CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	147753
EudraCT Number:	2020-003510-12
Clinical Trials.gov Identifier:	NCT04501952
Indication:	COVID-19
Protocol ID:	GS-US-540-9012
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 21 July 2020 Amendment 1: 11 August 2020 Amendment 1.1 (United Kingdom): 07 October 2020 Amendment 1.1 (Germany): 14 October 2020 Amendment 2: 06 November 2020 Amendment 3: 12 November 2020 Amendment 4: 14 January 2021

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations 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

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Study Title:	A Phase 3, Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting
IND Number:	147753
EudraCT Number:	2020-003510-12
Clinical Trials.gov Identifier:	NCT04501952
Study Centers Planned:	Approximately 150 centers globally
Objectives:	The purpose of this trial is to evaluate treatment with intravenous (IV) administered remdesivir (RDV, GS-5734) in an outpatient setting in participants with confirmed coronavirus disease 2019 (COVID-19) who are at risk for disease progression. The primary objectives of this study are as follows: • To evaluate the efficacy of RDV in reducing the rate of COVID-19 related hospitalization or all-cause death in non-hospitalized participants with early stage COVID-19 • To evaluate the safety of RDV administered in an outpatient setting The secondary objectives of this study are as follows: • To evaluate the efficacy of RDV in reducing the rate of COVID-19 related medically attended visits (MAVs; medical visits attended in person by the participant and a health care professional) or all-cause death in non-hospitalized participants with early stage COVID-19 • To determine the antiviral activity of RDV on severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 viral load • To assess the impact of RDV on symptom duration and severity CCI [redacted]

[redacted]

Study Design:	This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of RDV therapy for outpatients with early stage COVID-19 who are at higher risk of disease progression. Participants who meet all eligibility criteria may be randomized in a 1:1 ratio to RDV or placebo. Randomization will be stratified by participants who reside in a skilled nursing facility, by participant's age (< 60 vs ≥ 60 years), and by region (United States [US] vs ex-US): **Treatment Group A**: single dose of IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3 (RDV group) **Treatment Group B:** IV placebo-to-match (PTM) RDV on Days 1 to 3 (PTM group)
Number of Participants Planned:	Approximately 1264 participants
Target Population:	Non-hospitalized participants with early stage COVID-19 and at least one risk factor for disease progression.
Duration of Treatment:	Participants will receive study treatment with RDV or PTM for 3 days
Diagnosis and Main Eligibility Criteria:	Participants with COVID-19 who meet the following inclusion criteria may be included: • Willing and able to provide written informed consent (age ≥18) or assent (age ≥12 to <18, where locally and nationally approved), or with a legal representative who can provide informed consent (where locally and nationally approved)

- Either:

  At least 1 pre-existing risk factor for progression to hospitalization (chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes, obesity (BMI ≥ 30), immunocompromised, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease);

  OR age ≥ 60 years

- SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [eg, PCR] or antigen testing) ≤ 4 days prior to screening
- Presence of ≥ 1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomization (such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia)
- Not currently receiving, requiring, or expected to require supplemental oxygen
- Not currently requiring hospitalization (hospitalization defined as ≥ 24 hours of acute care)

Exclusion criteria for participation include:

- Participation in any other clinical trial of an experimental treatment and prevention for COVID-19
- Prior hospitalization for COVID-19 (hospitalization defined as ≥ 24 hours of acute care)
- Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 or administration of any SARS-CoV-2 (or COVID-19) vaccine
- Known hypersensitivity to the study drug, metabolites, or formulation excipient

Study Procedures/ Frequency:

At screening, after the participant has provided informed consent, demographic and baseline characteristics and medical history will be collected. Current clinical history, and concomitant medications will be documented. Physical examination findings, vital signs including temperature, respiratory rate, and SpO_2 on room air will be documented. Women of childbearing potential will have a urine pregnancy test.

After screening procedures, eligible participants may be randomized in a 1:1 ratio to receive treatment with RDV or PTM. Randomization will be stratified by residence in a skilled nursing facility, participant's age (<60 vs ≥ 60 years), and region (US vs ex-US).

After randomization, all participants randomized to receive RDV or PTM should receive their initial dose on Day 1.

Nasopharyngeal swabs and sputum samples will be collected on Days 1, 2, 3, 7, and 14 for SARS-CoV-2 quantitative reverse transcriptase polymerase chain reaction viral load testing and possible resistance testing.

On study Days 1 through 3, vital signs including respiratory status will be measured, and adverse events (AEs), medically attended visit information and concomitant medications will be documented. Laboratory tests for safety (hematology, chemistry, and coagulation) will be performed on Days 1, 3, 7, and 14. CCI [redacted] On study Day 14 physical examination findings, vital signs including temperature, respiratory rate, and SpO_2, AEs, medically attended visit information and concomitant medications will be documented.

Symptom severity will be assessed daily from Day 1 through Day 14 using the COVID-19-adapted FLU-PRO Plus questionnaire (if available).

On study Day 28, there will be an in-person or phone visit. Physical examination, vital signs including temperature, respiratory rate, and SpO_2, AEs, medically attended visit information and concomitant medications will be documented (only AEs, medically attended visit information and concomitant medications needed if performed by phone).

CCI [redacted]

Test Product, Dose, and Mode of Administration:	Remdesivir for injection, 100 mg, for IV administration
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-Match
Criteria for Evaluation:	The primary endpoints of this study are: • Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28 • Proportion of participants with treatment-emergent AEs The secondary endpoints of this study are: • Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 28 • All-cause mortality at Day 28 • Proportion of participants hospitalized by Day 28 • Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 14 • Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 14 • Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7 • Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19-adapted FLU-PRO Plus • Proportion of participants progressing to requiring oxygen supplementation by Day 28 CCI [redacted]

Statistical Methods:

The total sample size of the study will be approximately 1264 participants.

A sample size of approximately 1264 participants (632 in each group with 1:1 randomization) achieves > 90% power to detect a ratio of 0.55 (RDV to placebo in proportion of COVID-19 related hospitalization or all-cause death rate, which is equal to a hazard ratio of 0.534) using a 2-sided significance level of 0.05 assuming the overall hospitalization or death rate is 9.3% (12% in the placebo group and 6.6% in the RDV group) and a 5% drop out rate. The sample size provides approximately 80% power to detect a ratio of 0.60 (RDV to placebo). This analysis will be stratified by residence in skilled nursing facility, age (<60 vs ≥60 years), and region (US vs ex-US). An unblinded sample size re-estimation is planned after 50% participants completed Day 28.

The primary endpoint will be analyzed using Cox model with stratification factors as covariates. The null hypothesis being tested is whether the ratio of hospitalization or death is the same for either RDV or placebo treatment. The ratio and 95% confidence interval will be provided.

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

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATP	adenosine triphosphate
CI	confidence interval
CL_{cr}	creatinine clearance
CoV	coronavirus
COVID-19	coronavirus disease 2019
CP	conditional power
CRF	case report form
DAIDS	Division of AIDS
DMC	data monitoring committee
eCCGs	eCRF completion guidelines
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event
EU	European Union
FDA	Food and Drug Administration
FLU-PRO Plus©	InFLUenza Patient-Reported Outcome Plus
GCP	Good Clinical Practice
Gilead	Gilead Sciences, Inc.
GLPS	Global Patient Safety
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IXRS	interactive voice/web response system
LLOQ	lower limit of quantitation
MAV	medically attended visit
O_2	oxygen

PCR	polymerase chain reaction
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTM	placebo-to-match
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
SDV	source data verification
SOC	standard of care
SOP	standard operating procedure
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1. Background

Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2, a single-stranded RNA virus, is identified as the cause of an outbreak of respiratory illness that was first detected in Wuhan, China in December 2019. The virus has now spread globally, resulting in a global pandemic and causing severe respiratory illness throughout the world. Severe cases progress to pneumonia and multi-organ failure, which can lead to death. Gilead Sciences, Inc. (Gilead) has been working with global health authorities to respond to the ongoing pandemic and to evaluate the utility of intravenous (IV) remdesivir (RDV; GS-5734™) as a treatment option for coronavirus disease 2019 (COVID-19) through clinical trials. Remdesivir is approved for the treatment of COVID-19 in the United States (US), European Union (EU), Japan, and other countries for populations including adults and pediatric patients (12 years and older and weighing at least 40 kg).

1.2. Remdesivir (RDV, GS-5734)

Remdesivir is being developed by Gilead and is formulated for IV administration.

1.2.1. General Information

Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Metabolism of remdesivir to remdesivir triphosphate has been demonstrated in multiple cell types. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA.

For further information on RDV, refer to the investigator's brochure (IB) for RDV.

1.3. Rationale for This Study

Remdesivir is a novel antiviral drug that exhibits potent nanomolar antiviral activity against SARS-CoV-2 in primary human airway epithelial cells {Sheahan 2017}. In SARS-CoV-2-infected rhesus monkeys, administration of RDV resulted in a significant reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals {Williamson 2020}. The safety and efficacy of RDV has been demonstrated in clinical studies of patients hospitalized with COVID-19.

The risk of adverse outcomes from COVID-19 increases with age and the presence of chronic health conditions, such as cardiovascular disease, diabetes, and chronic lung disease{Stokes 2020, The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020, World Health Organization (WHO) 2020a}. In acute viral infection with influenza, a short course of antiviral treatment has shown improved clinical outcome {Nicholson 2000}. Treatment intervention in the earlier phase of COVID-19, such as in an outpatient setting, may prevent disease progression to moderate disease requiring hospitalization. The resulting reduction in hospitalizations would significantly benefit patients and would reduce the burden to health care systems.

There is currently no approved treatment for patients with COVID-19 who have not been hospitalized. This study will evaluate the potential for a 3-day treatment with IV RDV to change the clinical trajectory of early COVID-19. The double blinded design will allow stringent evaluation of the safety and efficacy of RDV in this population.

Participants in this study will be treated with RDV for a maximum of 3 days receiving a total of 400 mg RDV. This dose corresponds to a total administration of 12 g of sulfobutylether β-cyclodextrin sodium (SBECD) using the lyophilized powder. Based on the European Medicines Agency (EMA) review summarizing the safety of cyclodextrins as excipients {Committee for Medicinal Products for Human Use (CHMP) 2014}, which indicates approximately 250 mg/kg/day of SBECD (12 g/day based on a 48 kg human) is safe, participants will not be required to discontinue RDV if their creatinine clearance is < 30 mL/min during the dosing period.

1.4. Rationale for Duration of Treatment

In patients with severe COVID-19 who do not require mechanical ventilation, 5 days of RDV showed similar efficacy to a 10 day regimen. Similarly, 5 days treatment of RDV in participants with moderate COVID-19 was associated with a significant improvement in clinical status compared with standard of care (SOC) and approximately a third of participants were discharged prior to completion of 5 days RDV therapy.

In early viral infection, shorter courses of antivirals are often effective in preventing disease progression {Nicholson 2000}. As such, a shorter duration of 3 days of RDV treatment is proposed in participants with early stage COVID-19 not requiring hospitalization or oxygen supplementation with the goal of preventing disease progression.

1.5. Rationale for Dose Selection of Remdesivir

The dosing of RDV in this study, 200 mg on Day 1 and 100 mg on each of Days 2 and 3 is the initial dosing recommended by US Food and Drug Administration (FDA) and approved by EMA for adults and adolescents weighing ≥ 40 kg.

1.6. Risk/Benefit Assessment for the Study

In addition to the established risks associated with IV RDV, potential risks associated with the study include unknown adverse events (AEs) and laboratory abnormalities. There is the potential for resistance to develop with shorter treatment duration.

Intravenous RDV for up to 10 days is approved for the treatment of COVID-19 in the US, Japan, and the EU.

The shorter duration of treatment may lower the risk of some adverse findings associated with RDV, eg, the transient elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). However, other risks may not be ameliorated or may not have been evident in the studies of participants with more severe disease.

An independent data monitoring committee (IDMC) will review safety and efficacy data of the study when 50% of the participants have been enrolled. In addition, a futility interim analysis is planned when approximately 50% of the participants have completed the Day 28 visit to stop a non-efficacious treatment. The IDMC will make a recommendation of stopping enrollment to the study if the pre-specified futility stopping criteria are met.

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

- Exclusion of participants with contraindicated known hepatic or renal disease
- Exclusion of coadministration of other investigational agents against COVID-19
- Serum chemistry assessments, including liver function tests, will be monitored during the study period.

There are currently no investigational agents with demonstrated clinical efficacy or approved treatments for COVID-19 patients not requiring in-patient care. The timely evaluation of a safe and effective antiviral agent with demonstrated safety and efficacy 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 investigational therapy for the treatment of COVID-19. The benefit-risk balance for this study is considered positive.

1.7. 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 trial is to evaluate treatment with IV administered RDV in an outpatient setting in participants with confirmed COVID-19 who are at higher risk for disease progression.

The primary objectives of this study are as follows:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related hospitalization or all-cause death in non-hospitalized participants with early stage COVID-19
- To evaluate the safety of RDV administered in an outpatient setting

The secondary objectives of this study are as follows:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related medically attended visits (MAVs; medical visits attended in person by the participant and a health care professional) or all- cause death in non-hospitalized participants with early stage COVID-19
- To determine the antiviral activity of RDV on SARS-CoV-2 viral load
- To assess the impact of RDV on symptom duration and severity

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3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are as follows:

- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28
- Proportion of participants with treatment-emergent AEs

The secondary endpoints of this study are as follows:

- Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 28
- All-cause mortality at Day 28
- Proportion of participants hospitalized by Day 28
- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 14
- Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 14
- Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7
- Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19-adapted FLU-PRO Plus
- Proportion of participants progressing to requiring oxygen supplementation by Day 28

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[redacted]

3.2. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of RDV therapy for outpatients with early stage COVID-19 who are at higher risk of disease progression.

3.3. Study Treatments

Approximately 1264 participants who meet all eligibility criteria may be randomized in a 1:1 ratio into either treatment group:

Treatment Group A: single dose of IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3 (RDV group)

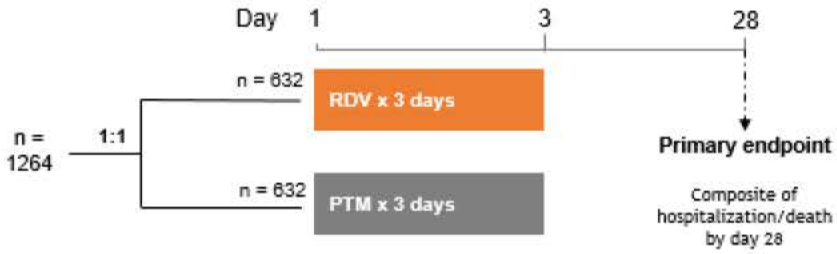
Treatment Group B: IV placebo-to-match (PTM) RDV on Days 1 to 3 (PTM group)

Randomization will be stratified by participants who reside in a skilled nursing facility, by participant's age (<60 vs ≥60 years), and by region (US vs ex-US).

3.4. Duration of Treatment

Participants will receive study treatment with RDV for 3 days (Treatment Group A) or PTM for 3 days (Treatment Group B).

Figure 1. Study Schema



3.5. End of Study

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

3.6. Poststudy 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.

3.7. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory, specialty laboratory CCI [redacted], and/or interactive voice/web response system (IXRS) data.

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 1264 participants who meet the eligibility criteria will be enrolled in one of 2 treatment groups. Participants will receive study drug in an outpatient, skilled nursing facility or home health setting.

4.1.1. Participant Replacement

Participants who discontinue before the end of study will not be replaced.

4.2. Inclusion Criteria

Participants 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) prior to performing study procedures. Participants aged ≥ 18 years may be enrolled with the consent of a legal representative where permitted according to local law and approved nationally and by the relevant institutional review board (IRB) or independent ethics committee (IEC). For participants ≥ 12 and < 18 years of age, a parent or legal guardian must be willing and able to provide written informed consent prior to performing study procedures
2) Either:

   Age ≥ 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 IRB or IEC) with at least 1 of the following pre-existing risk factors for progression to hospitalization:

   a) Chronic lung disease: chronic obstructive pulmonary disease, moderate-to-severe asthma, cystic fibrosis, pulmonary fibrosis
   b) Hypertension: systemic or pulmonary
   c) Cardiovascular or cerebrovascular disease: coronary artery disease, congenital heart disease, heart failure, cardiomyopathy, history of stroke, atrial fibrillation, hyperlipidemia
   d) Diabetes mellitus: Type 1, type 2, or gestational
   e) Obesity (BMI ≥ 30)
   f) Immunocompromised state; having a solid organ transplant, blood, or bone marrow transplant; immune deficiencies; HIV with a low CD4 cell count or not on HIV treatment; prolonged use of corticosteroids; or use of other immune weakening medicines
   g) Chronic mild or moderate kidney disease
   h) Chronic liver disease

i) Current cancer

j) Sickle cell disease

OR age ≥ 60 years, regardless of the presence of other pre-existing risk factors for progression

3) SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [eg, PCR] or antigen testing) ≤ 4 days prior to screening

4) Presence of ≥ 1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomization (such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia) {Stokes 2020, World Health Organization (WHO) 2020b}

5) Not currently receiving, requiring, or expected to require supplemental oxygen

6) Not currently requiring hospitalization (hospitalization defined as ≥ 24 hours of acute care)

7) Participants 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

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

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

2) Prior hospitalization for COVID-19 (hospitalization defined as ≥ 24 hours of acute care)

3) Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 or administration of any SARS-CoV-2 (or COVID-19) vaccine

4) Criterion removed

5) Requiring oxygen supplementation

6) ALT or AST ≥ 5 × upper limit of normal (ULN) at screening or within 90 days of screening

Note: if per local practice only ALT is routinely measured, exclusion criteria will be evaluated on ALT alone

7) Creatinine clearance < 30 mL/min at screening or within 90 days of screening using the Cockcroft-Gault formula in participants ≥ 18 years of age or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 at screening or within 90 days of screening using the Schwartz formula in participants < 18 years of age (see Section 6.7.2)

8) Currently breastfeeding (nursing)

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

10) Use or planned use of exclusionary medications, refer to Section 5.4

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Participants who meet all randomization eligibility criteria will be randomized in a 1:1 ratio to Treatment Group A or Treatment Group B and assigned a participant number. Randomization will be stratified by residence in a skilled nursing facility, age (<60 vs ≥ 60), and region (US vs ex-US).

Randomization may occur approximately one day prior to the Day 1 visit.

5.1.2. Blinding

During the randomized phase participants and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the participants. CCI [redacted] Individuals in clinical virology performing sample selection for resistance analysis may be unblinded. Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IXRS system for purposes of study drug inventory management will remain unblinded. Individuals in Global Patient Safety (GLPS) responsible for safety signal detection, investigational new drug (IND) safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries. External (ie, contract research organizations) biostatisticians and programmers will be unblinded for the IDMC, IND safety reporting. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

5.1.3. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the participant, the investigator may obtain treatment assignment directly from the IXRS system for that participant. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine participant emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study. Therefore, if a participant's treatment assignment is disclosed to the investigator, the participant will have study treatment discontinued. All participants will be followed until study completion unless consent to do so is specifically withdrawn by the participant.

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 RDV 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: 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.

The supplied PTM RDV for injection, 100 mg, is identical in physical appearance to the active formulation and contains the same inactive ingredients.

5.2.2. Packaging and Labeling

Remdesivir for injection and PTM, 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 rubber stopper and an aluminum over seal with a red, plastic flip-off cap. Following reconstitution, each single-use vial contains sufficient volume to allow withdrawal of 20 mL (100 mg RDV or PTM).

Remdesivir for injection and PTM, 100 mg, shall be labeled to meet all applicable requirements of the US 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 and PTM, 100 mg, vials 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.

The total storage time of reconstituted solution containing RDV or placebo should not exceed 24 hours at room temperature (20 °C to 25 °C) or 48 hours at refrigerated temperature (2 °C to 8 °C). Any unused reconstituted solution containing RDV or placebo should be discarded.

5.3. Dosage and Administration of Remdesivir

Remdesivir for injection, 100 mg, or PTM will be provided by Gilead.

Participants in Treatment Group A will receive IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3. Participants in the Treatment Group B will receive IV PTM on Days 1 to 3.

5.3.1. Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of RDV injection with IV solutions and medications other than 0.9% sodium chloride is not known. Administer RDV via IV infusion over 30 minutes. Slower infusion rates of up to 120 minutes can be considered to potentially prevent signs and symptoms of infusion related reaction. Infusion rates for different infusion volumes and times are described in Table 1.

Table 1. Recommended Rate of Infusion—Diluted RDV for Injection Lyophilized Powder in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

5.3.2. Infusion-related Reactions

Infusion-related reactions have been observed during and following administration of RDV. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a severe infusion-related reaction occur, immediately discontinue administration of RDV and initiate appropriate treatment. Please refer to Section 7.6.

5.4. Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to screening and up to and including 30 days after the last dose of study drug need to be recorded in the source documents and eCRFs.

Concomitant use of the following is prohibited in participants receiving RDV:

- Investigational or approved agents for the SARS-CoV-2 virus including approved HIV protease inhibitors such as lopinavir/ritonavir, interferon, etc. Use of these medications for an approved indication other than SARS-CoV-2 infection is not prohibited
- Use of hydroxychloroquine or chloroquine for any indication
- Strong inducers of P-glycoprotein (eg, rifampin or herbal medications)

5.5. Accountability for Investigational Medicinal Product

The investigator is responsible for ensuring adequate accountability of all used and unused study drug vials. 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 vials.
- The date, participant number, and the study drug vial number dispensed.
- The date, quantity of used and unused study drug vials returned, along with the initials of the person recording the information.

5.5.1. 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 standard operating procedure (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 or remote monitoring visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant 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 Gilead or the contract research organization.

6.1. Participant 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. Study visits may be performed in an outpatient setting, at the participant's home via tele-health, virtually or remotely, as permitted by local and institutional regulations.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Participants will be screened within 2 days before randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history including the following information: date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics, allergies and all other medical history
- Review and document prior and concomitant medications
- Complete physical examination including, vital signs (heart rate, temperature, blood pressure), body weight, and height.
- Respiratory status:

  Respiratory rate

  Oxygenation: SpO_2 on room air
- Obtain ALT (and AST where available), serum creatinine, and creatinine clearance/eGFR (calculated using Cockcroft-Gault or Schwartz formula; see Section 6.7.2) if not available within 90 days of screening, using a local laboratory.
- Women of childbearing potential will have a urine pregnancy test performed

- Documentation of SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [eg, PCR] or antigen testing) ≤ 4 days prior to screening
- Confirmation of presence of COVID-19 symptoms
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent form

Participants meeting all of the inclusion criteria and none of the exclusion criteria may be enrolled the same day as screening for randomization into the study.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated procedures on the Adverse Events eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be considered medical history. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Treatment Assessments (Baseline/Day 1, Day 2, and Day 3)

The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility before proceeding with randomization and the Day 1 visit. If the screening and Day 1 visits occur on the same day, no procedures need to be repeated except for clinical laboratory samples that must be collected locally to confirm eligibility. Clinical laboratory samples must be collected at Day 1 to be sent to the central laboratory, even if completed locally, as described in Section 6.7.2. Participants must complete the following assessments before being administered study drug:

- Vital signs (heart rate, temperature, blood pressure) pre-infusion, postinfusion, and when postinfusion observation is completed
- Respiratory status:

  Respiratory rate

  Oxygenation: SpO_2 on room air
- Complete physical examination (Day 1)
- Clinical symptom-directed physical examination (Day 2, Day 3)
- Review of AEs and concomitant medications
- Review any interactions with health care professionals, other than study staff or designees, including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care profession. Identify the nature and cause of the visit.

- Obtain blood samples as described in Section 6.7.2 (Day 1, Day 3)
- Nasopharyngeal swab samples for SARS-CoV-2 quantitative reverse transcriptase PCR (RT-qPCR) testing CCI [redacted]
- Sputum sample collection from participants with productive cough for SARS-CoV-2 RT-qPCR testing CCI [redacted]
- Completion of the COVID-19-adapted FLU-PRO Plus questionnaire (if available)
- Administration of study drug. Instructions on study drug administration are available in a separate manual.

Remdesivir infusions will be administered to participants at the site under close supervision or in the participant's home by a home health service provider. Health care professionals administering RDV infusions will have the appropriate medication available for immediate use in case of hypersensitivity or infusion-related reactions. The participant should be treated according to the SOC for management of hypersensitivity reaction or infusion-related reactions. Postinfusion monitoring should be done according to site or home health protocol. All information related to home administration of RDV will be provided to the investigator by the home health provider, wherever applicable, in a timely manner.

6.4. Post-treatment Assessments (Day 4 Through Day 14)

The following evaluations are to be completed at the specified study days. The study visits are to be completed on the protocol-specified visit date (based on the Day 1 visit). The Day 7 and Day 14 visits have a ± 1 day window.

- Vital signs (heart rate, temperature, blood pressure), body weight (Day 7, Day 14)
- Review of AEs and concomitant medications (Day 7, Day 14)
- Review MAV information, including any interactions with health care professionals other than study staff or designees including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care profession. Identify the nature and cause of the visit.
- Complete physical examination (Day 14).
- Clinical symptom-directed physical examination (Day 7).
- Respiratory status (Day 7, Day 14):

    Respiratory rate

    Oxygenation: SpO_2 on room air

- Obtain blood samples as described in Section 6.7.2 (Day 7, Day 14)
- Nasopharyngeal swab samples for SARS-CoV-2 RT-qPCR testing CCI [redacted]
- Sputum sample collection from participants with productive cough for SARS-CoV-2 RT-qPCR testing CCI [redacted]
- Completion of the COVID-19-adapted FLU-PRO Plus questionnaire (if available) (Days 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14)

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

The following evaluations are to be completed if the visit is conducted in person. The final evaluation can be performed by phone (only AEs, concomitant medications review, and MAV information needed if done by phone).

- Clinical symptom-directed physical examination, vital signs (heart rate, temperature, blood pressure), and body weight.
- Respiratory status:

  Respiratory rate

  Oxygenation: SpO_2 on room air

- Review of AEs and concomitant medications
- Review MAV information, including any interactions with health care professionals, other than study staff or designees, including hospitalization; in-person emergency, urgent, or primary care visits; or any other in-person visit attended by the participant and a health care profession. Identify the nature and cause of the visit.

6.6. Assessments for Early Discontinuation from Study

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures (see Section 6.8, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the participant or investigator, the participant may be withdrawn from the study.

6.7. Procedures and Specifications

6.7.1. Complete Physical Examination

A complete physical examination must include source documentation of general appearance and the following body systems: Head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. Urogenital and reproductive examination should only be completed if clinically indicated.

6.7.2. Clinical Laboratory Assessments

Blood sample collection for the following laboratory analyses will be performed at the specified time points:

- Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, lactate dehydrogenase, creatine phosphokinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, uric acid (Day 1, Day 3, Day 7, Day 14)
- Estimated glomerular filtration rate (screening [if required], Day 1, Day 3, Day 7, Day 14) according to:

  Schwartz formula for participants < 18 years of age, where S_{Cr} is serum creatinine (mg/dL)

Adolescent boys ≥ 12 years of age: $0.70 \times L / S_{Cr}$ (L is height in cm)

Adolescent girls ≥ 12 years of age: $0.55 \times L / S_{Cr}$ (L is height in cm)

Height at baseline will be used for all calculations using the Schwartz formula.

Cockcroft-Gault formula for creatinine clearance (CL_{cr}) for participants ≥ 18 years of age. Weight at screening will be used for Days 1-3.

Men: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})}$ CL_{cr} (mL/min)

Women: $\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$ CL_{cr} (mL/min)

- Hematology profile: complete blood count with differential (Day 1, Day 3, Day 7, Day 14)
- Coagulation: international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT) (Day 1, Day 3, Day 7, Day 14)
- CCI [redacted]

[redacted]

6.8. Criteria for Discontinuation of Study Treatment

Study medication will be discontinued for individual participants in the following instances, unless the potential for resuming dosing is specifically noted:

- 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 participant 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 participant's best interest
- ALT or AST $\geq 5 \times$ ULN; or ALT $> 3 \times$ ULN and total bilirubin $> 2 \times$ ULN, confirmed by immediate repeat testing
- Other Grade 3 or Grade 4 abnormal laboratory results related to RDV
- Lack of efficacy
- Participant request to discontinue for any reason
- Participant noncompliance
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB or IEC
- Infusion-related systemic reaction $\geq$ Grade 2 or infusion-related localized reaction $\geq$ Grade 3

6.9. End of Study

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

6.10. Poststudy 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.

CCI [redacted]

[redacted]


CCI

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 participant 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 the AE is considered related to the investigational product. AEs may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.7).

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 7.7.1)
- 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 participant 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 participant 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 event 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-defined 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 occur after the participant first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the post-treatment follow-up visit, must be reported on the applicable eCRFs and to GLPS 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 GLPS.

- All SAEs will be recorded in the case report form (CRF)/eCRF database within 24 hours.

7.3.3.1. Electronic Serious Adverse Event Reporting Process

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

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and submit within 24 hours to:

  Gilead GLPS
  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 eCCGs.

- 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 participant identification, maintaining the traceability of a document to the participant 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 participant'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 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, or 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 IB 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 coagulation) 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 (i.e., 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. Toxicity Management

Remdesivir infusions will be administered to participants at the site under close supervision or in the participant's home by a home health service provider. Health care professionals administering RDV infusions will have the appropriate medication available for immediate use in case of hypersensitivity or infusion-related reactions. The participant should be treated according to the SOC for management of hypersensitivity reaction or infusion-related reactions. Postinfusion monitoring should be done according to site or home health protocol. All information related to home administration of RDV will be provided to the investigator by the home health provider, wherever applicable, in a timely manner.

7.7. Special Situations Reports

7.7.1. 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 participant.

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 participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the participant 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.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

Refer to Section 7.3 for GLPS contact information and the eCCGs 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 Section 7.3.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead GLPS.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead GLPS 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 GLPS. Gilead GLPS contact information is as follows: email: PPD and fax: PPD

Pregnancies of female partners of male study participants exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead GLPS 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 GLPS, fax number PPD or email PPD

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

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead GLPS 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.

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 for GLPS contact information and the eCCGs 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 primary objectives of this study are as follows:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related hospitalization or all-cause death when given over 3 days to non-hospitalized participants with early stage COVID-19
- To evaluate the safety of RDV administered in an outpatient setting

The secondary objectives of this study are as follows:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death in non-hospitalized participants with early stage COVID-19. An MAV includes in-person clinic visit, urgent care visit, emergency room visit, or hospitalization
- To determine the antiviral activity of RDV on SARS-CoV-2 viral load
- To assess the impact of RDV on symptom duration and severity

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8.1.2. Primary Endpoint

The primary endpoints of this study are as follows:

- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28
- Proportion of participants with treatment-emergent AEs

8.1.3. Secondary Endpoint

The secondary endpoints of this study are as follows:

- Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all cause death by Day 28
- All-cause mortality at Day 28
- Proportion of participants hospitalized by Day 28
- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 14
- Composite endpoint of COVID-19 related (medical visits attended in person by the participant and a health care professional) or all cause death by Day 14
- Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7
- Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19-adapted FLU-PRO Plus
- Proportion of participants progressing to requiring oxygen supplementation by Day 28

CCI [redacted]

[redacted]

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 m.

8.2.1.1. Data Monitoring Committee Analysis

An external data monitoring committee (DMC) will review safety data on a regular basis. One futility interim analysis is planned after approximately 50% of participants complete Day 28. Enrollment may pause for the IDMC review if enrollment is faster than projected. The DMC will review the interim safety data and summary of primary efficacy data by treatment group and make recommendation of stopping enrollment to a treatment due to lack of efficacy and decision on sample size re-estimation.

8.2.2. Final Analysis

The final analysis will be performed after all participants have completed 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 of COVID-19 related hospitalization or all-cause death by Day 28 will be conducted at the time of the final analysis and will be tested at the 0.05 significance level.

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, which will include all participants who (1) are randomized into the study and (2) have received at least 1 dose of study treatment. 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. Participants will be grouped according to the treatment to which they received.

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[redacted]

8.3.2. Data Handling Conventions

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[redacted]

Laboratory data that are continuous in nature but are less than the LLOQ 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 (i.e., 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, randomization stratification group, 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 primary endpoint of the study is the composite endpoint of COVID-19 related hospitalization or all-cause death by Day 28. The null hypothesis being tested is whether the ratio of proportion of COVID-19 related hospitalization or all-cause death is the same for the 2 treatment groups (ie, whether ratio is equal to 1 across all strata).

The hazard ratio, p-value, and 95% CI for the hazard ratio will be calculated using a Cox model with stratification factors as covariates.

Participants with missing outcomes for the primary endpoint due to prematurely discontinuation of the study will be censored at the date of last contact.

8.5.2. Secondary Analyses

The secondary endpoint of COVID-19 related hospitalization or all-cause death by Day 14, COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or death by Day 28, and COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or death by Day 14 will be analyzed similarly as in the primary analysis. The all-cause mortality at Day 28 will be compared between the 2 treatment groups using a Fisher exact test. The proportion of participants hospitalized by Day 28 and the proportion of participants progressing to requiring oxygen supplementation by Day 28 will be estimated using the Kaplan-Meier method and compared between the 2 treatment groups using a log-rank test. Other endpoints of interest related to proportion of participants will be compared between treatment groups using a chi-square test or Fisher 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.

8.6. Safety Analysis

All safety data collected on or after the randomization date through the Day 28 visit will be summarized by treatment group (according to the study drug received). Data for the pretreatment 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.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities. System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term 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 AEs (by system organ class and preferred term) 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.

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

8.7. Adjustments for Multiplicity

No adjustments for multiple comparisons are needed for the primary analysis of this study.

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8.9. Sample Size

The total sample size of the study will be approximately 1264 participants.

The sample size computation is based on proportions of COVID-19 related hospitalization or all-cause death by Day 28 for the RDV and placebo treatment groups. The sample size needed for a 1:1 randomization using a 2-tailed test at level α is given by:

$$\frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{P(1-R^2)\sigma^2 B^2}$$

Where P is the overall rate of COVID-19 related hospitalization or all-cause death, B is the log hazard ratio, σ is the standard deviation of treatment indicator variable, R is the R-Squared that is obtained when treatment indicator variable is regressed on the other covariates, and $z_{1\ \alpha/2}$ and $z_{1\ \beta}$ are the 1-α/2 and 1-β quantiles of the standard normal distribution.

A sample size of 1264 participants (632 in each group with 1:1 randomization) achieves > 90% power to detect a ratio of 0.55 (RDV to placebo in proportion of COVID-19 related hospitalization or all-cause death, which is equal to a hazard ratio of 0.534) using a 2-sided significance level of 0.05 assuming the overall hospitalization or death rate is 9.3% (12% in the placebo group and 6.6% in the RDV group) and a 5% drop out rate. The sample size provides approximately 80% power to detect smaller treatment effect size with a ratio of 0.60 (RDV to placebo), assuming a 2-sided significance level of 0.05 and the overall hospitalization or death rate is 9.6% (12% in the placebo group and 7.2% in the RDV group) and a 5% drop out rate.

The sample size calculation was done using software PASS (Version 14.0, module of Cox regression for survival).

8.9.1. Sample Size Re-estimation

A sample size re-estimation is planned at the interim analysis with approximately 50% participants having completed Day 28 visit due to the uncertainty in hospitalization or death rate in the placebo arm. All possible interim results will be partitioned into 3 zones Favorable, Promising, and Unfavorable, depending on the size of observed conditional power (CP) under the current trend at the interim. If the CP falls into the Favorable zone, the trial will continue with the originally planned sample size of 1264 patients. If the CP falls into the Promising zone, the total sample size will be increased (up to 1500) according to the algorithm specified in the adaptation plan. If the CP falls into the Unfavorable zone but the interim result has not met the futility boundary, the trial will also continue with the originally planned sample size of 1264 patients.

The DMC will review the unblinded data at the interim and communicate the decision on sample size to the study team. The overall type I error is controlled at 0.05 using the method proposed by {Muller 2004}. Further details will be included in the DMC charter and an adaptation plan.

8.10. Independent Data Monitoring Committee

An external multidisciplinary IDMC will review the progress of the study, perform interim reviews of safety data on a regular basis and provide recommendation(s) to Gilead whether the nature, frequency, and severity of AEs 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 will review the interim futility analysis and make a recommendation of stopping enrollment to the study if the pre-specified futility stopping criteria are met.

The IDMC may also provide recommendations as needed regarding study design.

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 International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

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 participant 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 participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study participant 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 participant after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study participants.

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 participant or the participant'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.

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9.1.5. Confidentiality

The investigator must assure that participants' 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, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant 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 IB, 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) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, electronic completed participant CRFs, IRB or IEC and governmental approval with correspondence, informed consent form(s), 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 participant:

- Participant identification
- Documentation that participant meets eligibility criteria, i.e., medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant 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 (i.e., 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 participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each participant consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the 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 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 (eg, 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 participants, 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 will be prepared and provided to the regulatory agency. 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 participant 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 participants, appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page
Appendix 2. Study Procedures Table[a]
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, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

GS-US-540-9012, Amendment 4, 15 January 2021

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

PPD
PPD Clinical Research

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[a]

	Screening	Baseline/ Day 1	Day 2	Day 3	Day 7 (± 1 day)	Day 14 (± 1 day)	Day 28[t] Follow-up (± 5 days)
Written Informed Consent	X						
Medical History[b]	X						
Complete Physical Examination[c]	X	X				X	
Clinical Symptom Directed Physical Examination[d]			X	X	X		X
Height	X						
Vital Signs[e] and Weight	X	X[f]	X[f]	X[f]	X	X	X
Respiratory Status[g]	X	X	X	X	X	X	X
ALT, AST, Serum Creatinine, and Creatinine Clearance/eGFR[h]	X						
Chemistry[i], Hematology[j], and Coagulation[k] Panels		X		X	X	X	
CCI							
Urine Pregnancy Test[m]	X						
SARS CoV 2 RT qPCR Testing and Potential Resistance Testing[n]		X	X	X	X	X	
Documentation of SARS CoV 2 Infection	X						
CCI							
CCI							
CCI							
Medically Attended Visit Information[r]		X	X	X	X	X	X
FLU PRO Plus Questionnaire[s]		X	X	X	X	X	
Study Drug Dosing		X	X	X			
Adverse Events and Concomitant Medications	X	X	X	X	X	X	X

a Study visits may be performed in an outpatient setting, at the participant's home via tele health, virtually or remotely, as permitted by local and institutional regulations. The Day 28 visit may be performed via a phone call.

b Medical history will include the date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics, allergies and all other medical history.

c A complete physical examination must include source documentation of general appearance and the following body systems: Head, neck, and thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological. Urogenital and reproductive examination should only be completed if clinically indicated.

d Clinical symptom directed physical examination will include at least cardiac and respiratory evaluation.
e Vital signs include heart rate, temperature, and blood pressure.
f On Days 1, 2 and 3, vital signs to be completed pre infusion, postinfusion, and when postinfusion observation is completed; weight from Screening may be used at Days 1 3.
g Respiratory status includes respiratory rate and SpO_2 on room air.
h Obtain ALT (and AST where available), serum creatinine, and creatinine clearance/eGFR (calculated using Cockcroft Gault or Schwartz formula; see Section 6.7.2) if not available within 90 days of screening, using a local laboratory.
i Chemistry: alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, lactate dehydrogenase, creatine phosphokinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lipase, magnesium, phosphorus, potassium, sodium, uric acid.
j Hematology: Complete blood count with differential.
k Coagulation: INR, PT, aPTT
[redacted]
m Urine pregnancy test will only be done for women of childbearing potential.
n Nasopharyngeal swab and sputum samples will be collected and stored for SARS CoV 2 RT qPCR and potential resistance testing.
[redacted]
r Medically attended visit information includes any interactions with health care professionals other than study staff or designees including hospitalization; in person emergency, urgent, or primary care visits; or any other in person visit attended by the participant and a health care profession. Identify the nature and cause of the visit.
s FLU PRO Plus questionnaire should be completed daily from Day 1 through Day 14 (if available).
t Only AEs, medically attended visit information, and concomitant medications review are needed if the visit is done by phone.

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 participant 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.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Participants

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.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of non-pregnant female participants of childbearing potential requires the use at least an acceptable contraceptive measure. Female participants must agree to 1 of the following from screening until 30 days after the last study drug dose:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant'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 in conjunction with a barrier method)

  Bilateral tubal occlusion (upon medical assessment of surgical success)

  Vasectomy in the male partner (upon medical assessment of surgical success)

Or

- Female participants who wish to use a hormonally-based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

  Hormonal methods (each method must be used with a barrier method, preferably male condom)

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

  Barrier methods

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

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.

Female participants must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Male Participants

During the study male participants 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. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Participants will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Participants who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator. Participants 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 7.7.2.1.