CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment
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-540-5774
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-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment
IND Number:	147753
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	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 moderate COVID-19. The primary objective of this study is as follows: • To evaluate the efficacy of 2 RDV regimens compared to standard of care (SOC), with respect to the proportion of participants discharged on or before Day 14 The secondary objective of this study is as follows: • To evaluate the safety and tolerability of RDV compared to SOC
Study Design:	This is a Phase 3 randomized, open-labeled, multi-center study RDV therapy in adult participants with moderate COVID-19. Approximately 600 participants who meet all eligibility criteria may be randomized in 1:1:1 ratio into one of the following treatment groups: **Treatment Group 1:** continued SOC therapy together with intravenous (IV) RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 **Treatment Group 2:** continued SOC 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 **Treatment Group 3:** continued SOC therapy

Number of Subjects Planned:	Approximately 600
Target Population:	Adults with moderate 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 • SpO2 > 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 3 treatment groups in a 1:1:1 ratio to receive: **Treatment Group 1:** continued SOC 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 SOC 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

	Treatment Group 3: continued SOC therapy 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 maybe conducted at selected sites in a subset of participants enrolled into treatment groups 1 and 2. At participating sites, sparse PK samples will 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 study 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:	Treatment with SOC according to local practice
Criteria for Evaluation:	
Safety:	Incidence of treatment-emergent AEs and treatment-emergent clinical laboratory abnormalities
Efficacy:	The proportion of participants who are discharged by Day 14

Statistical Methods:	The proportion of participants in the Full Analysis Set who are discharged on or before Day 14 will be compared between each RDV group and the SOC group using a chi-square test. Point estimates of the treatment differences and the associated 95% confidence intervals 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 600 participants will be randomized in a 1:1:1 ratio to 3 groups (200 participants per group). A sample size of 200 participants in each group achieves approximately 89% power to detect a difference of 15% between the SOC group and an RDV group, assuming a response rate of 60% in the SOC group and 75% in the RDV group and a two-sided alpha 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

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CDC	Centers for Disease Control and Prevention
CoV	coronavirus
CRF	case report form
CSR	clinical study report
DAIDS	Division of AIDS
DMC	data monitoring committee
EBOV	Ebola virus
eCCGs	eCRF Completion Guidelines
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gilead	Gilead Sciences
HIV	human immunodeficiency virus
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
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
LLOQ	lower limit of quantitation
LPV	lopinavir
LPV/RTV-IFNb	LPV/RTV + interferon-beta
MERS	Middle East Respiratory Syndrome
OAT	organic anion transporter
PCR	polymerase chain reaction
PK	pharmacokinetic(s)

PT	preferred term
PVE	Pharmacovigilance and Epidemiology
RDV	remdesivir
RNA	ribonucleic acid
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SARS	Severe Acute Respiratory Syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TM	test method
ULN	upper limit of normal
US	United States

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 the 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 emergency 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 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 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 SARS-CoV-2 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 moderate COVID-19.

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens compared to standard of care (SOC), with respect to the time to discharge

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV compared to SOC

3. STUDY DESIGN

This is a Phase 3 randomized, open-labeled, multi-center study RDV therapy in adult participants with moderate COVID-19. All participants will continue to receive SOC therapy according to local guidelines. Participants randomized to receive RDV will receive this in addition to their other care.

3.1. Endpoints

The primary endpoint of this study is:

- The proportion of participants discharged by 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 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
- Plasma concentration of RDV and GS-441524

3.2. Study Design

This study is a randomized, open-label, multicenter study of RDV in participants with moderate COVID-19. Eligible participants will be randomized in equal proportions to 1 of 3 treatment groups. No stratification will be performed.

3.3. Study Treatments

Approximately 600 participants who meet all eligibility criteria may be randomized in a 1:1:1 ratio into 1 of the following treatment groups:

Treatment Group 1: continued SOC 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 SOC 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

Treatment Group 3: continued SOC therapy

3.4. Duration of Treatment

Participants will receive study treatment with RDV for 5 days (treatment group 1), study treatment with RDV for 10 days (treatment group 2), or no RDV (treatment group 3). 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 600 participants will be randomized in a 1:1:1 ratio into 1 of 3 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 ≤ 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) SpO2 > 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 agent 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) Requiring mechanical ventilation at screening

4) ALT or AST > 5 × ULN

5) Creatinine clearance < 50 mL/min

6) Positive pregnancy test (Appendix 3)

7) Breastfeeding woman

8) 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 1:1:1 ratio to 1 of 3 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. Remdesivir treatment will be stopped at discharge regardless of the scheduled duration of therapy.

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: noninvasive ventilation or high flow oxygen devices, mechanical ventilation, or ECMO
  - 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 serious adverse events and all adverse events 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 24 hours, 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)

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 AEs and document concomitant medications

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

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, 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 one 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 including vital signs (heart rate, respiratory rate, temperature, blood pressure, SpO2 at rest or PaO_2) should be performed at least daily.

6.8. Pharmacokinetic Assessments

Pharmacokinetic assessments maybe conducted at selected sites in a subset of participants enrolled into treatment groups 1 and 2. At participating sites, sparse PK samples will 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 study 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. Post-treatment Assessments

No assessments are required after Day 28.

6.10. 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.

6.10.1. 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)

6.11. End of Study

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

6.12. 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.

6.13. 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 AEs 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 will be followed until resolution or stability of the abnormality has been demonstrated 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 7-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.

7.3.4. 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: Safety_fc@gilead.com
  or
  Fax: 1-650-522-5477

- 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 Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Gilead PVE
Email: Safety_FC@gilead.com
or
Fax: +1-650-522-5477

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 7.3.2. 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: Safety_FC@gilead.com and fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead 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 +1-650-522-5477 or email Safety_FC@gilead.com.

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 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: Safety_fc@gilead.com
or
Fax: 1-650-522-5477

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

8.1.1. Analysis Objectives

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

The primary objective of this study is as follows:

- To evaluate the efficacy of 2 RDV regimens compared to standard of care (SOC), with respect to the time to discharge

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of RDV compared to SOC

8.1.2. Primary Endpoint

The primary endpoint of this study is:

- The proportion of participants discharged by Day 14

8.1.3. Secondary Endpoints

The secondary endpoint of this study is:

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

8.1.4. Other Endpoints of Interest

Other endpoints of interest are:

- Time from randomization to first fever normalization (temperature < 36.6 °C armpit, < 37.2 °C oral, < 37.8 °C rectal)
- Time to first fever normalization
- Time to first negative SARS-CoV-2 PCR
- Duration of oxygen therapy
- Duration of hospitalization (days)
- All-cause mortality at Day 28
- Plasma concentration 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 data on a regular basis. There will be one planned DMC safety and efficacy analysis conducted after approximately 50% of participants have been randomized. Stopping rules will be defined in the DMC charter.

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 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 study treatment if randomized to 1 of the RDV treatment groups. 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 study treatment if randomized to 1 of the RDV treatment groups. 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 sumtest will be used to compare treatment groups.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The proportions of participants in the FAS who are discharged on or before Day 14 will be compared between each RDV group and the SOC group using a chi-square test. The point estimates of the treatment differences and the associated 95% confidence intervals will be provided. Participants who die or drop out of the study prior to Day 14 will be considered as not being discharged.

8.5.2. Secondary Analyses

The secondary endpoint of proportion of participants with treatment emergent AEs leading to discontinuation from the study will be compared between each RDV group and the SOC group using a Fisher's Exact test. The point estimates of the treatment differences and the associated 95% confidence intervals will be provided. 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 first dose 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 randomization date 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.

8.6.1. Extent of Exposure

A participant'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 for the RDV groups.

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 randomization date up to the date of last dose of study drug plus 30 days.

Summaries (number and percentage of participants) of treatment-emergent adverse events (TEAEs) (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 Events, 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 the end date of the study, 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.

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 findings, along with alpha spending considerations. No other adjustments for multiple comparisons are planned.

8.9. Sample Size

A sample size of 600 participants (200 in each group) achieves approximately 89% power to detect a difference of 15% between the SOC group and an RDV group, assuming a response rate of 60% in the SOC group and 75% in the RDV group and a 2-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 efficacy and 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.

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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.

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11. APPENDICES

Appendix 1. Investigator Signature Page
Appendix 2. Study Procedures Table
Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

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 Moderate COVID-19 Compared to Standard of Care Treatment

Original Protocol 24 February 2020

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

HUYEN CAO, GSIMM
Name (Printed)
[Responsible Person's Title]

Signature

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
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, 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 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 adverse event and concomitant medications 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 remdesivir, 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 investigator's brochure 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 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:

- 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.