENDICES

Appendix 1. Study Procedures Table

	Screening	Baseline / Day 1[b]	Day 2	Day 3	Day 4	Day 5	Days 6 and 7	Day 8	Day 9	Day 10	Days 11, 12 and 13	Day 14	Day 28[c] Follow-up (±5 days)
Written Informed Consent	X												
Medical History	X												
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Laboratory Testing	X	X		X		X		X		X		X	
Respiratory Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Ordinal Scale		X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X												
PK Assessments[d]		X	X		X	X	X			X			
RDV Dosing for Group 1		X	X	X	X	X							
RDV Dosing for Group 2		X	X	X	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

a Includes heart rate, respiratory rate, temperature, blood pressure, SpO2 at rest, and body weight. Body weight collected on screening and Day 1 and otherwise if available.
b Assessments need not be repeated if performed the same calendar day as screening procedures.; data collection other than adverse events should stop Day 14 or discharge whichever is earlier.
c Day 28 evaluations completed if the visit is conducted in person. Only AEs, ordinal scale, and concomitant medication review completed if visit conducted by phone.
d PK assessments sparse *or* intensive (optional for subjects/sites participating in this portion of the study) on Day 1, 2, 4, 5, 7, and 10.

Appendix 2. Programming Specifications

1) If the age from the Day 1 eCRF is not available, age will be calculated as follows:

   Only year is provided for the date of birth (DOB). Use July 1 for the month and day.

   a) AGE (years) is calculated from the number of days between the DOB and Study Day 1,

   b) Use the SAS INTCK function to determine the number of "1st-of-month days" (eg, January 1st, February 1st, March 1st) between DOB and Day 1 (inclusive),

   c) Divide the result in (b) by 12,

   AGE the integer of the result in (c),

   Age for laboratory test reference range will be based on the age at the sample collection date.

2) All screened participants refer to all participants who are screened (ie, with non-missing screening date) and have a screening number. For summaries the same subject is counted only once.

3) Screen failure participants are the participants who were screened and answered "No" for any inclusion criteria or "Yes" for any exclusion criteria regardless of which version of protocol the subject was consent to.

4) Participants in the randomized analysis set are defined as participants randomized into the study. IXRSRAND is the source to determine whether the subject is randomized (ie, subject with non-missing RGMNDTN in the IXRSRAND dataset), and confirmed by the eCRF ENROLL dataset (ie, ENROLLYN "Yes" in ENROLL dataset).

5) Randomized treatment (ie, TRT01P in ADSL) is derived from IXRSRAND, while actual treatment received (ie, TRT01A in ADSL) is assigned as the randomized treatment if subject took at least 1 dose of study drug and assigned as blank if the subject was never dosed.

6) In the disposition table, the reasons for premature discontinuation are displayed in the order as they appear on the eCRF.

7) Body mass index (BMI)

   BMI will be calculated only at baseline as follows:

   BMI (weight [kg]) / (height [meters]^2)

   Baseline height and weight will be used for this calculation if available.

8) Definition of worst values for laboratory and SpO_2 and PaO_2 results.

Test	Result
ALT	Highest result
AST	Highest result
Creatinine	Highest result
Glucose	Highest result if any >ULN and none <LLN Lowest result if any <LLN and none >ULN Otherwise use the average
Total bilirubin	Highest result
GFR/Creatinine Clearance	Lowest result
Hemoglobin	Lowest result
Hematocrit	Lowest result
Platelet count	Lowest result
WBC	Lowest result
SpO_2	Lowest result
PaO_2	Lowest result

If there are 2 values with the same "worst" numerical result on the same day, the later value is chosen.

9) SAS codes for the treatment comparison for demographics and baseline characteristics tables.

CMH test for nominal variable (Y), the p-value from the general association test should be used for nominal variables:

```
proc freq;
tables trt * Y /cmh; /*general association test*/
run;
```

CMH test for ordinal variable (Y), the p-value from the row mean score test should be used for ordinal variables:

```
proc freq;
tables trt * Y / cmh2 ; /*row mean score test*/
run;
```

Wilcoxon rank sum test for continuous variable (Y), the p-value from the normal approximation two-sided test should be used for continuous variables:

```
proc npar1way wilcoxon;
class trt;
var Y;
run;
```

10) Please note, "Not Permitted", "Unknown", or missing categories will be excluded from percentage calculation and also excluded for p-value generation for categorical data analysis (eg, CMH test or Fisher exact test).

11) Proportional Odds

A proportional odds model is used for the primary efficacy endpoint:

```
proc logistic;
class trt/ param  ref order  data;
model outcome(descending)   trt baseline;
run;
```

where outcome is the ordinal scale response at Day 14.

12) Confidence Interval for single percentage

The 95% CI for percentage estimate for each treatment is calculated based on the Clopper-Pearson exact method.

```
proc freq;
by trt;
tables event/ binomial;
exact binomial;
run;
```

13) Treatment difference in percentages not adjusted by baseline clinical status

The percentage difference between two treatment groups and its 95% CIs are calculated based on the unconditional exact method using 2 inverted 1-sided tests in SAS v9.3 or above.

The following SAS code will be used to compute cell counts and p-values.

```
data example;
input  grp trt $  outcome $ count ;

datalines;
1      Treat-A      2-Fail      x
1      Treat-A      1-Succ     xxx
1      Treat-B      2-Fail      x
1      Treat-B      1-Succ     xxx
run;

proc freq data    example;
table trt*outcome /riskdiff(CL  (exact)) alpha  0.05;
weight count; exact RISKDIFF(METHOD  SCORE);
output out  ciexact(keep  _RDIF1_ XL_RDIF1 XU_RDIF1 _RSK11_  _RSK21) riskdiff;
run;
```

```
data final(keep  A1 B1 Estimate LowerCL UpperCL ocharc1);
set ciexact;
label Estimate   "Percentage Difference"
LowerCL    "95% Lower Confidence Limit"
UpperCL    "95% Upper Confidence Limit"
A1    "Percentage of Success in Treat-A"
B1    "Percentage of Success in Treat-B";
Estimate  100*  RDIF1  ;
LowerCL    100*XL_RDIF1;
UpperCL    100*XU_RDIF1;
A1    100*  RSK11  ;
B1    100*  RSK21  ;
ocharc1    right(compress(put(Estimate,8.1)) || '% (' || compress(put(LowerCL,8.1)) || '%
to ' || compress(put(UpperCL,8.1)) || '%)');
run;
```

The 95% CI for percentage estimate for each treatment is calculated based on the Clopper-Pearson exact method.

```
proc freq;
by trt;
tables event/ binomial;
exact binomial;
run;
```

14) Treatment difference in percentages adjusted by baseline clinical status

The baseline stratum weighted difference in rate ($P_1 \quad P_2$) and its 95% CI will be calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion as described as follows {Koch 1989}, where the stratification factor is baseline clinical status:

$$P_1 \quad P_2 \pm Z_{(1\ \alpha/2)} * SE(P_1 \quad P_2),$$

where

- $(P_1 \quad P_2) \quad \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h \quad p_{1h} \quad p_{2h}$ is the difference in the response rate between the Treatment Groups 1 and 2 in stratum h ($h \quad 1$ to 4).

- $w_h \quad \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{1h} and n_{2h} are the sample sizes of the Treatment Groups 1 and 2 in stratum h.

- SE(P_1 P_2) $\sqrt{\dfrac{\sum w_h^2\left[\dfrac{p_{1h}^*(1 \quad p_{1h}^*)}{n_{1h} \quad 1}+\dfrac{p_{2h}^*(1 \quad p_{2h}^*)}{n_{2h} \quad 1}\right]}{(\sum w_h)^2}}$, where $p_{1h}^* \quad \dfrac{m_{1h}+0.5}{n_{1h}+1}$ and $p_{2h}^* \quad \dfrac{m_{2h}+0.5}{n_{2h}+1}$. m_{1h} and m_{2h} are the number of subjects with the event in Treatment Groups 1 and 2 in stratum *h*.

- $\alpha \quad 0.05$

- $Z_{(1 \ \alpha/2)} \quad Z_{0.975} \quad 1.96$ is the 97.5th percentile of the normal distribution

Note that if the computed lower confidence bound is less than 1, the lower bound is defined as 1. If the computed upper confidence bound is greater than 1, the upper bound is defined as 1.

15) CMH test for difference in percentages

The following SAS code will be used to test percentages adjusting for baseline status:

```
proc freq;
tables base*trt*response/cmh; * p-value from general association;
run;
```

16) Log-rank test

Log-rank test for time to death between treatment groups:

```
proc lifetest;
strata base;
time days*censor(0);
test trt;
run;
```

The binary indicator variable (CENSOR) with a value of 1 indicates the time to the event of interest is complete or 0 indicates the time to the event is censored. DAYS is a time to event variable.

17) Hazard ratio

The following SAS code will be used to compute hazard ratio (HR) and its 95% CI:

```
proc phreg;
class trt;
model days*censor(0)    trt;
hazardratio '10 vs 4' trt;
strata base;
```

```
run;
```

18) Competing risk analysis

The following SAS code will be used to generate the cause-specific hazard ratio and 95% confidence intervals for the competing risk analysis:

```
proc phreg;
class trt;
model days*event(0, 2)    trt base/ rl;
hazardratio "Cause-specific hazard" trt;
run;
```

where EVENT 1 if the participant had the event; EVENT 2 if the participant died prior to having the event, and EVENT 0 if the subject did not have the event and did not die. BASE baseline value.

SAS code to obtain a cumulative incidence function plot and dataset for further processing for time to first event table:

```
proc lifetest outcif  outcif plots  cif;
strata trt;
time days*event(0) / failcode    1; *Note: this produces data for the event of interest only;
run;
```

SAS code to obtain support tables:

```
proc univariate;
 by trt event;
 var days;
 output pctlpre  P_ min  min max  max pctlpts   10, 25, 50, 75, 90;
run;
```

19) SAS code for stratified 2-sided Wilcoxon Rank sum test (stratified on baseline result)

```
proc freq;
  table base*trt*aval/cmh2 scores  modridit;
run;
```

where BASE is the baseline value.

20) TEAE

Events with Missing Onset Day and/or Month

An event is considered treatment emergent if the following 3 criteria are met:

i. The month and year (or year) of onset date is the same as or after the month and year (or year) of the first dose of study drug, and

ii. The month and year (or year) of the onset date is the same as or before the month and year (or year) of the 30th day after the date of the last dose of study drug, and

iii. End date is as follows:

The (complete) end date is on or after the first dose date, or

The month and year (or year) of end date is the same or after the month and year (or year) of the first dose of study drug, or

End date is completely missing

Events with Completely Missing Onset Date

An AE with a completely missing onset date is defined as TEAE if end date meets any of the 3 criteria specified above.

21) The number of decimal places in reporting p-values should be as follows:

a) values less than 0.001 → < 0.001

b) values 0.001 to less than 1.000 → 4 decimal places (no rounding)

22) The precision in reporting numerical values should be as follows:

Raw measurements will be reported the same as the data captured electronically or on the eCRF.

Standard deviation and standard error will be reported to one more significant decimal place than the raw measurement.

Mean, median, minimum, Q1, Q3, maximum, 95% CIs will be reported to the same number of decimal places of the raw measurements.

Exceptions may be considered; for example, if more than 4 significant digits are provided for the measurement.

23) Last dose date is not expected to be missing. However, if last dose date is missing due to data issues, it will be imputed using the maximum of non-missing, non-zero dose, study drug start and stop dates.

24) Ordinal scale and oxygen support status

The oxygen support status is derived from the ordinal scale:

Ordinal Scale		Oxygen Support Status
1	Death	Death
2	Hospitalized, on invasive mechanical ventilation or ECMO	Invasive Mechanical Ventilation
3	Hospitalized, on non-invasive ventilation or high flow oxygen devices	High Flow Oxygen
4	Hospitalized, requiring low flow supplemental oxygen	Low Flow Oxygen
5	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	Room Air
6	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration)	Room Air
7	Not hospitalized	Discharge

25) Censoring rules

Time to death: subjects are censored at the last known date alive (last study day)

Time to ≥ 2 point improvement, time to ≥ 1 point improvement, time to recovery; time to modified recovery; time to room air: if a subject does not experience the event of interest and does not die, the subject is censored at the last non-missing ordinal scale assessment date.

26) Graded Laboratory Abnormalities Summary

The following labels will be used for laboratory abnormalities and Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	ALT	Increase	ALT (Increased)
	AST	Increase	AST (Increased)
	Creatinine	Increase	Creatinine (Increased)
	Creatinine Clearance	Decrease	Creatinine Clearance (Decreased)
	Serum Glucose	Increase	Serum Glucose (Hyperglycemia)
	Serum Glucose	Decrease	Serum Glucose (Hypoglycemia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Regulatory Affairs eSigned	19-May-2020 02:51:23
PPD	Biostatistics eSigned	19-May-2020 03:20:19
PPD	Clinical Research eSigned	19-May-2020 16:57:30