CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	147753
EudraCT Number:	2020-005416-22
Clinical Trials.gov Identifier:	NCT04745351
Indication:	COVID-19
Protocol ID:	GS-US-540-5912
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 07 December 2020 Amendment 1: 28 January 2021 Amendment 2: 02 August 2021 Amendment 3: 27 August 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.

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19
IND Number:	147753
EudraCT Number:	2020-005416-22
Clinical Trials.gov Identifier:	NCT04745351
Study Centers Planned:	Approximately 150 centers globally
Objectives:	The primary objective of this study is as follows: • To evaluate whether remdesivir (RDV, GS-5734™) reduces the composite risk of death or invasive mechanical ventilation (IMV) through Day 29 in participants with severely reduced kidney function who are hospitalized for coronavirus disease 2019 (COVID-19) The secondary objectives of this study are as follows: • To evaluate whether RDV reduces the risk of death through Day 29 • To evaluate whether RDV reduces the risk of IMV through Day 29 • To evaluate the time to recovery (defined as satisfying category 1, 2, or 3 by the 8-point ordinal scale) • To evaluate the effect of RDV on clinical status assessed by an 8-point ordinal scale at Day 15 and Day 29 • To evaluate the effect of RDV on renal replacement therapy (RRT)-free days (among those without end-stage kidney disease [ESKD]) through Day 29 • To evaluate the effect of RDV on recovery through Day 29

- To evaluate the safety and tolerability of RDV in participants with severely reduced kidney function who are hospitalized for COVID-19

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Study Design:

This is a Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy and safety of RDV therapy in participants with severely reduced kidney function who are hospitalized for COVID-19.

In this study, primary and secondary end points will be evaluated through Day 29. Following screening, eligible participants will be randomized in a 2:1 ratio to receive RDV or saline as placebo according to the following treatment regimen, in addition to standard of care (SOC) therapy:

- Treatment Group A: Intravenous (IV) RDV 200 mg on Day 1 followed by IV RDV 100 mg once daily from Day 2 up to Day 5
- Treatment Group B: IV saline as placebo on Day 1 followed by IV saline as placebo once daily from Day 2 up to Day 5

	Randomization will be stratified by: • ESKD requiring chronic dialysis • High-flow oxygen requirement • Region (United States [US] versus ex-US)
Number of Participants Planned:	Approximately 1116
Target Population:	Participants with severely reduced kidney function who are hospitalized for COVID-19
Duration of Treatment:	The duration of treatment with RDV or saline as placebo will be up to 5 days
Study Duration:	Up to 29 days (not including screening window or Day 60 phone follow-up)
Diagnosis and Main Eligibility Criteria:	Participants who meet the following criteria: • SARS-CoV-2 positive as determined by polymerase chain reaction (PCR) or other commercially available or public health assay (eg, nucleic acid amplification test and antigen tests) in any respiratory specimen • Hospitalized for COVID-19 • Age ≥ 12 years and weighing at least 40 kg • O_2 saturation ≤ 94% on room air or requiring O_2 supplementation OR radiographic evidence of pulmonary infiltrates for COVID-19 • Have either: — Severely reduced kidney function (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and revised Schwartz equations for adults and adolescents, respectively, including people with ESKD requiring chronic dialysis but not people requiring RRT for AKI, OR — Ongoing AKI: defined as a 50% increase in SCr within a 48-hour period that is sustained (ie, requires confirmatory SCr) for ≥ 6 hours despite supportive care

	• Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (age ≥ 18) prior to performing study procedures • The interval between COVID-19 symptoms onset and randomization is no more than 10 days • Male participants and female participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4
Key Exclusion Criteria:	Participants who meet any of the following criteria at screening: • Received any investigational drug, RDV, or other antiviral treatment for COVID-19 • Alanine aminotransferase or aspartate aminotransferase > 5 × the upper limit of normal • IMV, noninvasive mechanical ventilation, extracorporeal membrane oxygenation, or RRT for AKI • Positive serum pregnancy test at screening for women of childbearing potential or currently breastfeeding • Known hypersensitivity to the investigational drug, metabolites, or formulation SBECD
Study Procedures/ Frequency:	At screening, after the participant has provided informed consent (or assent), demographic and baseline characteristics, focused medical history, complete physical examination findings, vital signs (including temperature, respiratory rate, and oxygen saturation), RRT status, 8-point ordinal scale of clinical status and concomitant medications will be documented. Women of childbearing potential will have a serum pregnancy test. Pulmonary radiographic imaging may be performed, if not already available from the past 72 hours and if needed to satisfy eligibility criteria. SARS-CoV-2 testing will be performed; if this testing has been performed within the last 4 calendar days, no repeat testing is required. If safety laboratory results from within 48 hours prior are not already available, laboratory analyses (chemistry, hematology, SCr, coagulation, urinalysis, and serum pregnancy test) will be performed according to local practice.

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

- Continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg once daily from Day 2 up to Day 5
- Continued SOC therapy together with IV saline as placebo on Day 1 followed by IV saline as placebo once daily from Day 2 up to Day 5

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

On Days 1 through 29 or until discharge from inpatient hospitalization, whichever is earlier, need for RRT, 8-point ordinal scale of clinical status, vital signs, respiratory status measurement, adverse events (AEs), and concomitant medications will be documented. Following discharge from inpatient hospitalization, RRT status, 8-point ordinal scale of clinical status, AEs, concomitant medications, and mortality will also be collected during the Day 29 and Day 60 phone follow-up. Laboratory testing during hospitalization will be performed according to SOC practice with results for chemistry, hematology, and any SARS-CoV-2 testing being reported to the sponsor.

Even if not performed as SOC, SCr will be completed at screening, and on Days 1 through 29, or until discharge, whichever is earlier. In addition, even if not performed as SOC, chemistry, hematology, and coagulation will be completed at screening and on Days 1, 3, 5, 8, 12, 16, 20, 24, and 29 or until discharge, whichever is earlier.

Test Product, Dose, and Mode of Administration:	Remdesivir for injection, 100 mg, for IV administration (lyophilized preparation)
Reference Therapy, Dose, and Mode of Administration:	Saline as placebo
Criteria for Evaluation:	
Safety:	The safety of RDV will be assessed during the study through the reporting of treatment-emergent AEs and serious adverse events (SAEs), as well as treatment-emergent clinical laboratory abnormalities.

A data monitoring committee (DMC) will meet regularly to evaluate all available safety data accumulated during the study, including kidney injury. The DMC will have 2 formal (unblinded data review) meetings. The first formal DMC meeting will be based on data collected after the first 100 participants complete the Day 29 assessment. The second formal DMC meeting will be based on data collected after 50% of participants complete the Day 29 assessment and will include review of safety, efficacy, and futility. The DMC will make a recommendation of stopping enrollment to the study at the second formal DMC meeting if the prespecified efficacy or futility stopping criteria are met. The DMC will also receive blinded safety listings for review up to every week for the first 2 weeks followed by every 2 weeks until the second DMC meeting occurs after 50% of participants complete the Day 29 assessment.

Efficacy:

Primary efficacy end point:

- The composite of all-cause mortality or IMV through Day 29

Key (α-controlled) secondary end point:

- All-cause mortality through Day 29

Other secondary end points:

- IMV through Day 29
- Time to recovery (defined as satisfying category 1, 2, or 3 by the 8 point ordinal scale)
- Clinical status assessed by an 8-point ordinal scale on Day 15 and Day 29
- RRT-free days (among those without ESKD at randomization) through Day 29
- Recovery through Day 29

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Statistical Methods:

The primary analysis set for efficacy analyses is the Full Analysis Set, which includes all participants who were randomized and received at least 1 dose of investigational drug. The primary clinical end point is the composite of all-cause mortality or IMV from date of first dose through Day 29.

The primary end point will be analyzed using a stratified log-rank test. The hazard ratio and 95% confidence interval will be provided.

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

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Sample Size:

A total of approximately 1116 participants will be randomized in a 2:1 ratio to 2 groups (744 in the RDV group and 372 in the saline as placebo group). This sample size achieves approximately 85% power to detect a hazard ratio of 0.70 at a two-sided alpha level of 0.05. In the sample size calculation, it is assumed that the event rate in the saline as placebo group is 35%. The hazard ratio and event rate in the saline as placebo group are based on the most conservative estimates of the primary end point (composite of all-cause mortality or IMV) and key α-controlled secondary end point (all-cause mortality) through Day 29 among a subset of participants with eGFR < 60 mL/min in the Division of Microbiology and Infectious Diseases Protocol 20-0006 Adaptive COVID-19 Treatment Trial (ACTT)-1 (hazard ratio of 0.67 and placebo rate of 33%). An unblinded interim analysis of efficacy and futility is planned after 50% of participants complete the Day 29 assessment.

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

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
ACE2	angiotensin-converting enzyme 2
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BIPAP	bilevel positive airway pressure
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed plasma drug concentration
CoV	coronavirus
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
C_{tau}	observed drug concentration at the end of the dosing interval
CVVH	continuous venovenous hemofiltration
DAIDS	Division of AIDS
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESKD	end-stage kidney disease
EU	European Union
FDA	Food and Drug Administration
FIO_2	fraction of inspired oxygen

FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLPS	Global Patient Safety
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
ICU	intensive care unit
IEC	independent ethics committee
IMV	invasive mechanical ventilation
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
LPV	lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
NIAID	National Institute of Allergy and Infectious Diseases
OR	odds ratio
PCR	polymerase chain reaction
PI	principal investigator
PK	pharmacokinetic(s)
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
RRT	renal replacement therapy
RTV	ritonavir
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBECD	sulfobutylether-beta-cyclodextrin
SCr	serum creatinine
SDV	source data verification
SmPC	Summary of Product Characteristics
SOC	standard of care
SOP	standard operating procedure
SpO_2	oxygen saturation
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)

T_{last}	time (observed time point) of C_{last}
T_{max}	time to maximum observed concentration
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China. Sequencing analysis from the patients' respiratory tract samples indicated a novel coronavirus (CoV), named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in a novel infectious disease called coronavirus disease 2019 (COVID-19). On 30 January 2020, the International Health Regulations Emergency Committee of the World Health Organization (WHO) declared the SARS-CoV-2 outbreak a public health emergency of international concern and a pandemic on 11 March 2020 {World Health Organization (WHO) 2020}. As of 11 July 2021, more than 186 million cases have been identified globally, with a death toll of over 4 million{World Health Organization (WHO) 2021}.

The clinical manifestations of COVID-19 are broad, ranging from mild symptoms to severe respiratory failure. However, the SARS-CoV-2 also manifests in several extrapulmonary organs by using angiotensin-converting enzyme 2 (ACE2) to enter human cells. ACE2 is expressed in the lung, heart, intestine, and kidney, and provides a probable mechanism for the systemic manifestations observed with this disease {Gupta 2020} Many patients with severe COVID-19 demonstrate signs of kidney damage that manifest as proteinuria, hematuria, and elevated serum creatinine (SCr) levels. Acute kidney injury (AKI) is a common complication of COVID-19 that is associated with high mortality rates, especially among people requiring renal replacement therapy (RRT) {Robbins-Juarez 2020}. Acute kidney injury is also more common among patients with respiratory failure, and most patients who require RRT also require mechanical ventilation, {Hirsch 2020}. Among those who require mechanical ventilation and develop AKI, about half have onset of AKI within 24 hours of intubation. In addition to need for ventilation and vasopressor medications, risk factors for AKI are similar to those at risk for severe COVID-19, including older age, diabetes mellitus, cardiovascular disease, black race, and hypertension {Hirsch 2020}.

The most common cause of AKI is likely related to acute tubular necrosis from the indirect effects of severe COVID-19, including alterations in systemic hemodynamics, inflammation, and immune function {Nadim 2020}. Several direct effects of SARS-CoV-2 have also been observed and are likely important mechanisms for AKI, including endothelial dysfunction, coagulopathy, and complement activation. The pathologic manifestations of these direct viral effects in the kidney include endothelial damage and capillary occlusions, deposition of complement complex on tubules, and glomerular lesions {Gupta 2020, Nadim 2020}. Several postmortem studies imply direct infection of the kidney by detection of SARS-CoV-2 mRNA and protein in glomerular and tubular cells, as well as visualization by electron microscopy of viral inclusion particles with distinctive spikes in podocytes, proximal tubular epithelial cells, and endothelial cells of the glomerular capillary loops {Farkash 2020, Puelles 2020, Su 2020, Varga 2020}. Finally, collapsing glomerulopathy associated with COVID-19 (an entity termed COVID-19-associated nephropathy, or COVAN) {Velez 2020} manifests as an aggressive morphological variant of focal segmental glomerulosclerosis, particularly among patients of

African ancestry, in whom the presence of high-risk *APOL1* alleles serve as a genetic risk factor {Nasr 2020}.

In addition to the direct and indirect acute effects of COVID-19 kidney function, preexisting kidney disease is a strong risk factor for severe COVID-19 and poor outcomes {Centers for Disease Control and Prevention (CDC) 2020}. Patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are particularly vulnerable to severe COVID-19 due to their older age and high burden of comorbid conditions including diabetes and hypertension {Alberici 2020, Williamson 2020}. In one study of critically-ill patients with COVID-19 across 68 intensive care units (ICUs; N = 4264), half of dialysis and CKD patients died within 28-days of ICU admission versus 35% of patients without preexisting kidney disease {Flythe 2020}. Among those with prehospitalization CKD who do not die, many require dialysis at hospital discharge {Ng 2020}. Despite the greater risk of adverse outcomes with COVID-19 among those with preexisting kidney disease, patients with CKD are being excluded from almost half of all registered clinical trials for COVID-19 {Major 2020}.

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). However, in the current US prescribing information (USPI) and EU Summary of Product Characteristics (SmPC), RDV is currently not recommended in people with severely reduced kidney function (glomerular filtration rate < 30 mL/min), leaving no alternative treatment options for those with COVID-19. The unmet need in this population remains large in the context of their poor outcomes with COVID-19, and providers around the world have expressed strong interest in treating these patients with RDV {Adamsick 2020}.

1.2. Remdesivir

Remdesivir is being developed by Gilead Sciences, Inc. (Gilead) and is formulated for intravenous (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 RDV to RDV 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 USPI and investigator's brochure (IB) for RDV.

1.3. Rationale for This Study

The restriction for RDV dosing among those with severely reduced kidney function is due primarily to the excipient betadex sulfobutyl ether sodium, also called sulfobutylether-beta-cyclodextrin (SBECD), which is renally cleared and accumulates in patients with decreased kidney function. Thus, administration of drugs formulated with SBECD, such as RDV, is not recommended in patients with estimated glomerular filtration rate (eGFR) < 30 mL per minute {VEKLURY 2020} (Veklury USPI). In terms of the renal tubular vacuolation associated with SBECD, it was observed in nonclinical studies in animals treated for 1 to 6 months with exposures that were 50- to 100-fold higher than would be expected for a 5- to 10-day course of RDV, and this change was largely reversible after cessation of treatment. For example, the amount of SBECD in a 5-day course of RDV (lyophilized formulation, 200 mg on Day 1 and 100 mg from Day 2 [Veklury USPI] {VEKLURY 2020}) would be 18 grams (SBECD:RDV is 30:1), or 257.1 mg/kg total and an average of 51.4 mg/kg/day over 5 days for a 70 kg adult, which is well below the maximum recommended safety dose of 250 mg/kg/day by the European Medicines Agency (EMA) safety review.

In addition, the clinical effects and pharmacokinetics (PK) of SBECD are well known from its use in other agents like IV voriconazole, which also requires this carrier to address its limited water solubility. Short courses of voriconazole have been well tolerated without significant adverse events (AEs) despite documented accumulation in some patients. For example, plasma exposures (AUC) increased 4-fold following intravenously administered SBECD to participants with moderate renal dysfunction (creatinine clearance 30-50 mL/min) {VFEND 2020}. In addition, SBECD is readily removed by dialysis (up to 100% of SBECD can be removed through continuous RRT and approximately 46% through high-flux hemodialysis), and liver function test elevation due to SBECD has been rare in patients with kidney failure. Finally, although tubular injury with RDV has been observed in nonclinical studies, the mechanism for nonclinical tubular injury is not understood, and RDV-related kidney injury has not been observed clinically in an Ebola trial {Mulangu 2019} or in COVID-19 trials (GS-US-540-5773, GS-US-540-5774, and Adaptive COVID-19 Treatment Trial [ACTT-1] conducted by National Institute of Allergy and Infectious Diseases [NIAID]).

To further explore the impact of RDV for COVID-19 in patients with reduced kidney function, Gilead performed a post hoc analysis on the ACTT-1 data. Although patients with baseline eGFR < 30 mL/min/1.73 m^2 were not included, the development of AKI with COVID-19 may provide some insights into the potential risk versus benefit of RDV treatment among those with lower levels of kidney function. We have the following preliminary findings:

1) The risk of developing AKI stage 2 or 3 may be lower in RDV-treated patients (Table 1; odds ratio [OR] 0.73 [95% CI, 0.48 to 1.10]; $P = 0.13$).

2) Among those who develop AKI stage 3, the risk of death at Day 15 also may be nominally lower in RDV-treated patients (Table 2; OR 0.66 [0.17, 2.40]; Fisher exact $P = 0.57$).

Table 1. Development of AKI Stages 2 or 3 in ACTT-1 Study, by Treatment Group

	RDV (N = 512)	SOC (N = 500)
Stage 2 or 3 AKI	43	56
None	469	444

AKI staging: Stage 1, Increase in serum creatinine (SCr) 1.5- to 2-fold from baseline; Stage 2, Increase in SCr > 2- to 3-fold from baseline; Stage 3, Increase in SCr > 3-fold from baseline, or SCr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL, or initiation of RRT {Kellum 2012}.

Table 2. Death Among Those With AKI Stage 3 in ACTT-1 Study, by Treatment Group

Stage 3 AKI	RDV (N = 28)	SOC (N = 34)
Died	6	10

AKI staging: Stage 1, Increase in serum creatinine (SCr) 1.5- to 2-fold from baseline; Stage 2, Increase in SCr > 2- to 3-fold from baseline; Stage 3, Increase in SCr > 3-fold from baseline, or SCr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL, or initiation of RRT {Kellum 2012}.

3) Among participants who were not receiving mechanical ventilation at baseline, the risk of developing AKI stage 2 or 3 seems lower in RDV-treated participants (Table 3; OR 0.61 [0.34, 1.09]; $P = 0.10$), and

4) The risk of death at Day 15 among those not receiving mechanical ventilation at baseline and having developed stage 3 AKI also seems lower in RDV-treated participants (Table 4; OR 0.13 [0.00, 1.25]; Fisher exact $P = 0.056$).

Table 3. Development of AKI Stages 2 or 3 in ACTT-1 Study Who Were Not Receiving Mechanical Ventilation at Baseline, by Treatment Group

	RDV (N = 382)	SOC (N = 349)
Stage 2 or 3 AKI	20	29
None	362	320

AKI staging: Stage 1, Increase in serum creatinine (SCr) 1.5- to 2-fold from baseline; Stage 2, Increase in SCr > 2- to 3-fold from baseline; Stage 3, Increase in SCr > 3-fold from baseline, or SCr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL, or initiation of RRT {Kellum 2012}.

Table 4. Death Among Those With AKI Stage 3 in ACTT-1 Study Who Were Not Receiving Mechanical Ventilation at Baseline, by Treatment Group

Stage 3 AKI	RDV (N = 13)	SOC (N = 20)
Died	1	8

AKI staging: Stage 1, Increase in serum creatinine (SCr) 1.5- to 2-fold from baseline; Stage 2, Increase in SCr > 2- to 3-fold from baseline; Stage 3, Increase in SCr > 3-fold from baseline, or SCr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL, or initiation of RRT {Kellum 2012}.

No differences in rate of AKI or death were observed in patients on mechanical ventilation at baseline (data not shown). With this context, the potential benefits of treatment with RDV, particularly before the need for mechanical ventilation, may outweigh the potential risks of its administration in patients with severely reduced kidney function.

1.4. Rationale for Dose Selection of Remdesivir

As the reduction in kidney function was commonly observed in COVID-19 patients at hospital admission, patients with eGFR ≥ 30 mL/min (mild to moderate renal disease) were included in the Phase 3 clinical development program and received RDV for treatment of COVID-19 with no dose adjustment.

Remdesivir is a prodrug. The metabolism of RDV, including metabolic routes leading to elimination and activation were characterized in vitro and in human mass balance studies. Inside the cell, RDV undergoes metabolic activation to form the intracellular active triphosphate metabolite, GS-443902, and ultimately, plasma terminal metabolite, GS-441524, that is not efficiently re-phosphorylated to the active triphosphate. The results of the RDV absorption, distribution, metabolism, and excretion (ADME) study showed that the mean total recovery of the radioactive dose was > 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively (GS-US-399-4231 clinical study report). Elimination through urine was the major elimination pathway for total radioactivity with the majority of the RDV dose recovered in urine being GS-441524 (48.6%) metabolite (little to no antiviral activity), while 10.3% was recovered as RDV. These data indicate that renal clearance is the major elimination pathway for GS-441524 and that renal impairment is likely to alter the PK of GS-441524. Considering that most of RDV elimination is via the nonrenal route, substantial increases in RDV PK, and corresponding active metabolite, GS-443902, are not expected. Available nonclinical and clinical data suggested that RDV, dosed once daily, is necessary to provide the active metabolite at the site of action; as such, dose interval modifications or RDV dose reduction to decrease GS-441524 exposure in this patient population are not deemed appropriate.

As such, the proposed dose for this study (hospitalized COVID-19 patients with eGFR < 30 mL/min/1.73 m^2) is a clinical dosing regimen approved for treatment of COVID-19 patients age ≥ 12 weighing ≥ 40 kg; single RDV 200 mg IV loading dose on Day 1 followed by RDV 100 mg IV once daily maintenance doses on Days 2 through 5 (EU SmPC) {VEKLURY 2020}. For participants on intermittent hemodialysis, if dosing falls on the same day as the hemodialysis session, RDV will be administered prior to initiation of the hemodialysis.

A dosing duration of up to 5 days will be evaluated in this study. The 5 days dosing duration is the recommended IV RDV duration for treatment of COVID-19 requiring hospitalization and not requiring invasive mechanical ventilation (IMV) and/or extracorporeal membrane oxygenation (ECMO) {VEKLURY 2020}. Moreover, patients with 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 order to fully characterize the relationship between kidney function and RDV disposition, an additional Phase 1 study in non-COVID-19 participants with chronic renal impairment (mild, moderate, severe chronic impairment, and end-stage renal disease) is ongoing (GS-US-540-9015). PK and safety data from both studies will be used to inform the recommendations for the use of RDV in COVID-19 patients with varying degrees of renal impairment.

1.5. Risk/Benefit Assessment for the Study

In addition to the established risks associated with IV RDV, potential risks associated with the study include unknown AEs and laboratory abnormalities associated with this study population. Intravenous RDV is approved for the treatment of COVID-19 in the US, Japan, and the EU.

An infectious disease pandemic may pose additional risks to investigational drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy.

There are currently no approved antiviral therapies for hospitalized patients with COVID-19 and severely reduced renal function (ie, eGFR< 30 mL/min). The timely evaluation of a safe and effective antiviral agent with previously demonstrated efficacy in patients with eGFR > 30 mL/min addresses a serious unmet need. The risk-benefit for this study is considered positive.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate whether RDV reduces the composite risk of death or IMV through Day 29 in participants with severely reduced kidney function who are hospitalized for COVID-19

The secondary objectives of this study are as follows:

- To evaluate whether RDV reduces the risk of death through Day 29
- To evaluate whether RDV reduces the risk of IMV through Day 29
- To evaluate the time to recovery (defined as satisfying category 1, 2, or 3 by the 8-point ordinal scale)
- To evaluate the effect of RDV on clinical status assessed by an 8-point ordinal scale at Day 15 and Day 29
- To evaluate the effect of RDV on RRT-free days (among those without ESKD) through Day 29
- To evaluate the effect of RDV on recovery through Day 29
- To evaluate the safety and tolerability of RDV in participants with severely reduced kidney function who are hospitalized for COVID-19

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3. STUDY DESIGN

This is a Phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy and safety of RDV therapy in participants with severely reduced kidney function who are hospitalized for COVID-19.

In this study, primary and secondary end points will be evaluated through Day 29. Following screening, eligible participants will be randomized in a 2:1 ratio to receive RDV or saline as placebo, according to the following treatment regimen, in addition to SOC therapy:

- Treatment Group A: IV RDV 200 mg on Day 1 followed by IV RDV 100 mg once daily from Day 2 up to Day 5
- Treatment Group B: IV saline as placebo on Day 1 followed by IV saline as placebo once daily from Day 2 up to Day 5

Randomization will be stratified by:

- ESKD requiring chronic dialysis
- High-flow oxygen requirement
- Region (US vs ex-US)

Study participants will receive RDV in a double-blind fashion as a 200 mg IV loading dose on Day 1, followed by 100 mg once daily IV maintenance doses up to a 5-day total treatment course (ie, Days 2 through 5) while hospitalized.

3.1. End Points

The primary efficacy end point of this study is as follows:

- The composite of all-cause mortality or IMV through Day 29

The key (α-controlled) secondary end point of this study is as follows:

- All-cause mortality through Day 29

Other secondary end points include:

- IMV through Day 29
- Time to recovery (defined as satisfying category 1, 2, or 3 by the 8-point ordinal scale)
- Clinical status assessed by an 8-point ordinal scale on Day 15 and Day 29

- RRT-free days (among those without ESKD at randomization) through Day 29
- Recovery through Day 29
- Serious adverse events (SAEs) and AEs leading to investigational drug discontinuation

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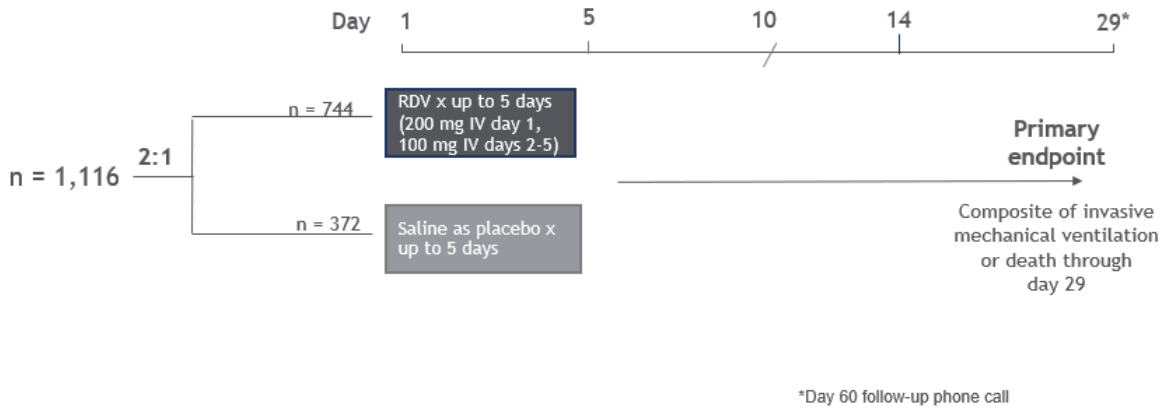
3.2. Study Design

This is a double-blind, placebo-controlled study.

Approximately 1116 participants aged ≥ 12 years of age, weighing at least 40 kg will be enrolled as described below:

Figure 1. Study Schema



3.3. Study Treatments

- Continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg once daily from Day 2 up to Day 5
- Continued SOC therapy together with IV saline as placebo on Day 1 followed by IV saline as placebo once daily from Day 2 up to Day 5

3.4. Duration of Treatment

Participants will be treated with RDV or saline as placebo for up to 5 days.

3.5. Discontinuation Criteria

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

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

Any elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × the upper limit of normal (ULN), confirmed by immediate repeat testing

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

- Participant request to discontinue for any reason

All participants will be requested to continue assessments during study hospitalization and any subsequent re-hospitalization to the same institution during Days 1 through 29 and attend the Day 60 phone follow-up (whether hospitalized or as an outpatient).

3.6. End of Study

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

3.7. 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 poststudy availability.

3.8. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory, and specialty laboratory (CCI and/or pharmacodynamic data).

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 1116 participants with severely reduced kidney function, who are hospitalized for COVID-19 will be enrolled into this study.

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) SARS-CoV-2 positive as determined by polymerase chain reaction (PCR) or other commercially available or public health assay (eg, nucleic acid amplification test and antigen tests) in any respiratory specimen

2) Hospitalized for COVID-19

3) Age ≥ 12 years and weighing at least 40 kg

4) O_2 saturation ≤ 94% on room air or requiring O_2 supplementation OR radiographic evidence of pulmonary infiltrates for COVID-19

5) Have either:

   a) Severely reduced kidney function (eGFR < 30 mL/min/1.73 m^2), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and revised Schwartz equations for adults and adolescents, respectively, including people with ESKD requiring chronic dialysis but not people requiring RRT for AKI {Levey 2009, Schwartz 2009}

   Adults: eGFR (mL/min/1.73 m^2) $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]

   $\kappa = 0.7$ for females; 0.9 for males
   $\alpha = -0.329$ for females; -0.411 for males

   Adolescents (age 12–17 years): eGFR (mL/min/1.73 m^2) = (0.41 × Height in cm) / SCr

   SCr in mg/dL, age in years

   (See Appendix 7 for web links to adult and adolescent eGFR calculators), OR

b) Ongoing AKI: defined as a 50% increase in SCr within a 48-hour period that is sustained (ie, requires confirmatory SCr) for ≥ 6 hours despite supportive care

6) Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (age ≥ 18) prior to performing study procedures

7) The interval between COVID-19 symptoms onset and randomization is no more than 10 days

8) Male participants and female participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4

4.3. Exclusion Criteria

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

1) Received any investigational drug, RDV, or other antiviral treatment for COVID-19

2) ALT or AST > 5 × ULN

3) IMV, noninvasive mechanical ventilation, ECMO, or RRT for AKI

4) Positive serum pregnancy test at screening for women of childbearing potential or currently breastfeeding

5) Known hypersensitivity to the investigational drug, metabolites, or formulation SBECD

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Participants who meet screening and randomization eligibility criteria will be randomized in a 2:1 ratio to RDV or saline as placebo starting on Day 1 and assigned a participant number. Randomization will be stratified by:

- ESKD requiring chronic dialysis
- High-flow oxygen requirement
- Region (US vs ex-US)

No more than 20% of enrolled participants will have ESKD requiring chronic dialysis.

5.1.2. Blinding

This is a double-blind, placebo-controlled study.

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 unblinded study pharmacist, or designee, in a blinded fashion to the blinded study care team. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management who facilitates the data transfer of PK files between Gilead and vendors will remain unblinded. 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 interactive voice/web response system for purposes of investigational drug inventory management will remain unblinded. Individuals in Gilead 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. A limited number of Gilead Clinical Operations personnel will be unblinded for specific unblinded study activities. The team performing the unblinded data reviews will be separate from the ongoing blinded study team. No Gilead personnel involved in the day-to-day conduct of the study will have access to any unblinded data. External (ie, contract research organizations [CROs]) biostatisticians and programmers will be unblinded for the data monitoring committee (DMC) and 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 interactive voice/web response system for that participant. The designated Site Unblinder may record an emergency unblinding transaction to immediately receive the participant's randomized treatment assignment. 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 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 or 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, remdesivir 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 0.9% normal saline will be used as placebo for remdesivir for injection, 100 mg. The 0.9% normal saline is identical in physical appearance to RDV once diluted into 0.9% normal saline as described above.

Compounding needs to be performed by the unblinded pharmacist and should remain blinded to the study care team.

5.2.2. Packaging and Labeling

Remdesivir for injection, 100 mg, is supplied as a sterile product in a single-use, 30-mL, Type I clear glass vial. Each vial is sealed with a fluoro-resin laminated rubber stopper and an aluminum seal with a red, plastic flip-off cap. The total amount of SBECD in a 5-day course of RDV (lyophilized) is 18 grams (SBECD:RDV is 30:1); 6 grams of SBECD on Day 1 (loading dose) followed by 3 grams of SBECD on each day from Day 2 through Day 5 (maintenance dose).

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

5.2.3. Storage and Handling

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

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

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

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

5.3. Dosage and Administration of Remdesivir

Remdesivir for injection, 100 mg, 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 once daily on Day 2 up to Day 5. Participants in Treatment Group B will receive IV saline as placebo on Day 1 followed by IV saline as placebo once daily on Day 2 up to Day 5.

Remdesivir will be administered via IV infusion over 30 to 120 minutes. Refer to the pharmacy manual for details. For participants on intermittent hemodialysis, if dosing falls on the same day as the hemodialysis session, RDV will be administered before initiation of the hemodialysis.

5.4. Infusion-related Reaction

Please refer to Section 7.7.

5.5. Prior and Concomitant Medications

Concomitant use of the following is prohibited during or within 30 days of the start of the study:

- Investigational medications for COVID-19 that have not received emergency use authorization or regulatory approval such as HIV protease inhibitors (eg, the combination of lopinavir [LPV]/ritonavir [RTV]), chloroquine, hydroxychloroquine, ivermectin, and interferon.

- This excludes medications that have received emergency use authorization or regulatory approval and are broadly recommended for the treatment of COVID-19 (eg, monoclonal antibodies).

Concomitant use of the following is prohibited during the study:

- Strong inducers of P-glycoprotein (eg, rifampin, rifabutin, carbamazepine, phenytoin, or herbal medications)

Prior medications:

- Any use of RDV prior to screening

Concomitant use of the following is allowed during the study:

- Parenteral drugs with SBECD as an excipient should be used with caution while participants are in the study, particularly during the 5-day dosing period (eg, EMA maximum recommended safety dose is 250 mg/kg/day)

- Medications that have emergency use authorization or regulatory approval and are broadly recommended for the treatment of hospitalized patients with COVID-19, and in the clinical opinion of the investigator, can be used in patients with severely reduced kidney function. Examples include tocilizumab and systemic corticosteroids.

5.6. Accountability for Investigational Medicinal Product

The unblinded pharmacist or designated unblinded personnel is responsible for ensuring adequate accountability of all used and unused investigational drug vials. This includes acknowledgment of receipt of each shipment of investigational drug vials (quantity and condition).

Each study site must keep accountability records that capture:

- The date received and quantity of investigational drug vials

- The date, participant number, and the investigational drug lot number dispensed

- The date, quantity of used and unused investigational drug vials returned, along with the initials of the person recording the information

5.6.1. Investigational Medicinal Product Return or Disposal

Gilead recommends that used investigational 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) investigational drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for electronic trial master file. If investigational drug is destroyed at the site, the unblinded pharmacist or designated personnel must maintain accurate records for all investigational drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the investigational drug. Upon study completion, copies of the investigational 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 investigational drug supplies are to be sent to the designated disposal facility for destruction. The unblinded study monitor will provide instructions for return.

The unblinded study monitor will review investigational drug supplies and associated records at periodic intervals with the unblinded pharmacist or designated personnel during remote or on-site monitoring visits.

For both disposal options listed above, the unblinded study monitor should first perform drug accountability during a remote or on-site 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 3 and described in the text that follows.

The investigator must document any deviation from the protocol procedures and notify Gilead or the CRO.

NOTE: Samples for laboratory safety assessments should be collected before dialysis on the day of dialysis for participants on intermittent RRT during the study.

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.

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 (participant ≥ 18 years of age) or assent from parent or legal guardian (participants < 18 years of age, where locally and nationally approved)
- Determine eligibility requirements as specified in the inclusion and exclusion criteria
- Focused medical history will include date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics, concomitant medications, kidney or other transplant history, and allergies
- Complete physical examination, including vital signs (heart rate, temperature, blood pressure), actual body weight, and height
- Documentation of respiratory status:
  - Respiratory rate
  - Oxygenation: oxygen saturation (SpO_2), room air, low-flow O_2, high-flow O_2
- CCI [redacted]

- Documentation of SARS-CoV-2 infection by PCR via 1 validated assay at a local laboratory, if not performed within the last 4 calendar days
- Document COVID-19 vaccine status (Note: It should be documented whether participant is fully or partially vaccinated, including any booster[s] received, if applicable.)
- Record the 8-point ordinal scale (see Section 6.9)
- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the informed consent (or assent) form
- IMV (yes/no; if yes, provide date when mechanical ventilation was started)
- RRT assessment
- If available, up to 3 SCr values prior to COVID-19 illness (eg, within the previous 6 months)
- Counsel participants of childbearing potential to use adequate birth control methods required during the trial to avoid pregnancy. See Appendix 4
- Laboratory evaluations: The following tests will be performed at screening. Results from within 48 hours prior to screening are acceptable; the entire panel of tests should be performed for all study participants if not done in the preceding 48 hours (see Section 6.5):
  - Chemistry, hematology, SCr, and coagulation
  - Urinalysis (participants who are oliguric are not required to provide a urine sample)
  - Pregnancy test (serum, for females of childbearing potential)

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.

6.2.2. Baseline/Day 1 Assessments

The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility (all inclusion/exclusion criteria must be met prior to randomization) before proceeding with Day 1 visit procedures.

Participants must complete the following assessments before being administered investigational drug:

- Vital signs (heart rate, temperature, blood pressure)
- Confirmed negative pregnancy test from screening visit (for women of childbearing age)

- Documentation of respiratory status:
  - Respiratory rate
  - Oxygenation: SpO_2, room air, low-flow O_2, high-flow O_2, and target fraction of inspired oxygen (FIO_2). The target FIO_2 value applies to all forms of O_2 nasal and mask delivery (nasal prongs, masks, CPAP/BIPAP) as well as mechanical ventilation.
- IMV (yes/no; if yes, provide date when mechanical ventilation was started)
- Assessment of need for RRT
- Record the 8-point ordinal scale twice (see Section 6.9)
- Review AEs and document concomitant medications
- Laboratory evaluations: Chemistry, hematology, coagulation, and SCr (see Section 6.5)
- Collection of nasopharyngeal swab sample for SARS-CoV-2 RT-qPCR testing CCI [redacted] (see Section 6.8)

[redacted]

CCI [redacted]

[redacted]

6.4. Assessments (Days 2 Through 29)

The following evaluations are to be completed daily (unless otherwise noted in indicated sections and Appendix 3) from Day 2 through Day 29 or until discharge from inpatient hospitalization, whichever is earlier. If the participant is readmitted to the hospital prior to Day 29, evaluation for RRT, ordinal scale and AEs are to be completed daily through Day 29.

Participants must complete the following assessments before being administered investigational drug:

- Vital signs (heart rate, temperature, blood pressure)
- Documentation of respiratory status:
  - Respiratory rate
  - Oxygenation: SpO_2, room air, low-flow O_2, high-flow O_2, CPAP/BIPAP, mechanical ventilation, venovenous ECMO, venoarterial ECMO, and target FIO_2. The target FIO_2 value applies to all forms of O_2 nasal and mask delivery (nasal prongs, masks, CPAP/BIPAP) as well as mechanical ventilation

- IMV (yes/no; if yes, provide date when mechanical ventilation was started)
- Assessment of need for RRT
- Record the 8-point ordinal scale (see Section 6.9)
- Review AEs and document concomitant medications
- Laboratory evaluations: Chemistry, hematology, coagulation, and SCr (see Section 6.5)
- [redacted]
- [redacted]
- Collection of nasopharyngeal swab sample for SARS-CoV-2 RT-qPCR testing CCI [redacted] (see Section 6.8)

6.5. Additional Assessments

Laboratory testing during hospitalization will be performed according to SOC practice with results for chemistry, hematology, and any SARS-CoV-2 testing being reported to the sponsor.

In addition, even if not performed as SOC, the following will be completed at screening and on Days 1, 3, 5, 8, 12, 16, 20, 24, and 29 or until discharge, whichever is earlier:

- Laboratory evaluations: Chemistry, hematology, coagulation

In addition, even if not performed as SOC, the following will be completed at screening and on Days 1 through 29, or until discharge, whichever is earlier:

- Laboratory evaluations: SCr

CCI [redacted]

[redacted]

CCI

CCI

CCI

CCI

CCI

CCI

CCI

6.8. Virology Assessments

[redacted]

Nasopharyngeal swab samples for SARS-CoV-2 RT-qPCR testing [redacted] will be collected from all participants on Days 1, 3, 5, 7, 14, 21, and 29 or until discharge, whichever is earlier

6.9. Ordinal Scale

The ordinal scale is an assessment of the clinical status of a given study day. Each day, the worst (ie, highest ordinal) score from the previous day will be recorded (ie, on Day 3, the highest ordinal score from Day 2 is obtained and recorded for Day 2). The ordinal scale needs to be completed twice on Day 1: prior to randomization (for baseline predose score) and the worst score on Day 1.

The scale is as follows:

8) Death

7) Hospitalized, on IMV or ECMO

6) Hospitalized, on noninvasive ventilation or high-flow oxygen devices

5) Hospitalized, supplemental oxygen

4) Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care for COVID-19−specific medical care (other than per-protocol RDV administration)

3) Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care (other than per-protocol RDV/saline as placebo administration)

2) Not hospitalized, limitation on activities and/or requiring home oxygen

1) Not hospitalized, no limitations on activities

6.10. Posttreatment Assessments

Upon discharge from inpatient hospitalization, the following assessments will be required at the Day 29 and Day 60 phone follow-up (see Appendix 3):

- Assessment of need for RRT
- Record the 8-point ordinal scale (see Section 6.9)
- Review AEs and document concomitant medications

- Mortality
- IMV (yes/no if yes, provide date when mechanical ventilation was started)
- Hospital readmission rate

6.11. Assessments for Early Discontinuation from Study

If a participant discontinues study dosing (eg, 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 6.11.1, 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.

6.11.1. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Any SAE or ≥ Grade 3 AE suspected to be related to RDV
- Any elevations in ALT or AST > 5 × ULN
- 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
- Participant request to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study (refer to Appendix 4)
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB) or independent ethics committee (IEC)

6.12. End of Study

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

6.13. 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 poststudy availability.

CCI [redacted]

[redacted]

[redacted]

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 drug, 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 drug, whether or not the AE is considered related to the investigational drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

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 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the informed consent form (ICF) is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after investigational drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

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

- Death
- A life-threatening situation (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.)

- Inpatient 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.

7.1.3. Investigational Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) 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 or 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 drug 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 drug by a participant.

Misuse is defined as any intentional and inappropriate use of an investigational drug 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 drug 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 drug as a result of one's professional or nonprofessional 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 drug.

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

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 Investigational Drugs and Procedures

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

- **No**: Evidence exists that the AE has an etiology other than the investigational drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE may have been caused by the investigational 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) Toxicity Grading Scale, Version 2.1. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 5).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Investigational Drug Initiation

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

7.3.2. Adverse Events

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

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

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the participant first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable eCRFs and Gilead GLPS (formerly known as Pharmacovigilance and Epidemiology) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment follow-up visit but within 30 days of the last dose of investigational 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 investigational drug, the investigator should promptly document and report the event to Gilead GLPS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Investigational Drug Special Situations Reports

All investigational drug SSRs that occur from investigational drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered investigational drug), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

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

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.

All clinical sequelae in relation to these SSRs 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.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted 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.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Electronic Serious Adverse Event Reporting Process Site personnel will 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 from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

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

Gilead GLPS
Email: PPD
or
Fax: PPD

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to Gilead GLPS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Investigational Drug

- All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from investigational drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead GLPS
Email: PPD
or
Fax: PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve Gilead concomitant medications that are not considered investigational drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

Gilead GLPS
Email: PPD
or
Fax: PPD

- 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.

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

7.4.2.3. Pregnancy Reporting Process

- The investigator should report pregnancies in female study participants and/or female partners of male participants that are identified after initiation of investigational drug and throughout the study, including the postinvestigational drug follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

  Gilead GLPS
  Email: PPD
  or
  Fax: PPD

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

- All other premature terminations 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, as described in Section 7.4.1. 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 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Gilead GLPS.

- The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy/partner 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

- Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Administration 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, which may be in the form of line-listings, 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 investigational 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.

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

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

Severity should be recorded and graded according to the DAIDS Toxicity Grading Scale, Version 2.1. 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.

7.7. Toxicity Management

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. Remdesivir infusions will be administered to participants at the site under close supervision. Healthcare professionals administering RDV infusions must 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. Participants should be monitored for at least 2 hours after the RDV infusion is completed.

All clinical events and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 6, and as outlined below.

Grade 3 or 4 clinically significant laboratory abnormalities that were not present at baseline should be confirmed by repeat testing as soon as possible, and preferably within 3 calendar days after receipt of the original test results.

The Gilead medical monitor should be consulted prior to investigational drug discontinuation when medically feasible.

7.7.1. Grade 1 and 2 Laboratory Abnormalities

Continue investigational drug at the discretion of the investigator.

7.7.2. Grade 3 Laboratory Abnormalities

For a Grade 3 clinically nonsignificant laboratory abnormality (eg, clinically insignificant Grade 3 cholesterol, triglyceride abnormalities, or creatine kinase (CK) elevations) that were not present at baseline, the investigational drug may be continued if the event is considered to be unrelated to the investigational drug.

For a Grade 3 clinically significant laboratory abnormality confirmed by repeat testing (as soon as possible, and preferably within 3 calendar days after receipt of the original test results), that was not present at baseline and considered to be related to the investigational drug, the investigational drug should be permanently discontinued and the participant managed according to local practice. The Gilead medical monitor should be consulted prior to investigational drug discontinuation when medically feasible.

7.7.3. Grade 4 Laboratory Abnormalities

For a Grade 4 clinically significant laboratory abnormality by repeat testing (as soon as possible, and preferably within 3 calendar days after receipt of the original test results), that was not present at baseline and considered to be related to the investigational drug, the investigational drug should be permanently discontinued and the participant managed according to local practice. The Gilead medical monitor should be consulted prior to investigational drug discontinuation when medically feasible. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational drug may be continued without dose interruption for a clinically nonsignificant Grade 4 laboratory abnormality (eg, Grade 4 CK elevation after strenuous exercise, triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to the investigational drug.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and End Points

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate whether RDV reduces the composite risk of death or IMV through Day 29 in participants with severely reduced kidney function who are hospitalized for COVID-19

The secondary objectives of this study are as follows:

- To evaluate whether RDV reduces the risk of death through Day 29
- To evaluate whether RDV reduces the risk of IMV through Day 29
- To evaluate the time to recovery (defined as satisfying category 1, 2, or 3 by the 8-point ordinal scale)
- To evaluate the effect of RDV on clinical status assessed by an 8-point ordinal scale at Day 15 and Day 29
- To evaluate the effect of RDV on RRT-free days (among those without ESKD) through Day 29
- To evaluate the effect of RDV on recovery through Day 29
- To evaluate the safety and tolerability of RDV in participants with severely reduced kidney function who are hospitalized for COVID-19

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8.1.2. Primary End Point

- The composite of all-cause mortality or IMV through Day 29

8.1.3. Secondary End Points

The key (α-controlled) secondary end point of this study is as follows:

- All-cause mortality through Day 29

Other secondary end points include:

- IMV through Day 29
- Time to recovery (defined as satisfying category 1, 2, or 3 by the 8-point ordinal scale)
- Clinical status assessed by an 8-point ordinal scale on Day 15 and Day 29
- RRT-free days (among those without ESKD at randomization) through Day 29
- Recovery through Day 29
- SAEs and AEs leading to investigational drug discontinuation

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8.2. Planned Analyses

8.2.1. Interim Analysis

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

8.2.1.1. Data Monitoring Committee Analysis (Safety Analysis)

The first DMC meeting will be based on data collected after the first 100 participants complete the Day 29 assessment and will include safety data, including renal and hepatic toxicity. No formal efficacy evaluations are planned for this meeting.

8.2.1.2. Data Monitoring Committee Analysis (Efficacy and Futility Interim Analysis)

The second DMC meeting will be based on data collected after 50% of participants complete the Day 29 assessment and will include review of safety, and formal evaluation of futility and efficacy. The DMC may provide recommendation on stopping enrollment to the study if the prespecified boundaries for efficacy (outlined in Section 8.7) or futility are crossed. If the conditional power (ie, the probability of obtaining a statistically significant result after all participants have completed the Day 29 assessment assuming the trend of treatment effect observed at interim is retained for the remainder of the study) is 15% or less, consideration should be given to stopping the study for futility. An interim analysis communication plan will be created.

8.2.2. Primary Analysis

The primary analysis will be performed after all participants have completed Day 29 of the study or prematurely discontinued from the study before Day 29. The analysis of the primary end point of all-cause mortality or IMV through Day 29 and key α-controlled secondary end point of all-cause mortality through Day 29 will be conducted at the time of the interim analysis (after 50% of participants complete the Day 29 assessment) and will only be evaluated in this analysis based on results observed at the interim analysis (see Section 8.7 for prespecified boundaries). The overall Type I error rate will be controlled at the two-sided 0.05 significance level.

8.2.3. 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.

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 which they received.

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8.3.1.4. Biomarker

The biomarker analysis set will include all randomized participants who received at least 1 dose of study treatment and for whom biomarker samples are available.

8.3.2. Data Handling Conventions

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Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation, will be imputed to the value of the lower or upper limit plus or minus 1 significant digit, respectively (ie, 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 pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

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

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, 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 clinical end point is the composite of all-cause mortality or IMV from date of first dose through Day 29.

The primary end point will be analyzed using a stratified log-rank test stratified by the randomization stratum. The hazard ratio and 95% confidence interval will be provided. The null hypothesis being tested is that there is no difference between treatment groups in the probability of death or IMV through Day 29.

Participants with missing outcomes for the primary end point due to premature discontinuation of the study on or prior to Day 29 will be censored at the date of last contact.

8.5.2. Secondary Analyses

The secondary end points of all-cause mortality through Day 29 (α-controlled) and of recovery through Day 29 will be analyzed in a similar manner to the primary end point.

The clinical status assessed by an 8-point ordinal scale on Day 15 and Day 29 will be analyzed using a proportional odds model including treatment as the independent variable to compare the treatment groups.

Other end points related to proportion of participants will be compared between treatment groups using a chi-square test or Fisher exact test. End points that are measured as time to first event will be compared between treatment groups using the log-rank test and continuous end points 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 first investigational drug dose date through 30 days after the date of the last investigational drug dose will be summarized by treatment group (according to the investigational drug received). Data for the pretreatment period and after the date of last investigational drug dose plus 30 days will be included in data listings.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class, 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 first dose date up to the date of last dose of investigational 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 after baseline up to and including the date of last dose of investigational drug plus 30 days will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

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

8.7. Adjustments for Multiplicity

The overall two-sided Type I error rate of 0.05 for the primary and key α-controlled secondary end points will be controlled using the Lan-DeMets approach with O'Brien-Fleming type spending function accompanying a gatekeeping testing strategy (ie, the primary efficacy end point will be tested first and the key α-controlled secondary end point will be tested only if the primary efficacy end point is met). The α-spending and gatekeeping details are specified in Table 5.

Table 5. Gatekeeping and Boundaries for Efficacy Analysis

Efficacy Analysis	Primary End Point	Key α-controlled Secondary End Point (Will be Tested ONLY IF Primary End Point is Met)
Interim Analysis (50% of Participants Completed Day 29)	0.0031	0.0031
Primary Analysis (All Participants Completed Day 29)	0.0490 (will be tested **ONLY IF** the primary end point is **NOT** met at interim)	0.0490

Note: P-values are based on two-sided stratified log-rank test.

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[redacted]

8.9. Sample Size

A total of approximately 1116 participants will be randomized in a 2:1 ratio to 2 groups (744 in the RDV group and 372 in the saline as placebo group). This sample size achieves approximately 85% power to detect a hazard ratio of 0.70 at a two-sided alpha level of 0.05. In the sample size calculation, it is assumed that the event rate in the saline as placebo group is 35%. The hazard ratio and event rate in the saline as placebo group are based on the most conservative estimates of the primary end point (composite of all-cause mortality or IMV) and key α-controlled secondary end point (all-cause mortality) through Day 29 among a subset of participants with eGFR < 60 mL/min in the Division of Microbiology and Infectious Diseases Protocol 20-0006 Adaptive COVID-19 Treatment Trial (ACTT)-1 (hazard ratio of 0.67 and placebo rate of 33%).

The sample size calculation was done using software EAST (Version 6.5, module for log-rank test given accrual duration [120 days] and study duration [149 days] and 1 interim analysis using the Lan-DeMets approach with O'Brien-Fleming type spending function).

8.10. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study, perform interim reviews of safety data and provide recommendation 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 whether the study should continue with modifications. The DMC will have 2 formal (unblinded data review) meetings. The first formal meeting will review safety data after the first 100 participants complete the Day 29 assessment. The second formal meeting will review safety, efficacy and futility data after 50% of participants complete the Day 29 assessment. The DMC may make a recommendation of stopping enrollment to the study if the prespecified efficacy or futility stopping criteria are met. The DMC will also receive blinded safety listings for review up to every week for the first 2 weeks followed by every 2 weeks until the second DMC meeting occurs after 50% of participants complete the Day 29 assessment. The DMC may also provide recommendations as needed regarding study design.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

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

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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, ICF, 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 ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the participant or the participant's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform participants about genomic testing and/or planned sample retention. CCI [redacted] CCI [redacted] The results of the tests done on the samples will not be given to the participant or the investigator.

9.1.5. Confidentiality

The investigator must ensure 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 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. 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, case report forms (CRFs)/eCRFs, investigational drug information, 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, CRFs/eCRFs, governmental approval with correspondence, the ICF(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, ie, 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 investigational drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end dates; 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 for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, the US, the EU, 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, for 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 CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification 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, 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 login 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 in accordance with local requirements and receive documented IRB 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 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 authorities and IRB. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGMENT

A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19

Protocol Amendment 3: 27 August 2021

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

PPD

Medical Monitor

27 AUGUST 2021

Date

PPD

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 Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study treatment supplies to participants and sites:

    a) Participants may be unable to return to the site for a number of visits to get the investigational drug, or the site may be unable to accept any participant visits. Without investigational drugs, the participant would not be able to stay on the investigational drug as planned per protocol.

    Mitigation plan: Investigational drug supplies may be provided to the participant from the site without a clinic visit, once it is confirmed that the participant may safely continue on investigational drug as determined by the principal investigator (PI). A virtual study visit, via phone or video conferencing, must be performed prior to remote investigational drug resupply. At the earliest opportunity, the site will schedule in-person participant visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the investigational drug from sites to study participants if permitted by local ethics committee (EC)/institutional review boards (IRB)/Regulatory Authority as applicable and with sponsor's approval.

    b) Shipments of investigational drug could be delayed because of transportation issues. Without investigational drug participant would not be able to stay on the investigational drug as planned per protocol.

    Mitigation plan: The sites' investigational drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in investigational drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the investigational drug depot and study sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow-up:

    a) Participants may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

    Mitigation plan: For participants who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

        i) Confirm if participant has experienced any AEs/SAEs/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

iv) If applicable, confirm participants investigational drug supply is sufficient to last until the next planned visit date. If investigational drug resupply is needed it will be provided as described above in (1).

v) If applicable, remind participant to maintain current dosing and to keep all dispensed investigational drug kits for return at the next on-site visit.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central lab analyses.

Mitigation plan: Local labs may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local lab pregnancy testing is not feasible.

Participants may be unable or unwilling to attend the study visit to sign an updated ICF version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification (SDV), or investigational drug accountability or assess protocol and GCP compliance.

This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. In compliance with Gilead policy, a remote SDV should not be arranged. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of [investigational drug(s)] in study participants remains unchanged.

Appendix 3. Study Procedures Table

	Screening	Baseline/ Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9, 10, 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17, 18, 19	Day 20	Day 21	Day 22, 23	Day 24	Day 25, 26, 27, 28	Day 29*	Day 29 and Day 60 Phone Follow-up Visits (+ 5 days)
Written Informed Consent	X																						
Inclusion/Exclusion Criteria	X																						
Focused Medical History, including SCr values[a]	X																						
Documentation of SARS-CoV-2 Infection[b]	X																						
Complete Physical Examination	X																						
Height	X																						
Weight	X																						
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Respiratory Status[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Invasive Mechanical Ventilation[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Radiographic Imaging[e]	X																						
8-Point Ordinal Scale[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[g]	X																						
Chemistry[h,r]	X	X		X		X			X		X				X		X			X		X	
Hematology[i,r]	X	X		X		X			X		X				X		X			X		X	

	Screening	Baseline/ Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9, 10, 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17, 18, 19	Day 20	Day 21	Day 22, 23	Day 24	Day 25, 26, 27, 28	Day 29*	Day 29 and Day 60 Phone Follow-up Visits (+ 5 days)
Coagulation[j,r]	X	X		X		X			X		X				X		X			X		X	
Serum Creatinine[r,s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[t]	X																						
RRT Assessment[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Virologic Testing[l]		X		X		X		X					X					X				X	
CCI																							
CCI																							
CCI																							
Investigational Drug Dosing		X	X	X	X	X																	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mortality																							X
Hospital Readmission Rate																							X

* All assessments to be completed through Day 29, or until discharge, whichever is earlier. If participant is discharged prior to Day 29, a phone follow-up is to be completed at Day 29 and Day 60.

a Focused medical history will include date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics, concomitant medications, kidney or other transplant history, and allergies. If available, up to 3 SCr values prior to COVID-19 illness (eg, within the previous 6 months) should be provided. Document COVID-19 vaccine status. (Note: It should be documented whether participant is fully or partially vaccinated, including any booster[s] received, if applicable.)

b Positive as determined by PCR via 1 validated assay at a local laboratory, if not performed within the last 4 calendar days.

c Includes heart rate, temperature, and blood pressure.

d Respiratory status includes respiratory rate and oxygenation: see Sections 6.2.1, 6.2.2, and 6.4.

e Pulmonary radiographic imaging may be performed within 72 hours, if not already available and if needed to satisfy eligibility criteria.

f Ordinal scale to be performed twice on Day 1: prior to randomization (for baseline predose score) and the worst score on Day 1.

g Serum pregnancy test will only be done for women of childbearing potential. Women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range > 40 IU/L and they are not using hormonal contraception or hormonal replacement therapy. Results from within 48 hours prior to screening are acceptable.

h 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. Results from within 48 hours prior to screening are acceptable.

i Hematology: complete blood count with differential, hemoglobin and/or hematocrit, platelets. Results from within 48 hours prior to screening are acceptable.

j Coagulation performed by central lab: international normalized ratio, prothrombin time, activated partial thromboplastin time, D-dimer, fibrinogen. Results from within 48 hours prior to screening are acceptable.

k RRT will be measured at screening through Day 29 or until discharge from inpatient hospitalization, as well as at the Day 60 phone follow-up.

l Nasopharyngeal swab collection for virologic (SARS-CoV-2) testing for participants on Days 1, 3, 5, 7, 14, 21, and 29 or until discharge, whichever is earlier.

[redacted]

q If on invasive mechanical ventilation at screening, participant should be excluded from the study.

r For participants on intermittent RRT, laboratory safety assessments should be drawn before dialysis on the day of dialysis.

s Refer to Inclusion Criterion #5 to determine the need for a confirmatory SCr evaluation.

t Participants who are oliguric are not required to provide a urine sample.

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definition

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 postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

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

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female 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 medical documentation.

2) Contraception Requirements for Female Participants

a. Investigational Drug Effects on Pregnancy and Hormonal Contraception

Data from clinical PK interaction studies of RDV have demonstrated that a clinically relevant interaction with contraceptive steroids was observed or suspected, but the effect is considered to be of limited clinical significance. In addition, nonclinical toxicity studies of RDV have demonstrated no adverse effect on fertility or embryo-fetal development. However, there is no clinical data available for RDV in pregnant women. Before enrolling into studies with RDV, women of childbearing potential must have pregnancy testing performed at screening. Refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of non-pregnant female participants of childbearing potential requires the use of at least 1 acceptable contraceptive measure. They must have a negative serum pregnancy test at screening and a confirmed negative pregnancy test from screening visit on Day 1, prior to randomization. In the event of a delayed menstrual period (over 1 month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is also applicable for women of childbearing potential with infrequent or irregular periods.

Duration of required contraception for female participants in this clinical trial should start from screening visit until 30 days after last dose of investigational drug.

Female participants must agree to 1 of the following contraceptive methods:

- 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 must use condoms when engaging in intercourse of reproductive potential during treatment and until 30 days after last dose of investigational drug. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male participants must also refrain from sperm donation during treatment and until the end of contraception requirement.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation 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

Female participants will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 30 days after last investigational drug dose.

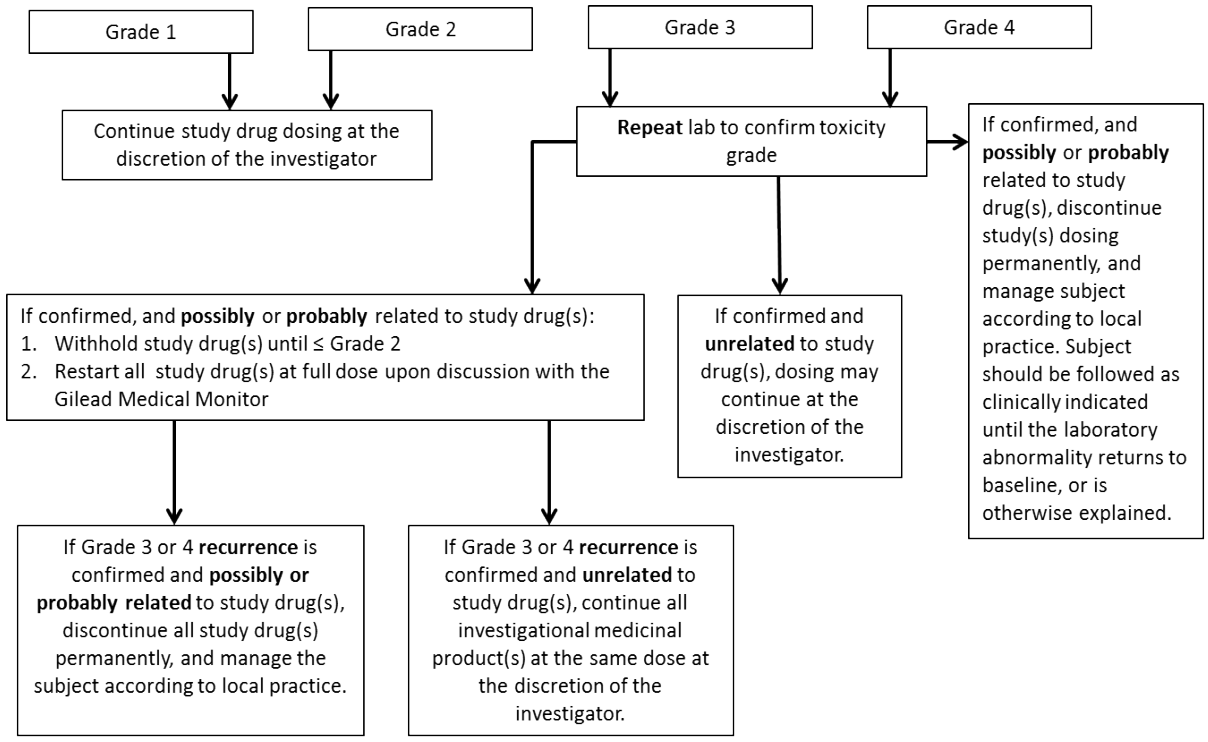
Note: Female participants who become pregnant during the study or are discovered to be pregnant after receiving at least 1 dose, may continue investigational drug after discussion with the investigator.

Male participants whose partner has become pregnant or suspects she is pregnant from start of study to 30 days after last investigational drug dose must also report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 5. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

The DAIDS Toxicity Grading Scale Version 2.1 dated July 2017 is available at the following location:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

Appendix 6. Management of Clinical and Laboratory Adverse Events



Appendix 7. eGFR Automated Calculators

Automated calculators are provided by the National Institute of Diabetic and Digestive and Kidney Diseases.

Adults:
https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units

Adolescents:
https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/children-conventional-units