CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants from Birth to < 18 Years of Age with COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	147753
EudraCT Number:	2020-001803-17
Clinical Trials.gov Identifier:	NCT04431453
Indication:	COVID-19
Protocol ID:	GS-US-540-5823
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 29 May 2020 Amendment 1: 18 June 2020 Amendment 2: 22 September 2020 Amendment 3: 16 February 2021 Amendment 4: 06 January 2022

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, the United Kingdom, and Switzerland are not included under the IND and are considered non-IND sites.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants from Birth to < 18 Years of Age with COVID-19
IND Number:	147753
EudraCT Number:	2020-001803-17
Clinical Trials.gov Identifier:	NCT04431453
Study Centers Planned:	Approximately 35 global centers
Objectives:	The primary objectives of this study are as follows: • To evaluate the safety and tolerability of remdesivir (RDV; GS-5734™) in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years • To evaluate the pharmacokinetics (PK) of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years The secondary objectives of this study are as follows: • To evaluate the efficacy of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years • To determine the antiviral activity of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years • Change from baseline in oxygenation use • Change from baseline in the use of mechanical ventilation or extracorporeal membrane oxygenation • To evaluate clinical improvement using the PEWS scale in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years • Determine sulfobutylether β-cyclodextrin sodium (SBECD) exposures (where possible) • To provide data on use of medications other than RDV for treatment of COVID-19

The exploratory objectives of this study are as follows:

- CCI
- CCI
- CCI

Study Design:

This is a Phase 2/3 single-arm, open-label study of the safety, tolerability, PK, and efficacy of RDV in pediatric participants from birth to < 18 years of age with laboratory-confirmed infection with COVID-19.

At least 52 participants aged 0 days to < 18 years will be enrolled as described in the table below.

Cohort	Description
1	≥ 12 years to < 18 years and weight ≥ 40 kg
2	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg
3	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg
5	≥ 14 days to < 28 days of age, gestational age (GA) > 37 weeks and weight at Screening ≥ 2.5 kg
6	0 days to < 14 days of age, GA > 37 weeks and birth weight ≥ 2.5 kg
7	0 days to < 56 days of age, GA ≤ 37 weeks and birth weight ≥ 1.5 kg
8	< 12 years and weight ≥ 40 kg

Pediatric participants ≥ 28 days to < 18 years old

Cohorts 1-4 (n = 12 for each Cohort) will be enrolled into a single arm of RDV:

- Cohort 1: Weight ≥ 40 kg: Intravenous (IV) RDV 200 mg on Day 1 followed by IV RDV 100 mg daily for up to 10 days.
- Cohorts 2-4: Weight 3 kg to < 40 kg: IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily for up to 10 days.

Cohort 8: < 12 years and weight ≥ 40 kg: IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily for up to 10 days.

	Term neonatal participants 0 days to < 28 days old Cohorts 5 and 6 (n = 4 for Cohort 5) will be enrolled into a single arm of RDV: • Cohort 5: Weight ≥ 2.5 kg and GA > 37 weeks: IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily for up to 10 days. • Cohort 6: Birth weight ≥ 2.5 kg and GA > 37 weeks: IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily for up to 10 days. **Preterm neonates and infants 0 days to < 56 days old** • Cohort 7: Birth weight ≥ 1.5 kg and GA ≤ 37 weeks: IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily for up to 10 days. Cohorts 1-5 will be enrolled in parallel. Participants in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined. There is no minimum number of participants to be enrolled in Cohorts 6 and 7 due to the rarity of such participants. CCI [redacted]
Number of Participants Planned:	At least 52 participants
Target Population:	Pediatric participants 0 days to < 18 years of age with laboratory-confirmed COVID-19 who are hospitalized
Duration of Treatment:	Participants will be treated up to 10 days. Those participants who have demonstrated clinical improvement may be considered for a shorter treatment period.
Diagnosis and Main Eligibility Criteria:	Participants with COVID-19 confirmed by polymerase chain reaction (PCR) via a validated assay at a local laboratory who meet the following criteria: • Hospitalized and requiring medical care for COVID-19 • **Cohort 1:** ≥ 12 years to < 18 years of age and weight at screening ≥ 40 kg • **Cohorts 2-4:** ≥ 28 days to < 18 years of age and weight at screening ≥ 3 kg and < 40 kg • **Cohort 5:** ≥ 14 days to < 28 days of age, GA > 37 weeks and weight at screening ≥ 2.5 kg

- **Cohort 6:** 0 days to < 14 days of age, GA > 37 weeks and birth weight of ≥ 2.5 kg
- **Cohort 7:** 0 days to < 56 days of age, GA of ≤ 37 weeks and birth weight of ≥ 1.5 kg
- **Cohort 8:** < 12 years of age and weight at screening ≥ 40 kg

Study Procedures/ Frequency:

Screening is to be completed within 2 days of the Day 1 visit.

At the screening visit and all subsequent study visits (or until hospital discharge - whichever comes first) laboratory analyses (hematology, chemistry, inflammatory markers, urinalysis, and routine coagulation test), vital signs (heart rate, temperature, blood pressure [mean arterial pressure if available, systolic and diastolic], respiratory rate [if not on a ventilator], oxygen saturation), complete or symptom-directed physical examinations will be performed. Nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined), and rectal or fecal swab will be collected on Days 1, 3, 5, 7, and 10 (if feasible) for SARS-CoV-2 reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) viral load testing and possible viral resistance testing. Endotracheal tube aspirates will also be collected if the participant is intubated. If the participant is discharged prior to Day 10, the samples for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above, if feasible. Serum for SARS-CoV-2 IgG, IgM, and IgA serology will be collected at Screening, Day 5, Day 10 (if feasible), and the Day 30 Follow-up visit (≥ 12 kg).

Clinical scoring using the PEWS Improvement Scale and Ordinal Scale will occur at Screening and daily through the duration of dosing.

Day 30 Follow-up visit, as outpatient or inpatient depending on clinical status, will include vital signs, complete or symptom-directed physical examination and chemistry laboratory evaluation.

Adverse events and concomitant medications will be assessed from Screening through the Day 30 Follow-up visit.

Pharmacokinetic Assessments

As many of the specified PK time points should be obtained from each participant as is feasible.

	Cohorts 1-4 (12 participants for each cohort) and Cohort 8 (all available): • Day 2: end of infusion (±15 minutes) and 4 hours (±30 minutes) post end of infusion • Day 3: pre-infusion (≤ 60 minutes) and 2 hours (±15 minutes) post end of infusion • CCI [redacted] Cohorts 5 (minimum of 4 participants), 6, 7 (all available), Day 2 or Day 3: • Day 2: end of infusion (±15 minutes) and 4 hours (±30 minutes) post end of infusion • Day 3: pre-infusion (≤ 60 minutes) and 2 hours (±15 minutes) post end of infusion All blood samples for PK assessments will be drawn from the opposite arm or separate anatomical location than that used to administer RDV.
Test Product, Dose, and Mode of Administration:	**Cohort 1:** RDV 200 mg IV dose on Day 1, followed by RDV 100 mg IV daily for up to 10 days **Cohorts 2-5:** RDV 5 mg/kg IV on Day 1, followed by RDV 2.5 mg/kg IV daily for up to 10 days **Cohorts 6-7:** RDV 2.5 mg/kg IV on Day 1, followed by RDV 1.25 mg/kg IV daily for up to 10 days **Cohort 8:** RDV 200 mg IV dose on Day 1, followed by RDV 100 mg IV daily for up to 10 days
Reference Therapy, Dose, and Mode of Administration:	None
Criteria for Evaluation:	
Safety:	• Incidence of treatment-emergent AEs and clinical laboratory abnormalities • Bilirubin concentrations in < 14-day-old participants • The proportion of participants with concomitant use of medications other than RDV for treatment of COVID-19

Efficacy:	The efficacy endpoints are: • Oxygen requirement and mechanical ventilation • Clinical score on 7-point Ordinal Scale • Time (days) to discharge from hospital • Days to the first confirmed negative PCR result, where confirmed is defined as 2 consecutive negative PCR results • Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first) • Clinical improvement based on scoring using the PEWS Improvement Scale
Pharmacokinetics:	• PK assessed by plasma concentrations of RDV and metabolites • Plasma concentrations of SBECD (where possible)
Statistical Methods:	Treatment-emergent AEs and laboratory abnormalities will be summarized using descriptive statistics and listed by participant. The efficacy endpoints will be summarized using descriptive statistics and listed by participant. Plasma concentrations for RDV and the metabolites will be listed and summarized using descriptive statistics. **Sample Size:** Twelve (12) participants from each cohort (Cohorts 1-4) compared to 25 healthy adult participants in GS-US-399-5505 study, will provide >99% power to conclude exposure equivalence of RDV AUC_{tau} in adolescent participants and children vs in healthy adult participants, assuming the expected geometric mean ratio is 1, equivalency boundary is 70% to 143%, two one-sided tests are each performed at an alpha level of 0.05, and the inter-participant standard deviations (natural log scale) of RDV AUC_{tau} is 0.18 ng•hr/mL.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{tau}	area under the concentration-time curve from the time of dosing to the start of the next dosing interval
AUC_{0-24}	partial area under the concentration- time curve from time zero to time 24 hours
BIPAP	bi-level positive airway pressure
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
C_{24}	observed drug concentration at 24 hours post dose
C_{max}	maximum observed concentration of drug
CoV	coronavirus
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CRF	case report form
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CSR	clinical study report
CV	coefficient of variation
DAIDS	Division of AIDS
DMC	data monitoring committee
DRC	Democratic Republic of Congo
EBOV	Ebola virus
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	endotracheal tube
EU	European Union
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GA	gestational age
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GLPS	Global Patient Safety

HCV	hepatitis C virus
HFOV	high-frequency oscillating ventilation
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IFN-β	interferon-beta
Ig	immunoglobulin
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
LPV	lopinavir
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
PaO_2	partial pressure of oxygen
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	peritoneal dialysis
PEWS	Pediatric Early Warning Score
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PT	prothrombin time
Q1	first quartile
Q3	third quartile
qCRP	quantitative C-reactive protein
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
RT-qPCR	reverse transcriptase quantitative polymerase chain reaction
RTV	ritonavir
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
SD	standard deviation
SOP	standard operating procedure
SpO_2	peripheral oxygen saturation

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1. Background

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China. Sequencing analysis from the patients' respiratory tract samples indicated a novel coronavirus (CoV), named severe acute respiratory syndrome (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 WHO declared COVID-19 a pandemic on 11 March 2020 {World Health Organization (WHO) 2020b}. As of 10 April 2020, more than 1.5 million cases have been identified globally, with a death toll of approximately 93,000 {World Health Organization (WHO) 2020a}.

There are a number of experimental therapeutic strategies in consideration for the treatment of COVID-19. Antiviral drugs that are being evaluated as potential treatments for COVID-19 include lopinavir (LPV)/ritonavir (RTV) (used in the treatment of HIV infection) and remdesivir (RDV, GS-5734™). The use of LPV/RTV for severe COVID-19 did not result in a significant difference in clinical improvement compared to standard care in a randomized study reported recently {Cao 2020}. Other experimental antiviral approaches in consideration for treatment of COVID-19 include darunavir/cobicistat, emtricitabine/tenofovir disoproxil fumarate (both used for the treatment of HIV infection) as well as sofosbuvir (used for hepatitis C virus [HCV]) and galidesivir (developed for HCV), interferon-beta (IFN-β), and ribavirin {Elfiky 2020}. The antimalarial drug, hydroxychloroquine, with or without azithromycin has also been trialed in a small nonrandomized study in France with possible benefit {Gautret 2020}.

Remdesivir shows potent in vitro activity against SARS-CoV-2, as well as the human pathogenic CoVs Middle East respiratory syndrome (MERS)-CoV and SARS-CoV in multiple relevant human cell types. In addition, RDV exhibited in vivo therapeutic efficacy against SARS-CoV-2 infection in rhesus monkeys, and prophylactic and therapeutic efficacy against SARS-CoV-2 and MERS-CoV infection in mice as well as MERS-CoV infection in rhesus monkeys.

Although the minority of children display severe COVID-19, reports of hospitalized pediatric patients from neonates to adolescents have emerged. In those with severe disease, symptoms and radiological findings are similar to those of adults. Furthermore, underlying conditions such as pulmonary disease, immunocompromised state, or co-existing respiratory infections might predispose to severe respiratory disease. A statistically higher chance of severe lower respiratory tract disease has been noted in children infected with human CoVs and underlying pulmonary disorders, an immunocompromised state, and coinfection with a respiratory copathogen(s) {Ogimi 2019}.

As of 23 December 2021, over 7.5 million pediatric COVID-19 cases had been reported in the United States (US), and children represented 17.4% of all cases in patients of all ages. The overall incidence rate was 10,052 cases per 100,000 children in the population. At this time, it appears that severe illness due to COVID-19 is uncommon among children {American Academy of Pediatrics 2021}. Although children with COVID-19 frequently have mild or moderate symptoms {Gotzinger 2020, Liguoro 2020, Zimmermann 2020}, COVID-19 can result in severe disease. Among a cohort of 3116 hospitalized children and adolescents with COVID-19 in the US from 01 March 2020 to 19 June 2021, 26.5% were admitted to an intensive care unit (ICU), 6.1% required invasive mechanical ventilation, and 0.7% died {Delahoy 2021}. In Europe, children made up an increasing proportion of weekly reports of cases of COVID-19 infection during the period from 04 January to 20 June 2021, coinciding with the availability of vaccines for adults, although the percentage of children across different age groups from 1 to 18 years who were admitted to the hospital remained low (0.1% to 0.2%) {European Centre for Disease Prevention and Control 2021}.

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

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 a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, Ebola virus [EBOV], Marburg virus), CoVs (eg, SARS-CoV-2, SARS-CoV, MERS-CoV), and paramyxoviruses (eg, respiratory syncytial virus, Nipah virus, Hendra virus). For further information on RDV, refer to the current investigator's brochure (IB) for RDV. Information in the IB includes:

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

Additional relevant information regarding RDV are described below.

1.3. Rationale for This Study

At the time this study was designed, there was no approved treatment available for COVID-19. The recommendation for using RDV as treatment of COVID-19 was based on the in vitro and in vivo activity of RDV against SARS-CoV-2 as well as safety and efficacy data from clinical studies in hospitalized participants and from patients who received RDV in a compassionate use program. Remdesivir subsequently has been approved in the US and Europe for the treatment of COVID-19 in adults and pediatric patients ≥ 12 years old and weighing ≥ 40 kg, based on safety and efficacy data from clinical studies in hospitalized participants and from patients who received RDV in a compassionate use program. As of December 2021, there is no approved treatment available for the treatment of COVID-19 in pediatric patients < 12 years old or weighing < 40 kg. A summary of the nonclinical and clinical data supporting the evaluation of RDV in pediatric participants follows.

Remdesivir has acceptable nonclinical tolerability and safety profiles. In addition, RDV has been shown to be generally safe and tolerable. Key attributes of the RDV nonclinical and clinical profile supporting its initial use for emergency treatment of COVID-19 are as follows:

- Remdesivir inhibited the in vitro replication of SARS-CoV-2 with a half-maximal effective concentration (EC_{50}) value of 0.0099 μM in human airway epithelial cells after 48 hours of treatment.

- Remdesivir potently inhibited a recombinant chimeric virus expressing the polymerase (nsp12) gene of SARS-CoV-2 in a backbone of SARS-CoV with a luciferase reporter in Huh7 cells (EC_{50} = 0.0035 μM).

- Remdesivir showed therapeutic efficacy in SARS-CoV-2-infected rhesus monkeys. Administration of 10/5 mg/kg (10 mg/kg first dose, followed by 5 mg/kg once-daily thereafter) RDV using IV bolus injection initiated 12 hours postinoculation with SARS-CoV-2 resulted in a significant reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals.

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

- In Study GS US-399-1812, single doses of up to 225 mg were evaluated in healthy volunteers. In Study GS-US-399-1954, 7-day and 14-day dosing of 150 mg IV once daily were evaluated in healthy volunteers. In this study, Grade 1 or 2 liver enzyme elevations were observed in a proportion of treated participants without other evidence of hepatic effects and returned to normal limits during the study. The onset of these events occurred as early as Day 5 in participants. The mechanism of these elevations is unknown. In GS-US-399-5055 multiple doses of 200 mg at Day 1 and then 100 mg once daily for 4 or 9 days was generally safe and well tolerated.

- Transient treatment-emergent elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed during the studies, none of which were graded in the single-ascending dose study, and all of which were Grade 1 or Grade 2 in the multiple-dose studies. Some ALT and AST elevations were associated with graded prothrombin time (PT) elevations; however, there were no graded changes in international normalized ratio (INR). Laboratory results for these participants indicated no systemic sign of drug reaction. Overall, no other clinically relevant consistent patterns of laboratory abnormalities or changes from baseline in laboratory parameters were noted during the studies. Additional detail is available in the IB.

- A total of 174 patients received RDV in the Pamoja Tulinde Maisha (PALM 1) EBOV therapeutics trial in the Democratic Republic of Congo (DRC). An additional 221 patients received RDV for acute EBOV under the Monitored Emergency Use for Unregistered Interventions protocols in the DRC.

- Other patients who have received RDV include male EBOV survivors with evidence of persistent viral shedding, participants exposed to EBOV, as well as patients who received RDV for other indications under compassionate use. Among these participants and patients, no significant adverse events (AEs) or laboratory abnormalities were attributed to RDV.

Data from Phase 3 studies and a compassionate use program in adults and adolescents hospitalized with COVID-19 infection (GS-US-540-5773, GS-US-540-5774, and NIAID ACTT-1), as well as from Study GS-US-540-9012 in non-hospitalized adults and adolescents support the evaluation of RDV in pediatric participants with COVID-19 infection.

1.3.1. Additional Clinical Experience with RDV

National Institute of Allergy and Infectious Diseases Adaptive COVID-19 Treatment Trial-1 Study in Participants with Mild/Moderate and Severe COVID-19 (NIAID ACTT-1)

This was a randomized, double-blind, placebo-controlled multicenter clinical trial that evaluated RDV 200 mg once daily for 1 day followed by RDV 100 mg once daily for up to 9 days (for a total of up to 10 days of IV administered therapy) in hospitalized adult participants with COVID-19 with evidence of lower respiratory tract involvement.

The trial enrolled 1062 hospitalized participants: 112 (10.5%) participants with mild/moderate disease and 950 (89.5%) participants with severe disease. A total of 282 participants (26.6%) (n = 129 received RDV) were on mechanical ventilation/ extracorporeal membrane oxygenation (ECMO). Participants were randomized in a 1:1 manner, stratified by disease severity at enrollment, to receive RDV (n = 541) or placebo (n = 521), plus standard of care (SOC).

At baseline, mean age was 59 years (with 36% of participants aged 65 or older); 64% of participants were male, 53% were White, 21% were Black, and 13% were Asian; 11% of participants had mild/moderate disease (12% in the RDV group vs 11% in placebo group) and 89% had severe disease (88% in the RDV group vs 89% in placebo group). The most common comorbidities were hypertension (51%), obesity (45%), and type 2 diabetes mellitus (31%) The primary clinical endpoint was time to recovery within 28 days after randomization, defined as either discharged from the hospital or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the RDV group compared to 14 days in the placebo group (recovery rate ratio: 1.31 [95% CI: 1.12 to 1.53]; $p < 0.001$). Among participants with mild/moderate disease at enrollment (n = 112), the median time to recovery was 5 days in both the RDV and placebo groups (recovery rate ratio: 1.16 [95% CI: 0.77 to 1.72]). Among participants with severe disease at enrollment (n = 950), the median time to recovery was 11 days in the RDV group compared to 17 days in the placebo group (recovery rate ratio: 1.34 [95% CI: 1.13 to 1.58]; $p < 0.001$).

Overall, the odds of improvement in the ordinal scale were higher in the RDV group at Day 15 when compared to the placebo group (odds ratio: 1.46 [95% CI: 1.15 to 1.86]; $p = 0.002$).

The collection of AE data in this trial was limited to severe (Grade 3) or potentially life-threatening (Grade 4) AEs, serious adverse events (SAEs), AEs leading to study drug discontinuation, and moderate (Grade 2) severity or higher hypersensitivity reactions. Rates of adverse reactions (ie, AEs considered related to study drug by the investigator) ≥ Grade 3, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 1-1.

Table 1-1. Summary of Adverse Reaction Rates in Participants with Mild, Moderate, or Severe COVID-19 in Study NIAID ACTT-1 (As Treated Population)

Types of Adverse Reactions	RDV N=532 n (%)	Placebo N=516 n (%)
Adverse reactions, Grades ≥ 3	41 (8%)	46 (9%)
Serious adverse reactions	2 (0.4%)[a]	3 (0.6%)
Adverse reactions leading to treatment discontinuation	11 (2%)[b]	15 (3%)

a Seizure (n = 1), infusion-related reaction (n = 1).
b Seizure (n = 1), infusion-related reaction (n = 1), transaminases increased (n=3), alanine aminotransferase increased and aspartate aminotransferase increased (n = 1), glomerular filtration rate decreased (n = 2), acute kidney injury (n = 3).

Study GS-US-540-5773 (Part A) in Participants with Severe COVID-19

This was a randomized, open-label, multicenter clinical trial of participants at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation of ≤ 94% on room air, and radiological evidence of pneumonia. Study participants were randomized to receive RDV for 5 days (n = 200) or RDV for 10 days (n = 197). Participants on mechanical ventilation at screening were excluded.

All participants received 200 mg of RDV on Day 1 and 100 mg once daily on subsequent days, plus SOC. The primary endpoint was clinical status on Day 14 assessed by a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

At baseline, the median age of participants was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian. More participants in the 10-day group than the 5-day group required invasive mechanical ventilation or ECMO (5% vs 2%) or high-flow oxygen support (30% vs 25%) at baseline. Median duration of symptoms and hospitalization prior to first dose of RDV were similar across treatment groups.

Overall, after adjusting for between-group differences at baseline, participants receiving a 5-day course of RDV had similar clinical status at Day 14 as those receiving a 10-day course (odds ratio for improvement: 0.75 [95% CI: 0.51 to 1.12]). In addition, recovery rates were 70% and 58%, and mortality rates were 8% and 11%, in the 5-day and 10-day groups, respectively. There were no significant differences once adjusted for between-group differences at baseline. All-cause mortality at Day 28 was 12% vs 14% in the 5- and 10-day treatment groups, respectively.

The most common AEs, regardless of whether they were considered related to study drug by the investigator, are recorded in Table 1-2.

Table 1-2. Most Common Adverse Events Reported for Participants Overall in Study GS-US-540-5773

n (%)	5 Days N = 200	10-Days N = 197
Nausea	20 (10)	17 (9)
Acute respiratory failure	12 (6)	21 (11)
Acute kidney injury	4 (2)	16 (8)

Adverse reactions (ie, AEs considered related to study drug by the investigator) were reported in 33 (17%) participants in the 5-day group and 40 (20%) participants in the 10-day group. The most common adverse reactions occurring in at least 5% of participants in either the RDV 5-day or 10-day group, respectively, were nausea (5% vs 3%), AST increased (3% vs 6%), and ALT increased (2% vs 7%). Rates of any adverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 1-3.

Table 1-3. Summary of Adverse Reaction Rates in Participants with Severe COVID-19 in Study GS-US-540-5773

Types of Adverse Reactions	RDV 5 Days N = 200 n (%)	RDV 10 Days N = 197 n (%)
Any adverse reaction, all Grades	33 (17%)	40 (20%)
Serious adverse reactions	3 (2%)[a]	4 (2%)[a]
Adverse reactions leading to treatment discontinuation	5 (3%)[b]	9 (5%)[b]

a Transaminases increased (n = 5), hepatic enzyme increased (n = 1), hypertransaminasaemia (n = 1).
b Transaminases increased (n = 4), hepatic enzyme increased (n=2), liver function tests increased (n = 2), hypertransaminasaemia (n = 1), alanine aminotransferase increased (n = 1), alanine aminotransferase increased and aspartate aminotransferase increased (n = 2), injection site erythema (n = 1), rash (n = 1).

Study GS-US-540-5774 (Part A) in Participants with Moderate COVID-19

This was a randomized, open-label multicenter clinical trial in hospitalized participants at least 12 years of age with confirmed SARS-CoV-2 infection and radiological evidence of pneumonia without reduced oxygen levels. Participants were randomized to RDV for 5 days (n = 191), RDV for 10 days (n = 193), or SOC only (n = 200).

Participants treated with RDV received 200 mg on Day 1 and 100 mg once daily on subsequent days. The primary endpoint was clinical status on Day 11 assessed by a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

At baseline, the median age of participants was 57 years (range, 12 to 95 years); 61% were male, 61% were white, 19% were black, and 19% were Asian. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalization prior to first dose of RDV were similar across treatment groups.

Overall, the odds of improvement in the ordinal scale were higher in the 5-day RDV group at Day 11 when compared to those receiving only SOC (odds ratio: 1.65 [95% CI: 1.09 to 2.48]; p = 0.017). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only SOC were not statistically significant (odds ratio: 1.31 [95% CI: 0.88 to 1.95]; p = 0.18). At Day 11 observed mortality rates for the 5-day, 10 day, and SOC groups were 0, 1%, and 2%, respectively. All-cause mortality at Day 28 was 2%, 1%, and 3% in the 5-day, 10-day, and SOC groups, respectively.

The most common AEs, regardless of whether they were considered related to study drug by the investigator, are recorded in Table 1-4.

Table 1-4. Most Common Adverse Events Reported for Participants Overall in Study GS-US-540-5774

n (%)	5 Days N = 200	10 Days N = 193	Standard of Care N = 200
Nausea	19 (10)	18 (9)	6 (3)

Adverse reactions (AEs considered related to study drug by the investigator) were reported in 36 (19%) participants in the 5-day group and 25 (13%) participants in the 10-day group. The most common adverse reaction occurring in at least 5% of participants in the RDV groups was nausea (7% in the 5-day group, 4% in the 10-day group). Rates of any adverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 1-5.

Table 1-5. Summary of Adverse Reaction[a] Rates in Participants with Moderate COVID-19 in Study GS-US-540-5774 (Part A)

Types of Adverse Reactions	RDV 5 Days N = 191 n (%)	RDV 10 Days N = 193 n (%)
Any adverse reaction, all Grades	36 (19%)	25 (13%)
Serious adverse reactions	1 (<1%)[b]	0
Adverse reactions leading to treatment discontinuation	4 (2%)[c]	4 (2%)[c]

a Attribution of events to study drug was not performed for the SOC group.
b Heart rate decreased.
c Alanine aminotransferase increased (n = 2), alanine aminotransferase increased and aspartate aminotransferase increased (n = 1), hypertransaminasaemia (n = 1), blood alkaline phosphatase increased (n = 1), rash (n = 2), heart rate decreased (n = 1).

Study GS-US-540-9012 in Participants With Confirmed COVID-19 at High Risk for Disease Progression

A randomized, double-blind, placebo-controlled, clinical study (GS-US-540-9012) evaluated RDV 200 mg once daily for 1 day followed by RDV 100 mg once daily for 2 days (for a total of 3 days of IV therapy) in 562 adult and pediatric participants (12 years of age and older and weighing at least 40 kg) with confirmed SARS-CoV-2 infection and at least 1 risk factor for progression to hospitalization. Participants were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (< 60 vs ≥ 60 years), and region (US vs ex-US) to receive RDV (n = 279) or placebo (n = 283), plus standard of care.

At baseline, mean age was 50 years (with 30% of participants aged 60 years or older); 52% were male, 82% were White, 8% were Black, 2% were Asian, and 44% were Hispanic or Latino; median body mass index was 30.7 kg/m^2. The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (first quartile [Q1], third quartile [Q3]) duration of symptoms prior to the first dose of treatment was 5 (3, 6) days, and median viral load was 6.3 $\log_{10}$ copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the RDV and placebo treatment groups.

The primary endpoint was the proportion of participants with COVID-19–related hospitalization (defined as at least 24 hours of acute care) or all-cause mortality through Day 28. Events occurred in 2 (0.7%) participants treated with RDV compared to 15 (5.4%) participants concurrently randomized to placebo, demonstrating an 87% reduction in COVID-19–related hospitalization or all-cause mortality through Day 28 compared to placebo (hazard ratio: 0.134 [95% CI: 0.031 to 0.586]; p = 0.0076). No deaths were observed through Day 28.

Treatment with RDV for 3 days resulted in an 81% reduction in medically attended visits (defined as medical visits attended in person by the participant and a healthcare professional) or all-cause mortality through Day 28 compared with placebo (4 of 246 participants [1.7%] in the RDV group and 21 of 252 participants [8.5%] in the placebo group) (hazard ratio: 0.191 [95% CI: 0.065 to 0.555]; p = 0.0024). Similar results were observed at Day 14.

Study GS-US-540-5823 in Pediatric Participants With COVID-19

The safety, PK, and efficacy of RDV in pediatric participants with COVID-19 enrolled in Cohorts 1 to 4 and 8 (≥ 28 days to < 18 years and weighing ≥ 3 kg) of the current Study GS-US-540-5823 were evaluated in an interim analysis. A total of 53 participants were included in the analysis: 12 participants ≥ 12 years and weighing ≥ 40 kg; 5 participants < 12 years and weighing ≥ 40 kg; 12 participants ≥ 28 days and weighing ≥ 20 to < 40 kg; 12 participants ≥ 28 days and weighing ≥ 12 to < 20 kg; and, 12 participants ≥ 28 days and weighing ≥ 3 to < 12 kg. Participants weighing ≥ 40 kg received 200 mg of RDV on Day 1 followed by RDV 100 mg once daily on subsequent days; participants weighing ≥ 3 kg to < 40 kg received RDV 5 mg/kg on Day 1 followed by RDV 2.5 mg/kg once daily on subsequent days.

At baseline, median age was 7 years (Q1, Q3: 2, 12); 57% were female; 70% were White, 30% were Black, and 44% were Hispanic or Latino; mean weight was 38 kg (range: 4 to 192). A total of 12 participants (23%) were on invasive mechanical ventilation; 18 (34%) were on noninvasive ventilation or high-flow oxygen, 10 (19%) were on low-flow oxygen, and 13 (25%) were on room air at baseline. The overall median (Q1, Q3) duration of symptoms and hospitalization prior to the first dose of RDV was 5 (3, 7) days and 1 (1, 3) day, respectively.

Treatment with RDV for up to 10 days resulted in an overall median (Q1, Q3) change from baseline in clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to ventilatory support and decreasing levels of oxygen to hospital discharge [score of 7]) of +2.0 (1.0, 4.0) points on Day 10.

Recovery (defined as an improvement from a baseline clinical status score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7) was reported for 62% of participants on Day 10; median (Q1, Q3) time to recovery was 7 (5, 16) days. Overall, 60% of participants were discharged by Day 10. Three participants died during the study.

1.4. Integrated Safety Findings from Clinical Studies

Assessment of adverse reactions is based on data from 4 Phase 1 studies in 131 healthy adult participants, 3 Phase 3 studies in 1313 hospitalized participants with COVID-19 (NIAID ACTT-1, GS-US-540-5773, and GS-US-540-5774), 1 Phase 3 study in 279 non-hospitalized participants with COVID-19 (GS-US-540-9012), and hospitalized patients with COVID-19 who received RDV in a compassionate use program.

The most common adverse reactions (incidence ≥ 5%, all grades) observed with treatment with RDV are nausea, ALT increased, and AST increased. Infusion-related reactions were rare (defined as frequency ≥ 0.01% and < 0.1%).

In clinical Study GS-US-540-9012 in participants with confirmed COVID-19 and at high risk for disease progression, including hospitalization, the incidence of adverse reactions was similar in participants who received RDV compared to participants who received placebo.

Hypersensitivity Including Infusion-Related and Anaphylactic Reactions

Hypersensitivity reactions, including infusion-related and anaphylactic 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. See Section 5.4 for information on administration of RDV and Section 7.7 for toxicity management.

Laboratory Abnormalities

Study GS-US-399-5505 was a Phase 1, randomized, blinded, placebo-controlled clinical trial in healthy participants administered RDV 200 mg on Day 1 and 100 mg for either 4 days or 9 days. Mild (Grade 1, n = 8) to moderate (Grade 2, n = 1) elevations in ALT were observed in 9 of 20 participants receiving 10 days of RDV; the elevations in ALT resolved upon discontinuation of RDV. No participants (0 of 9) who received 5 days of RDV had graded increases in ALT. The incidence of increased transaminases was higher in participants who received RDV compared with participants who received placebo.

Transaminase elevations have also been reported in study participants with COVID-19 who received RDV. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in participants receiving placebo or standard of care versus RDV, discerning the contribution of RDV to transaminase elevations in patients with COVID-19 can be challenging.

The incidence of increased PT or INR in hospitalized participants with moderate/severe COVID-19 (NIAID ACTT-1) was higher in participants who received RDV compared with participants who received placebo (predominantly Grades 1 and 2), with no difference observed in the incidence of bleeding events between the 2 groups. In Study GS-US-540-9012, the incidence of increased PT or INR was similar in participants treated with RDV compared with participants who received placebo.

The frequencies of Grades 3 through 4 laboratory abnormalities occurring in at least 3% of participants with COVID-19 receiving RDV in Studies NIAID ACTT-1, GS-US-540-5773, GS-US-540-5774, and GS-US-540-9012 are presented in Table 1-6, Table 1-7, Table 1-8, and Table 1-9, respectively.

Table 1-6. Grade 3-4 Laboratory Abnormalities Reported in ≥ 3% of Participants Receiving RDV in Study NIAID ACTT-1

Laboratory Parameter Abnormality[a]	RDV 10 Days N = 532	Placebo N = 516
ALT increased	3%	6%
AST increased	6%	8%
Bilirubin increased	2%	5%
Creatinine clearance decreased[b]	18%	20%
Creatinine increased	15%	16%
eGFR decreased	18%	24%
Glucose increased	12%	13%
Hemoglobin decreased	15%	22%
Lymphocytes decreased	11%	18%
Prothrombin time increased	9%	4%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate
a Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b Based on the Cockcroft-Gault formula.

Table 1-7. Grade 3-4 Laboratory Abnormalities Reported in ≥ 3% of Participants Receiving RDV in Study GS-US-540-5773

Laboratory Parameter Abnormality[a]	RDV 5 Days N = 200	RDV 10 Days N = 197
ALT increased	6%	8%
AST increased	7%	6%
Creatinine clearance decreased[b]	10%	19%
Creatinine increased	5%	15%
Glucose increased	11%	8%
Hemoglobin decreased	6%	8%

ALT = alanine aminotransferase; AST = aspartate aminotransferase
a Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b Based on the Cockcroft-Gault formula.

Table 1-8. Grade 3-4 Laboratory Abnormalities Reported in ≥ 3% of Participants Receiving RDV in Study GS-US-540-5774

Laboratory Parameter Abnormality[a]	RDV 5 Days N = 191	RDV 10 Days N = 193	SOC N = 200
ALT increased	2%	3%	8%
Creatinine clearance decreased[b]	2%	5%	8%
Glucose increased	4%	3%	2%
Hemoglobin decreased	3%	1%	6%

ALT = alanine aminotransferase
a Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b Based on the Cockcroft-Gault formula.

Table 1-9. Grade 3-4 Laboratory Abnormalities Reported in ≥ 3% of Participants Receiving RDV in Study GS-US-540-9012

Laboratory Parameter Abnormality[a]	RDV 3 Days (N)	Placebo (N)
Creatinine increased	3% (273)	1% (275)
Creatinine clearance decreased[b]	6% (270)	2% (270)
Glucose increased (fasting)[c]	4% (52)	4% (48)
Glucose increased (fasting, maximum postbaseline grade)[d]	5% (100)	7% (103)
Glucose increased (nonfasting)[c]	3% (197)	3% (197)
Glucose increased (nonfasting, maximum postbaseline grade)[d]	6% (235)	6% (245)

a Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b Based on the Cockcroft-Gault formula.
c For fasting glucose, nonfasting glucose, and glucose (regardless of fasting/nonfasting status), maximum treatment-emergent toxicity grades were derived for participants with baseline values.
d For all fasting glucose, nonfasting glucose, and glucose, maximum postbaseline toxicity grades were derived.

An interim analysis of Cohorts 1 through 4 and 8 of Study GS-US-540-5823 did not identify new safety concerns in participants < 18 years of age who were administered RDV for a median of 5 days.

1.5. Rationale for Dose Selection of Remdesivir

The clinical regimen evaluated for the treatment of participants weighing ≥ 40 kg with COVID-19 (Cohorts 1 and 8) is as follows: single RDV 200 mg IV loading dose on Day 1 followed by RDV 100 mg IV once-daily maintenance doses for up to 9 days (Days 2 to 10).

The clinical regimen evaluated for the treatment of participants weighing < 40 kg with COVID-19 (Cohorts 2 through 5; 14 days old, born full term [gestational age (GA) > 37 weeks]) and with serum creatinine < 0.6 mg/dL) is as follows: Single RDV 5 mg/kg IV loading dose on Day 1 followed by RDV 2.5 mg/kg IV once-daily maintenance doses for up to 9 days (Days 2 to 10).

The clinical regimen to be evaluated in Cohorts 6 and 7 (with serum creatinine below the cut-off value, as defined in Table 1-12) is as follows: Single RDV 2.5 mg/kg IV loading dose on Day 1 followed by RDV 1.25 mg/kg IV once-daily maintenance doses for up to 9 days (Days 2 to 10).

Selection of these dosing regimens is based on the PK bridge from animal data to human doses and efficacy using the results of in vivo efficacy studies conducted in SARS-CoV-2- and MERS-CoV-infected rhesus monkeys, and available PK data in healthy rhesus monkeys and Phase 1 studies in healthy participants.

Remdesivir showed therapeutic efficacy in SARS-CoV-2-infected rhesus monkeys and prophylactic and therapeutic efficacy in MERS-CoV-infected rhesus monkeys. Administration of RDV 10/5 mg/kg (RDV 10 mg/kg first dose, followed by RDV 5 mg/kg once daily thereafter for 6 days) using IV bolus injection initiated 12 hours postinoculation with SARS-CoV-2 resulted in a significant reduction of clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals.

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

For the treatment of COVID-19, the approach has been to target exposures (plasma and peripheral blood mononuclear cells [PBMCs]) associated with efficacy at 10 mg/kg and 5 mg/kg in the SARS-CoV-2- and MERS-CoV-infected rhesus monkeys. Using allometric scaling, the proposed clinical maintenance dose of daily 100 mg provides systemic exposure of RDV in plasma and GS-443902 (active triphosphate) in PBMCs similar with that observed in rhesus monkeys at 5 mg/kg IV dose of RDV (Study AD-399-2030, Study GS-US-399-5505) (Table 1-10).

Table 1-10. Pharmacokinetics of RDV in Plasma and Nucleoside Triphosphate Metabolite GS-443902 (PBMCs) following Repeat RDV Doses (30-minute IV Infusion) to Healthy Rhesus Monkeys (5 mg/kg) and Healthy Humans (100 mg)

	Mean (SD)	
	Healthy Rhesus Monkeys	Healthy Human Participants
PK Parameter (Mean [SD])	RDV 5 mg/kg (N = 8)	RDV 100 mg (N = 26)
Plasma RDV		
AUC[a] (h•ng/mL)	1430 (230)	1590 (264)
C_{max} (ng/mL)	3350 (390)	2230 (427)
PBMC GS-443902		
C_{24} (µM)	7.1 (6.7)	10.2 (5.05)[b]

N = number in a population; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RDV = remdesivir (GS-5734™); SD = standard deviation
a AUC: healthy rhesus monkeys AUC_{0-24}; healthy human participants AUC_{tau}; PK data reported to 3 significant figures
b N = 25
Source: AD-399-2030, Tables 8 and 10, GS-US-399-5505 CSR, Tables 15.10.1.1.6.1, 15.10.1.1.6.4, and 16

To target efficacy seen at 10 mg/kg loading dose in infected rhesus monkeys requires a loading dose of 200 mg in humans. As shown in Table 1-11 PK of a single dose of 200-mg RDV in healthy participants is similar to the expected exposure in rhesus monkeys at 10 mg/kg (AUC 5 mg/kg × 2 based on dose proportionality; AD-399-2002).

High intracellular trough concentrations of the active triphosphate metabolite GS-443902 have been observed in human PBMCs following a single RDV 200 mg dose or multiple IV doses of RDV 100 mg (Study GS-US-399-5505). These concentrations are approximately 1000-fold above the in vitro EC_{50} against SARS-CoV-2 (EC_{50} = 0.0099 µM) and SARS-CoV in primary human airway epithelial cells (EC_{50} = 0.0066 µM). These concentrations are also comparable with those observed in rhesus monkeys receiving RDV 5 mg/kg doses for 7 days, and the doses associated with efficacy in SARS-CoV-2- and MERS-CoV-infected rhesus monkey models.

Table 1-11. Pharmacokinetics of Plasma RDV and Nucleoside Triphosphate Metabolite GS-443902 (PBMCs) Following a 200-mg Single Dose of RDV to Healthy Volunteers

	Mean (%CV)
	Healthy Human Participants
PK Parameter (Mean [%CV])	RDV 200 mg (N = 28)
Plasma RDV	
AUC_{0-24} (h•ng/mL)	2860 (18.6)
C_{max} (ng/mL)	4380 (23.5)
PBMC GS-443902	
C_{24} (µM)	6.9 (45.8)

CV = coefficient of variation; N = number in a population; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)
Source: GS-US- 399-5505 CSR, Table 15.10.1.1.6.1 and Table 15.10.1.1.6.4

Dose selection of RDV in pediatric participants enrolled in Cohorts 1 through 5 and 8 was informed by a physiologically based pharmacokinetic (PBPK) model developed to characterize the PK of RDV and the primary circulating nucleoside metabolite, GS-441524, in adults (SimCYP v.17, Certara). The adult PBPK model was subsequently used to predict pediatric participant exposure, accounting for age-dependent changes in organ volume or size (liver and kidney), esterase expression, plasma protein binding, and organ blood flow. Simulations indicated that use of the adult dosage regimen in pediatric participants ≥ 40 kg is predicted to maintain RDV and GS-441524 exposures generally within the expected adult steady-state exposure range following the adult dosage regimen. For pediatric participants > 14 days old, born full term (GA > 37 weeks) and with serum creatinine below thresholds in Table 1-12 below, a loading dose of 5 mg/kg followed by 2.5 mg/kg once-daily maintenance dose of RDV should be administered. Use of these doses in these pediatric participants was expected to maintain exposures of both RDV and GS-441524 at or below that which was previously observed to be well tolerated in healthy volunteers (N = 24, GS-US-399-1954). These simulations did not account for possible diminished liver or kidney function due to SARS-CoV-2 infection because the impact of infection on the PK of RDV and GS-441524 was unknown at the time of these simulations.

Dose selection of RDV in pediatric participants enrolled in Cohorts 6 and 7 was informed by a population PK (PopPK) model developed to characterize PK of RDV and its metabolites (GS-704277 and GS-441524) in adult and pediatric COVID-19 patients. Simulation of representative neonatal populations (n = 1000 per cohort, based on demographics from CDC and Fenton preterm growth charts, serum creatinine below the threshold defined in Table 1-12) indicated that the use of a 2.5 mg/kg loading dose followed by 1.25 mg/kg once-daily maintenance dose of RDV should be administered to pediatric participants in Cohort 6 (0 days to < 14 days of age, GA > 37 weeks and birth weight ≥ 2.5 kg) and Cohort 7 (0 days to < 56 days of age, GA ≤ 37 weeks and birth weight ≥ 1.5 kg). At these doses, the range of exposures is expected to be similar to adult Phase 3 and adolescent study participants (≥ 40 kg) with COVID-19 infection who received a 200 mg loading dose followed by 100 mg maintenance doses for up to 10 days.

Table 1-12. Creatinine Value Cut-Off by Age Group

Gestational age	Chronological age	Creatinine value cut-off in mg/dL
24-27 weeks	0-28 days	≥ 1.6
28-29 weeks	0-14 days	≥ 1.1
30-32 weeks	0-7 days	≥ 1.0
	≥ 7 days to 1 month	≥ 0.8*
	≥ 1-2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*
≥ 32 weeks	0-2 days	≥ 1.0*
	≥ 2-7 days	≥0.8*
	≥ 7 days to 2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*

* Creatinine values exceed the 97.5th percentile {Vieux 2010} or upper limit {Colantonio 2012} of creatinine for age
¶Critical serum creatinine values for preterm infants {Bruel 2013, Kastl 2017}

Use of these doses in these pediatric participants is expected to maintain exposures of both RDV and GS-441524 at or below that which was previously observed to be well tolerated in healthy volunteers (N = 24, GS-US-399-1954). These simulations did not account for possible diminished liver or kidney function due to SARS-CoV-2 infection because the impact of infection on the PK of RDV and GS-441524 is currently unknown.

1.6. Risk/Benefit Assessment for the Study

Potential risks associated with the study include unknown AEs and laboratory abnormalities. An interim analysis upon completion of Cohorts 1 through 4 and 8 did not identify new safety concerns in this population of participants < 18 years of age who were administered RDV for a median of 5 days relative to the safety profile in adults. Adverse events were reported in a majority of participants, with the incidences and types of AEs consistent with the participant's medical status, including preexisting conditions. No additional safety monitoring is required for pediatric participants and no dose adjustments, other than the weight-based dose adjustments in participants weighing < 40 kg and < 12 years of age are required.

A pertinent specific risk for participants in this study is the potential for treatment-emergent elevations in ALT and AST, which were observed in healthy volunteers and study participants with COVID-19. Another pertinent risk is the potential for hypersensitivity reactions which have been observed during and following administration of RDV.

To date in human studies, no serious adverse events (SAEs) have occurred in healthy individuals who have received at least 1 dose of RDV. Remdesivir has been tested in healthy volunteers as a single ascending dose over a dose range of 3 to 225 mg and in a multi-dose study of 150 mg for up to 14 days and at 200 mg loading dose followed by 100 mg for a total of 10 days (GS-US-399-5505).

Remdesivir formulation in addition to active contains sulfobutylether β-cyclodextrin sodium (SBECD) and HCl and NaOH for pH adjustment. The amount of SBECD administered to children is well within established safe doses for existing commercial products. Based on the review by the European Medicines Agency doses up to 250 mg/kg/day of SBECD are considered safe for children > 2 years. The above review also highlights that small number of neonates treated with SBECD-containing products corresponding with up to 336 mg/kg/day for 18 to 24 days did not show significant toxicity. Doses of SBECD based on 5 mg/kg loading and 2.5 mg of maintenance dose are 150 mg/kg and 75 mg/kg, respectively. The proposed RDV dosing regimen is not anticipated to pose a safety risk to participants enrolled in this study.

Administering RDV concurrent with other investigational anti-CoV agents may lead to antagonism or synergy or have no effect.

During a pandemic, additional potential risks to participants may include adequate study drug availability, interruptions to the study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 6 for further details on the risks and risk mitigation strategy.

1.7. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the safety and tolerability of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To evaluate the PK of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years

The secondary objectives of this study are:

- To evaluate the efficacy of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To determine the antiviral activity of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- Change from baseline in oxygenation use
- Change from baseline in the use of mechanical ventilation or ECMO
- To evaluate clinical improvement using the PEWS scale in participants with laboratory confirmed COVID-19 aged 0 days to < 18 years
- Determine SBECD exposures (where possible)
- To provide data on use of medications other than RDV for treatment of COVID-19

The exploratory objectives of this study are:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

3. STUDY DESIGN

This is a Phase 2/3 single-arm, open-label study of the safety, tolerability, PK, and efficacy of RDV in pediatric participants from birth to < 18 years of age with laboratory-confirmed infection with COVID-19.

3.1. Endpoints

The primary endpoints of this study are:

- The proportion of participants with treatment-emergent adverse events (TEAEs)
- The proportion of participants with treatment-emergent graded laboratory abnormalities
- PK assessed by plasma concentrations of RDV and metabolites

The secondary endpoints of this study are:

- Oxygen usage and ventilation modality and settings
- Clinical improvement based on scoring using the 7-point Ordinal Scale
- Time (days) to discharge from hospital
- Days to the first confirmed negative polymerase chain reaction (PCR) result, where confirmed is defined as 2 consecutive negative PCR results
- Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)
- Bilirubin concentrations in < 14-day-old participants
- Clinical improvement based on scoring using the PEWS Improvement Scale
- Plasma concentrations of SBECD (where possible)
- The proportion of participants with concomitant use of medications other than RDV for treatment of COVID-19

The exploratory endpoints of this study are:

- CCI [redacted]
- CCI [redacted]

3.2. Study Design

This is a single-arm, open-label study.

At least 52 participants aged 0 days to < 18 years will be enrolled as described in the table below.

Cohort	Description	Dose
Pediatric participants ≥ 28 days to < 18 years old		
1	≥ 12 years to < 18 years and weight ≥ 40 kg	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days
2	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days
3	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg	
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg	
Term neonatal participants 0 days to < 28 days old		
5	≥14 days to < 28 days of age, GA > 37 weeks and weight at screening ≥ 2.5 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days
6	0 days to < 14 days of age, GA > 37 weeks and birth weight ≥ 2.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily up to 10 days
Preterm neonates and infants 0 days to < 56 days old		
7	0 days to < 56 days of age, GA ≤ 37 weeks and birth weight ≥ 1.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily up to 10 days
Exploratory cohort for CCI		
CCI		

GA = gestational age; RDV = remdesivir (GS-5734™)

3.3. Study Treatments

Pediatric participants ≥ 28 days to < 18 years old

Cohorts 1-4 (n = 12 for each Cohort) will be enrolled into a single arm of RDV:

- Cohort 1: Weight ≥ 40 kg: IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days
- Cohorts 2-4: Weight 3 kg to < 40 kg: IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days

Cohort 8: < 12 years and weight ≥ 40 kg: IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily for up to 10 days.

Term neonatal participants 0 days to < 28 days old

Cohorts 5 and 6 (n = 4 for Cohort 5) will be enrolled into a single arm of RDV:

- Cohort 5: Weight ≥ 2.5 kg and GA > 37 weeks: IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days
- Cohort 6: Birth weight ≥ 2.5 kg and GA > 37 weeks: IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily up to 10 days

Preterm neonates and infants 0 days to < 56 days old

- Cohort 7: Birth weight ≥ 1.5 kg and GA ≤ 37 weeks: IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily up to 10 days

Cohorts 1 through 5 will be enrolled in parallel. Participants in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined. There is no minimum number of participants to be enrolled in Cohorts 6 and 7 due to the rarity of such participants. CCI [redacted]

3.4. Duration of Treatment

Participants will be treated for up to 10 days. Those participants who have demonstrated clinical improvement may be considered for a shorter treatment period.

3.5. Discontinuation Criteria

- Study drug dosing in an individual participant will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if any of the following occurs:
  - Any SAE, or ≥ Grade 3 AE suspected to be related to RDV
  - Any elevations in ALT > 5 × the upper limit of normal (ULN); or ALT > 3 × ULN and total bilirubin > 2 × ULN, confirmed by immediate repeat testing
  - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using Schwartz formula if ≥ 1 year of age
    - Schwartz formula (mL/min/1.73 m^2) = k × L/S_{Cr}

      k is a proportionality constant with the value based on creatinine measured by the Jaffe (colorimetric) method, L is height or length in centimeters (cm), and S_{Cr} is serum creatinine (mg/dL). The value of k is 0.55 for children (≥ 1 to < 12 years old) and adolescent girls (≥ 12 years old) and 0.70 for adolescent boys (≥ 12 years old).

— Creatinine (mg/dL) above the thresholds described in Table 3-1 below if age < 1 year

— Participant requires renal replacement therapies (intermittent hemodialysis [iHD], peritoneal dialysis [PD], and continuous renal replacement therapy [CRRT]) on Day 1 through Day 5

Table 3-1. Creatinine Value Cut-Off by Age Group

Gestational age	Chronological age	Creatinine value cut-off in mg/dL
24-27 weeks	0-28 days	≥ 1.6
28-29 weeks	0-14 days	≥ 1.1
30-32 weeks	0-7 days	≥ 1.0
	≥ 7 days to 1 month	≥ 0.8*
	≥ 1-2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*
≥ 32 weeks	0-2 days	≥ 1.0*
	≥ 2-7 days	≥0.8*
	≥ 7 days to 2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*

* Creatinine values exceed the 97.5th percentile {Vieux 2010} or upper limit {Colantonio 2012} of creatinine for age
¶Critical serum creatinine values for preterm infants {Bruel 2013, Kastl 2017}

— 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

— Participant noncompliance

- Discontinuation of a cohort:

  — Enrollment into a cohort and dosing of study drug in participants in the cohort will be stopped if 2 or more participants in the cohort meet the following criteria:

    ■ If 2 related SAEs of the same system organ class are reported

- Discontinuation of the study will be at the request of Gilead, a regulatory agency, or an IRB/IEC.

All participants will be requested to continue safety assessments if hospitalized and attend the Day 30 Follow-Up visit (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. Post Study Care

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

3.8. Samples for Optional Future Research

In addition to the study-specific informed consent to be signed by each participant participating in the study, participants will be required to document agreement to provide additional serum/blood samples in accordance with applicable regulations.

CCI [redacted]

CCI [redacted].

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

At least 52 participants will be enrolled into this study including 12 participants per cohort from Cohort 1-4, and a minimum 4 participants from Cohort 5. Participants in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined. There is no minimum number of participants to be enrolled in Cohorts 6 and 7 due to the rarity of such participants. CCI [redacted] There is no minimum number of participants to be enrolled in Cohort 8.

4.1.1. Participant Replacement

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

4.2. Inclusion Criteria

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

1) Willing and able to provide assent or a parent or legal guardian willing and able to provide written informed consent (participants < 18 years of age, where locally and nationally approved) prior to performing study procedures.

2) Aged < 18 years of age who meet one of the following weight criteria (where permitted according to local law and approved nationally and by relevant institutional review board [IRB] or independent ethics committee [IEC]).

   a) Cohort 1: ≥ 12 years to < 18 years of age and weight at screening ≥ 40 kg

   b) Cohorts 2-4: ≥ 28 days to < 18 years of age and weight at screening ≥ 3 kg and < 40 kg

   c) Cohort 5: ≥ 14 days to <28 days of age, GA > 37 weeks and weight at screening ≥ 2.5 kg

   d) Cohort 6: 0 days to < 14 days of age, GA > 37 weeks and birth weight of ≥ 2.5 kg

   e) Cohort 7: 0 days to < 56 days of age, GA ≤ 37 weeks and birth weight of ≥ 1.5 kg

   f) Cohort 8: < 12 years of age and weight at screening ≥ 40 kg

3) SARS-CoV-2 infection confirmed by PCR

4) Hospitalized and requiring medical care for COVID-19

4.3. Exclusion Criteria

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

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

2) ALT or AST > 5 × ULN

3) eGFR < 30 mL/min/1.73m^2 using Schwartz formula for participants ≥ 1 year of age

4) Creatinine above thresholds in Table 4-1 for participants < 1 year of age

Table 4-1. Creatinine Value Cut-Off by Age Group

Gestational age	Chronological age	Creatinine value cut-off in mg/dL
24-27 weeks	0-28 days	≥ 1.6
28-29 weeks	0-14 days	≥ 1.1
30-32 weeks	0-7 days	≥ 1.0
	≥ 7 days to 1 month	≥ 0.8*
	≥ 1-2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*
≥ 32 weeks	0-2 days	≥ 1.0*
	≥ 2-7 days	≥0.8*
	≥ 7 days to 2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*

* Creatinine values exceed the 97.5th percentile {Vieux 2010} or upper limit {Colantonio 2012} of creatinine for age
¶Critical serum creatinine values for preterm infants {Bruel 2013, Kastl 2017}

5) If < 28 days of age, any major congenital renal anomaly

6) If < 24 hours of age, Apgar score < 5 when last recorded

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

8) Positive pregnancy test at Screening only for female of child bearing potential.

   Note: Female participants who become pregnant during the study or are discovered to be pregnant after receiving at least one dose may continue study drug, after discussion with the investigator. See Appendix 3

9) On renal replacement therapies (iHD, PD, CRRT)

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Participants in Cohorts 1-8 who meet eligibility criteria will be enrolled into a single arm of RDV on Day 1 using an interactive web response system, and assigned a participant number.

Randomization and treatment codes are not applicable.

5.1.2. Blinding

This is an open-label study and blinding of treatment assignments or data will not be performed.

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 or 5% dextrose prior to administration by IV infusion.

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

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 over seal with a red, plastic flip-off cap.

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

5.2.3. Storage and Handling

CCI [redacted].

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, prepared RDV material should be discarded.

5.3. Dosage and Administration of Remdesivir

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

Participants in Cohorts 1 and 8 will receive IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily for up to 10 days.

Participants in Cohorts 2-5 will receive IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily for up to 10 days.

Participants in Cohorts 6-7 will receive IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily up to 10 days.

5.4. Infusion-Related Reaction

Infusion-related reactions have been observed during and following administration of RDV. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a severe infusion-related reaction occur, immediately discontinue administration of RDV and initiate appropriate treatment. Please refer to Section 7.7

5.5. Accountability for Investigational Medicinal Product

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

Each study site must keep accountability records that capture:

- The date received and quantity of study drug vials.
- The date, participant number, and the quantity of study drug vials dispensed.
- The date, quantity of used and unused study drug vials returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

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

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

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

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

Gilead will provide instructions for handling of unused study drug at the end of the study.

5.6. Prior and Concomitant Medications

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

- Investigational agents for COVID-19 with direct antiviral effect including approved HIV protease inhibitors such as LPV/RTV, chloroquine, interferon, etc.
- Strong inducers of P-glycoprotein (e.g. rifampin, rifabutin, carbamazepine, phenytoin or herbal medications)

Concomitant use of investigational antiviral agents such as approved HIV protease inhibitors like LPV/RTV, chloroquine or hydroxychloroquine, interferon, etc while receiving RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations. Immune modulators are allowed as well as IVIG and convalescent plasma.

Medications will be assessed from Screening to the Day 30 Follow-up visit.

6. STUDY PROCEDURES

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Blood volume tables per cohort for all clinical laboratory studies to be performed at each visit and the estimated total over the course of the study are included in Appendix 5. If a participant weights ≤ 4 kg, please contact the medical monitor to further discuss the participant's schedule.

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

6.1. Participant Enrollment and Treatment Assignment

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

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Participants will be screened within 2 days prior to Day 1 to determine eligibility for participation in the study. Rescreening may occur at the investigator's discretion. The following procedures will be performed and documented at Screening:

- Obtain assent or written informed consent from a parent or legal guardian (participants < 18 years of age, where locally and nationally approved)

After assent (or consent) the following assessments are performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Focused medical history including date of first symptoms, overall symptoms, exposure source, demographics, baseline characteristics, and allergies
- Documentation of SARS-CoV-2 infection by PCR via one validated assay at a local laboratory
- Review and record all medications and therapies for this current illness
- Counsel participants of childbearing potential to use adequate birth control methods required during the trial to avoid pregnancy. See Appendix 3
- Electrocardiogram

- Complete or symptom-directed (targeted) physical examination including vital signs (heart rate, temperature, blood pressure [mean arterial pressure (MAP) if available, systolic and diastolic], respiratory rate, oxygen saturation), body weight, and height/length
  - If < 24 hours of age, record head circumference and last recorded Apgar score
  - If < 56 days, record GA and birth weight
  - Documentation of respiratory status:
    - Respiratory rate (if not on ventilator)
    - Oxygen supplementation: room air (no O_2 supplementation), low-flow O_2 (L/min and %), high-flow O_2 (L/min and %), continuous positive airway pressure (CPAP)/bi-level positive airway pressure (BIPAP) (fraction of inspired oxygen [FiO_2] or %), high-frequency oscillating ventilation (HFOV) (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO
    - Oxygenation: peripheral oxygen saturation (SpO_2) or partial pressure of oxygen (PaO_2)
- If available, record chest x-ray impression (or other imaging) but not mandatory to perform otherwise
- Evaluate the PEWS Improvement Scale (see Section 6.8)
- Record the Ordinal Scale (see Section 6.9)
- Laboratory evaluation (the following tests will be performed on 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)
  - Hematology: Complete blood count (CBC) with differential
  - Comprehensive metabolic panel (Chemistry 14): Alanine aminotransferase (ALT/SGPT), albumin:globulin (A:G) ratio, albumin, alkaline phosphatase, aspartate aminotransferase (AST/SGOT), total bilirubin (and neonatal bilirubin panel for all neonates < 14 days, and any neonate presenting with jaundice), BUN and creatinine (include BUN:Cr ratio, and eGFR using Schwartz formula if ≥ 1 year of age), ionized calcium, carbon dioxide, chloride, total serum protein, serum globulins, glucose, potassium, sodium
  - Inflammatory markers: D-dimer, ferritin, quantitative C-reactive protein (qCRP), procalcitonin, IL-6; ESR (if > 4 kg, Cohorts 1-4 and 8 only)
    - **Note:** Inflammatory markers (ferritin, qCRP, procalcitonin, and IL-6) will be batched with Chemistry 14 testing and D-dimer with PT/activated partial thromboplastin time (aPTT) for Cohorts 4-7 and those with smaller volumes in Cohort 3 as described in Appendix 5.

- Urinalysis
- Routine coagulation test: PT/aPTT with calculated INR
- Pregnancy test (blood/urine, for female participants of childbearing potential). Please see Appendix 3 for participants of childbearing potential.
- Serology for SARS-CoV-2 if ≥ 12 kg (Cohorts 1-3 and 8)

- Record any SAEs and all AEs related to protocol-mandated procedures occurring after signing of the consent (or assent) form.

Study participants who qualify should be immediately enrolled.

6.2.2. Day 1 Assessments

The following evaluations are to be completed at the Day 1 visit. The investigator must have confirmed eligibility before proceeding with Day 1 visit procedures.

- CCI [redacted]

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

- CCI [redacted]
  - Documentation of respiratory status:
    - Respiratory rate (if not on a ventilator)
    - Oxygen supplementation: room air (no O_2 supplementation), low-flow O_2 (L/min and %), high-flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), HFOV (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO
    - Oxygenation: SpO_2 or PaO_2

- If available, record chest radiograph impression (or other imaging), but not mandatory to perform otherwise
- Perform Tanner Stage assessment (Appendix 4) for participants ≥ 6 years of age at the time of the visit. Date of first menses will be documented.

- Evaluate the PEWS Improvement Scale (see Section 6.8)
- Record the Ordinal Scale (see Section 6.9)
- Collect samples for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing:
  - Nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined) and,
  - Rectal or fecal swab.
  - Endotracheal tube (ET) aspirates will also be collected if the participant is intubated.

  Swab collection technique for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing should be consistent on Day 1, 3, 5, 7, and 10.
- IV administration with either IV RDV 200 mg (Cohorts 1 and 8), IV RDV 5 mg/kg (Cohorts 2-5), or IV RDV 2.5 mg/kg (Cohorts 6 and 7)
- CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]
- Review AEs and document concomitant medications
  - All participants presenting with multisystem inflammatory syndrome in children (MIS-C; https://emergency.cdc.gov/han/2020/han00432.asp) should be monitored and treated as clinically indicated.

6.3. Study Assessments (Days 2-10)

The following evaluations are to be completed daily (unless otherwise noted) on Days 2-10 or until discharge, whichever comes earlier. For virologic and serologic assessments specified on study days beyond discharge, participants will be asked to continue to provide such samples if feasible. Participants must complete the following assessments before being administered study drug:

- A complete or symptom-directed (targeted) physical examination will be performed to evaluate for any possible AE

- CCI [redacted]
  - Documentation of respiratory status:
    - Respiratory rate
    - Oxygen supplementation: room air (no O_2 supplementation), low-flow O_2 (L/min and %), high-flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), HFOV (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO
    - Oxygenation: SpO_2 or PaO_2
- If available, record chest radiographic impression (or other imaging), but not mandatory to perform otherwise
- Evaluate the PEWS Improvement Scale (see Section 6.8)
- Record the Ordinal Scale (see Section 6.9)
- Laboratory evaluation **(Days 2, 5, 8, and 10, unless otherwise noted)**
  - Hematology: CBC with differential
  - Comprehensive metabolic panel (Chemistry 14): ALT/SGPT, A:G ratio, albumin, alkaline phosphatase, AST/SGOT, total bilirubin (and neonatal bilirubin panel for all neonates < 14 days, and any neonate presenting with jaundice **at Day 10 only**), BUN and creatinine (include BUN:Cr ratio, and eGFR using Schwartz formula if ≥ 1 year of age), ionized calcium, carbon dioxide, chloride, total serum protein, serum globulins, glucose, potassium, sodium
  - Urinalysis
  - Inflammatory markers: D-dimer, ferritin, qCRP, procalcitonin, IL-6; ESR (if > 4 kg, Cohorts 1-4 and 8 only)
    - **Note:** Inflammatory markers (ferritin, qCRP, procalcitonin, and IL-6) will be batched with Chemistry 14 testing and D-dimer with PT/aPTT for Cohorts 4-7 and those with smaller volumes in Cohort 3 as described in Appendix 5.
  - Routine coagulation test: PT/aPTT with calculated INR **(Screening, and Day 10 OR Discharge only for Cohorts 5, 6, and 7)**

- Serology for SARS-CoV-2 if ≥ 12 kg (Cohorts 1-3 and 8): **[Day 5, Day 10 (if feasible) or discharge if sooner]** If the participant is discharged prior to Day 10, the SARS-CoV-2 serology can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above.
- Collect samples for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing on **Days 3, 5, 7, and 10 (if feasible) or discharge if sooner**.
  - — Nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined) and,
  - — Rectal or fecal swab
  - — ET aspirates will also be collected if the participant is intubated.

  Swab collection technique for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing should be consistent on Day 1, 3, 5, 7 and 10. If the participant is discharged prior to Day 10, the SARS-CoV-2 RT-qPCR can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above. Endotracheal tube aspirates will also be collected on the same days as specified above while the participant is intubated.
- IV administration with either IV RDV 100 mg (Cohort 1 and 8), IV RDV 2.5 mg/kg (Cohorts 2-5), or IV RDV 1.25 mg/kg (Cohorts 6 and 7)
- Pharmacokinetic assessments (see Section 6.7)
- CCI [redacted]
  - — CCI [redacted]
  - — CCI [redacted]
  - — CCI [redacted]
- Review AEs and document concomitant medications
  - — All participants presenting with multisystem inflammatory syndrome in children (MIS-C; https://emergency.cdc.gov/han/2020/han00432.asp) should be monitored and treated as clinically indicated.

6.4. Day 30 Follow-up Assessment (± 5 days)

The following evaluations are to be completed as outpatient or inpatient depending on clinical status. If a participant discontinues the study drug early (i.e., less than 10 days), they are still required to complete a 30-day Follow-up visit.

- Vital signs (heart rate, temperature, blood pressure [MAP if available, systolic and diastolic], respiratory rate, oxygen saturation), body weight, length and head circumference (if < 28 days at enrollment).
  - Documentation of respiratory status:
    - Respiratory rate
    - Oxygen supplementation: room air (no O_2 supplementation), low-flow O_2 (L/min and %), high-flow O_2 (L/min and %), CPAP/BIPAP (FiO_2 or %), HFOV (FiO_2 or %), mechanical ventilation (FiO_2 or %), ECMO
    - Oxygenation: SpO_2 or PaO_2
- A complete or symptom-directed (targeted) physical examination will be performed to evaluate for any possible AE
- Laboratory evaluation
  - Comprehensive metabolic panel (Chemistry 14): Alanine aminotransferase (ALT/SGPT), albumin: globulin (A:G) ratio, albumin, alkaline phosphatase, aspartate aminotransferase (AST/SGOT), total bilirubin (and neonatal bilirubin panel for all neonates < 14 days, and any neonate presenting with jaundice), BUN and creatinine (include BUN:Cr ratio, and eGFR using Schwartz formula if ≥ 1 year of age), ionized calcium, carbon dioxide, chloride, total serum protein, serum globulins, glucose, potassium, sodium
- Serology for SARS-CoV-2, if ≥ 12 kg (Cohorts 1-3 and 8)
- Review AEs and document concomitant medications
  - All participants presenting with multisystem inflammatory syndrome in children (MIS-C; https://emergency.cdc.gov/han/2020/han00432.asp) should be monitored and treated as clinically indicated.

6.5. Clinical Laboratory Assessments

Clinical laboratory assessments are required at Screening and as indicated under Section 6.3. The smallest possible blood vials, such as microtainer tubes, must be used for participants weighing < 15 kg. Clinical laboratory assessments at other days may be conducted if required by clinical need or local practice. The results of all clinical laboratory tests that are performed as part of clinical care, even if not required by the protocol, should be reported.

Nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined), rectal or fecal swab, and ET aspirates will be collected and assayed using RT-qPCR to quantify SARS-CoV-2 viral load. Once viral load testing is complete, the remnant samples may be used to evaluate the emergence of viral resistance by SARS-CoV-2 sequencing and/or phenotypic testing. Swab collection technique for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing should be consistent on Day 1, 3, 5, 7, and 10.

6.6. Physical Examination

A symptom-directed (targeted) physical examination and vital signs (heart rate, temperature, blood pressure, respiratory rate, and oxygen saturation) should be performed at least daily.

6.7. Pharmacokinetic Assessments

As many of the specified PK time points should be obtained from each participant as is feasible.

Cohorts 1-4 (12 participants in each cohort) and Cohort 8 (all available):

- Day 2: end of infusion (± 15 minutes) and 4 hours (±30 minutes) post end of infusion
- Day 3: pre-infusion (≤ 60 minutes) and 2 hours (± 15 minutes) post end of infusion
- CCI [redacted]

Cohorts 5 (minimum of 4 participants), 6 and 7 (all available), Day 2 **OR** Day 3:

- Day 2: end of infusion (± 15 minutes) and 4 hours (±30 minutes) post end of infusion
- Day 3: pre-infusion (≤ 60 minutes) and 2 hours (± 15 minutes) post end of infusion

All blood samples for PK assessments will be drawn from the opposite arm or separate anatomical location than that used to administer RDV.

6.8. Pediatric Early Warning Score Improvement Scale

Clinical scoring using the PEWS Improvement Scale {Akre 2010, Monaghan 2005} will be performed at Screening and daily through the duration of dosing. If a participant is on a ventilator, a score of 3 should be given in the respiratory category. If a participant is being supported with ECMO, then the participant will be labeled as an ECMO patient and further analysis based on hemodynamics and clinical course will be analyzed. The scale/scoring is as follows:

	0	1	2	3
Behavior	• Playing • Appropriate	• Sleeping	• Irritable	• Lethargic **and/or** • Confused **and/or** • Reduced response to pain
Cardiovascular	• Within normal parameters for age • Pink **and/or** • Capillary refill 1-2 seconds	• Tachycardia < 20 above normal for age **and/or** • Pale **and/or** • Capillary refill 3 seconds	• Tachycardia 20-29 above normal for age • Gray **and/or** • Capillary refill 4 seconds	• Tachycardia ≥ 30 above or bradycardia ≥ 10 below normal for age **or** • Gray • Capillary refill ≥ 5 seconds
Respiratory	• Within normal parameters • No retractions	• Respiratory rate > 10 above normal parameters using accessory muscles **and/or** • 30+ %FiO_2 or 3+ L/min	• Respiratory rate > 20 above normal parameters and retractions **and/or** • 40+ %FiO_2 or 6+ L/min	• Respiratory rate ≥ 5 below normal parameters with retractions and grunting **and/or** • 50% FiO_2 or 8+ L/min

FiO_2 = fraction of inspired oxygen

6.9. Ordinal Scale

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

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

6.10. Posttreatment Assessments

No assessments are required after the Day 30 Follow-up visit.

6.11. Assessments for Early Discontinuation from Study

If a participant discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the participant in the study and continue to perform the required study-related follow-up and procedures through the study duration (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 an individual participant in the following instances:

- Any SAE or ≥ Grade 3 AE suspected to be related to RDV
- Any elevations in ALT > 5 × ULN; or ALT > 3 × ULN and total bilirubin > 2 × ULN, confirmed by immediate repeat testing
- eGFR using Schwartz formula < 30 mL/min/1.73m^2, if ≥ 1 year of age
- Creatinine above thresholds in Table 6-1 for participants < 1 year of age

Table 6-1. Creatinine Value Cut-Off by Age Group

Gestational age	Chronological age	Creatinine value cut-off in mg/dL
24-27 weeks	0-28 days	≥ 1.6
28-29 weeks	0-14 days	≥ 1.1
30-32 weeks	0-7 days	≥ 1.0
	≥ 7 days to 1 month	≥ 0.8*
	≥ 1-2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*
≥ 32 weeks	0-2 days	≥ 1.0*
	≥ 2-7 days	≥0.8*
	≥ 7 days to 2 months	≥ 0.6*
	≥ 2 months to < 1 year	≥ 0.5*

* Creatinine values exceed the 97.5th percentile {Vieux 2010} or upper limit {Colantonio 2012} of creatinine for age
¶ Critical serum creatinine values for preterm infants {Bruel 2013, Kastl 2017}

- 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 requires renal replacement therapies (iHD, PD, and CRRT) on Day 1 through Day 5
- Participant request to discontinue for any reason
- Participant noncompliance

6.12. End of Study

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

6.13. Post Study Care

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

6.14. PK Sample Storage

Th CCI [redacted]

6.15. Sample Disposition and Storage (Non-PK Samples Including Serology)

CCI [redacted]

6.16. Sample Storage

CCI [redacted]

CCI [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 product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.6).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented as medical history.
- Preexisting events or conditions that increase in severity or change in nature after the consent form is signed or as a consequence of participating in the clinical study will 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
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- 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.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

7.2.2. Assessment of Severity

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

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

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

7.3.1. Requirements for Collection Prior to Study Drug Initiation

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

7.3.2. Adverse Events

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

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

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the 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 period, must be reported on the applicable eCRFs and Global Patient Safety (GLPS) (formerly known as Pharmacovigilance an Epidemiology) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

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

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

7.3.3.1. Electronic Serious Adverse Event Reporting Process

- Site personnel record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically (ie, the eCRF database is not yet available or not functioning), record the SAE on the paper SAE reporting form and submit within 24 hours to:

Gilead GLPS
Email: PPD
or
Fax: PPD

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

7.4. Gilead Reporting Requirements

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

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

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

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

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

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports (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 of falsified medicine, and pregnancy regardless of an associated AE.

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

Gilead GLPS
Email: PPD
or
Fax: PPD

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

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

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

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

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

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

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

7.6.2.2. Reporting Other Special Situations

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

Gilead GLPS
Email: PPD
or
Fax: PPD

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

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

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

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

7.7. Toxicity Management

Remdesivir infusions will be administered to participants at the site under close supervision. Healthcare professionals administering RDV infusions should 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.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

The purpose of this study is to evaluate the safety, tolerability, PK, and efficacy of RDV in participants from birth to < 18 years of age with COVID-19.

8.1.1. Analysis Objectives

The analysis objectives of this study are as follows:

- To evaluate the safety and tolerability of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To evaluate the PK of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To evaluate the efficacy of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- To determine the antiviral activity of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years
- Change from baseline in oxygenation use
- Change from baseline in the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
- To evaluate clinical improvement using the PEWS scale in participants with laboratory confirmed COVID-19 aged 0 days to < 18 years
- Determine SBECD exposures (where possible)
- To provide data on use of medications other than RDV for treatment of COVID-19
- To evaluate the emergence of viral resistance to RDV
- To evaluate the safety, efficacy, and PK of RDV in participants with laboratory-confirmed COVID-19 with body mass index (BMI) for age $\geq 95^{th}$ percentile as defined by the Center for Disease Control and Prevention (CDC): https://www.cdc.gov/healthyweight/bmi/calculator.html

8.1.2. Primary Endpoint

The primary endpoints of this study are:

- The proportion of participants with TEAEs
- The proportion of participants with treatment-emergent graded laboratory abnormalities
- PK assessed by plasma concentrations of RDV and metabolites

8.1.3. Secondary Endpoint

The secondary endpoints of this study are:

- Oxygen usage and ventilation modality and settings
- Clinical improvement based on scoring using the 7-point Ordinal Scale
- Time (days) to discharge from hospital
- Days to the first confirmed negative PCR result, where confirmed is defined by 2 consecutive negative PCR results
- Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)
- Bilirubin concentrations in < 14-day-old participants
- Clinical improvement based on scoring using the PEWS Improvement Scale
- Plasma concentrations of SBECD (where possible)
- The proportion of participants with concomitant use of medications other than RDV for treatment of COVID-19

8.1.4. Other Endpoints of Interest

- Correlation between duration of SARS-CoV-2 shedding and timing and amplitude of SARS-CoV-2-specific IgG, IgM, and IgA
- Emergence of viral resistance to RDV

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, the data monitoring committee (DMC) interim analysis will be conducted. Interim data reviews by the Sponsor may also be conducted. These reviews may be submitted to regulatory agencies to seek guidance regarding the overall clinical development program.

8.2.1.1. DMC Analysis

The DMC will review safety, PK (if available), and efficacy data once approximately 50% of participants across the age range of 0 days to < 18 years have reached their Day 10 visit or have been discharged, whichever comes first.

8.2.2. Final Analysis

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

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 enrolled into the study and (2) have received at least 1 dose of study drug.

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 enrolled into the study and (2) have received at least 1 dose of study drug.

8.3.1.3. Pharmacokinetics

The RDV and metabolites PK analysis set will include all participants who are enrolled and have received at least 1 dose of RDV and for whom PK concentrations of analyte RDV are available.

The SBECD PK analysis set will include all participants who are enrolled and have received at least 1 dose of RDV and for whom PK concentrations of SBECD are available.

8.3.2. Data Handling Conventions

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and one-half of the lower limit of quantitation for postdose time points.

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

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed; however, a missing 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 for each cohort. Demographic summaries will include weight, height/length, sex, race/ethnicity, age, last recorded Apgar score if < 24 hours of life, GA and birth weight if < 56 days of age.

8.5. Efficacy Analysis

The following efficacy endpoints will be summarized using descriptive statistics for each cohort.

- Oxygen usage and ventilation modality and settings
- Clinical improvement based on scoring using the 7-point Ordinal Scale
- Time (days) to discharge from hospital
- Days to the first confirmed negative PCR result, where confirmed is defined as 2 consecutive negative PCR results
- Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)
- Clinical improvement based on scoring using the PEWS Improvement Scale

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed through the Day 30 Follow-up visit will be summarized (according to the study drug received) for each cohort. Data for the pretreatment period will be included in data listings. Summaries will be provided for each cohort.

8.6.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be summarized for each cohort.

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 TEAE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days, or up to Day 30, whichever is the later date.

Summaries (number and percentage of participants) of TEAEs (by system organ class and preferred term) will be provided for each cohort.

8.6.3. Laboratory Evaluations

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

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

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

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

8.7. Adjustments for Multiplicity

No adjustments for multiple comparisons are planned.

8.8. Pharmacokinetic Analysis

Plasma concentrations for RDV and metabolites, SBECD (where possible) will be listed and summarized using descriptive statistics.

8.9. Sample Size

Twelve (12) participants from each cohort (Cohorts 1-4) compared to 25 healthy adult participants in GS-US-399-5505 study, will provide > 99% power to conclude exposure equivalence of RDV AUC_{tau} in adolescent participants and children vs in healthy adult participants, assuming the expected geometric mean ratio is 1, equivalency boundary is 70% to 143%, two one-sided tests are each performed at an alpha level of 0.05, and the inter-participant standard deviations (natural log scale) of RDV AUC_{tau} is 0.18 ng•hr/mL.

8.10. Data Monitoring Committee

An external independent DMC includes independent experts who do not have direct involvement in the conduct of the study. The DMC will review the progress of the study, perform interim reviews of safety, PK (if available), and efficacy 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's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

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9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

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

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

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

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

9.1.4. Informed Consent (or Assent)

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

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9.1.5. Emergency Situation Assent (ICH E6(R2) 4.8.15)

When prior assent of the participant is not possible, and the participant's parent or legal guardian is not available, enrollment of the participant should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or the participant's parent or legal guardian should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

9.1.6. Confidentiality

The investigator must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, or laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study, in accordance with the site procedures and regulations. Participant data will be processed in accordance with all applicable regulations.

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

9.1.7. 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, paper or electronic completed participant CRFs, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each 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 study drug, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity), and documentation that adequate medical care has been provided for any AE;
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. CCI [redacted]

9.1.8. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the electronic data capture (EDC) system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the CRF completion guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel, who routinely review the data for completeness, correctness, and consistency. The site investigator or site coordinator or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the principal investigator of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature 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. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.7.

9.1.9. 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.

9.1.10. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.

STUDY ACKNOWLEDGMENT

A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants from Birth to < 18 Years of Age with COVID-19

Amendment 4 06 January 2022

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

PPD

PPD

Name (Printed)
Medical Monitor

PPD

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

	Screening	Administration Period[b]										Follow-up Period
		Baseline/ Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30 (± 5 days)
Assent/Parent or Legal Guardian consent	X											
Inclusion/Exclusion criteria	X											
Focused medical history	X											
Documentation of SARS-CoV-2 confirmation by PCR	X											
ECG	X											
Complete or symptom-directed physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[c]	X	X	X	X	X	X	X	X	X	X	X	X
Height/Length	X											X[d]
Head circumference and last recorded Apgar score if < 24 hours of age	X											X[d]
Birth weight and GA if < 56 days	X											
Vital signs (heart rate, temperature, blood pressure [MAP if available, systolic and diastolic], respiratory rate, oxygen saturation)	X	X	X	X	X	X	X	X	X	X	X	X
Documented respiratory status	X	X	X	X	X	X	X	X	X	X	X	X
If available, record chest radiographic impression (or other imaging) but not mandatory to perform otherwise	X	X	X	X	X	X	X	X	X	X	X	

	Screening	Administration Period[b]										Follow-up Period
		Baseline/ Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30 (± 5 days)
Tanner Stage assessment if ≥ 6 years of age		X										
Hematology, chemistry, urinalysis	X[e]		X			X			X		X	X[f]
Routine coagulation test (Screening and Day 10 OR Discharge only for Cohorts 5-7)	X		X			X			X		X	
Inflammatory Markers (D-dimer, ferritin, qCRP, procalcitonin, and IL-6)	X		X			X			X		X	
ESR if ≥ 4 kg (Cohorts 1-4 and 8 only)	X		X			X			X		X	
Neonatal bilirubin panel for all neonates < 14 days, and any neonate presenting with jaundice	X										X	
Serology for SARS-CoV-2 if ≥ 12 kg (IgG, IgM, and IgA)[g]	X					X					X	X
Pregnancy test (urine/blood)	X											
Nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined), rectal or fecal swab, and ET aspirates (if intubated) for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing[g]		X		X		X		X			X	

	Screening	Administration Period[b]										Follow-up Period
		Baseline/ Day 1[a]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30 (± 5 days)
Pediatric Early Warning Score Improvement Scale[h]	X	X	X	X	X	X	X	X	X	X	X	
Ordinal Scale	X	X	X	X	X	X	X	X	X	X	X	
Plasma PK assessmentsi			X	X		X						
IV RDV administration		X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]												

CoV = coronavirus; CRP = C-reactive protein; ECG = electrocardiogram; ET = endotracheal tube; GA = gestational age; Ig = immunoglobulin; IV = intravenous; MAP = mean arterial pressure; PK = pharmacokinetic; RDV = remdesivir (GS-5734™); SARS = severe acute respiratory syndrome; TBD = to be determined

a If the Screening and Day 1 visits occur within 24 hours, only the following procedures need to be completed: Tanner Stage assessment and samples for SARS-CoV-2 RT-qPCR testing and possible viral resistance testing

b The following evaluations are to be completed on Days 2-10 or until discharge, whichever comes earlier.

c CCI [redacted]

d Record length and head circumference if < 28 days at enrollment.

e 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.

f Comprehensive metabolic panel (Chemistry 14) only.

g Swab collection technique for SARS-CoV-2 RT-qPCR viral load testing and possible viral resistance testing should be consistent from Day 1, 3, 5, 7 and 10. If the participant is discharged prior to Day 10, the Serology for SARS-CoV-2 and SARS-CoV-2 samples/swabs will be collected on the day of discharge. Thereafter, these samples can be collected by assigned study staff at the participant's home or as an outpatient on the assigned days noted above.

h If a participant is on a ventilator, a score of 3 should be given in the respiratory category.

i CCI [redacted]

j IV administration on Day 1 with either IV RDV 200 mg (Cohorts 1 and 8), IV RDV 5 mg/kg (Cohorts 2-5), or IV RDV 2.5 mg/kg (Cohorts 6 and 7).

k IV administration daily up to Day 10 with either IV RDV 100 mg (Cohorts 1 and 8), IV RDV 2.5 mg/kg (Cohorts 2-5), or IV RDV 1.25 mg/kg (Cohorts 6 and 7).

l All participants presenting with multisystem inflammatory syndrome in children (MIS-C; https://emergency.cdc.gov/han/2020/han00432.asp) should be monitored and treated as clinically indicated.

m CCI [redacted]

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

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female-born participant is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal, unless the participant is permanently sterile or has medically documented ovarian failure.

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. Study Drug Effects on Pregnancy and Hormonal Contraception

Remdesivir use on pregnant women is limited. Data from nonclinical toxicity studies of remdesivir have demonstrated no adverse effect on fertility or embryo-fetal development. Available data indicate that remdesivir potentially causes an interaction with hormonal contraception that is considered of limited significance. Before enrolling in studies with remdesivir, women of child bearing potential must have a pregnancy test performed at screening. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female participants of childbearing potential requires using an acceptable effective contraceptive measure. They must have a negative pregnancy test at the screening visit prior to enrollment. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This also is applicable for women of childbearing potential with infrequent or irregular periods.

Female participants also must agree to 1 of the following from screening until the last dose of study drug.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
- Non-hormonal intrauterine device (IUD)
- Hormonal IUD (must be used in conjunction with a barrier method)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

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

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - — Oral contraceptives (either combined or progesterone only)
  - — Injectable progesterone
  - — Subdermal contraceptive implant
  - — Transdermal contraceptive patch
  - — Contraceptive vaginal ring
- Barrier methods
  - — Male condom (with or without spermicide)
  - — Female condom (with or without spermicide)
  - — Diaphragm with spermicide
  - — Cervical cap with spermicide
  - — Sponge with spermicide

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

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

3) Contraception Requirements for Male Participants

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Participants will be instructed to notify the investigator if they become pregnant at any time during the study. Participants who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator immediately. Female participants who become pregnant during the study or are discovered to be pregnant after receiving at least one dose may continue study drug, after discussion with the investigator on the risk/benefits of continuing in the study, taking into consideration the limited data on Remdesivir use during pregnancy balanced against the risk of COVID-19 infection during pregnancy and the unknown risk of mother-to-child transmission of Remdesivir. Participants whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 4. Tanner Stages

1. Pubic hair (male and female)	
Tanner I	no pubic hair at all (prepubertal Dominic state)
Tanner II	small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females)
Tanner III	hair becomes more coarse and curly, and begins to extend laterally
Tanner IV	adult-like hair quality, extending across pubis but sparing medial thighs
Tanner V	hair extends to medial surface of the thighs
2. Genitals (male) (One standard deviation around mean age)	
Tanner I	testes, scrotum, and penis about same size and proportion as in early childhood
Tanner II	enlargement of scrotum and testes; skin of scrotum reddens and changes in texture; little or no enlargement of penis (10.5-12.5)
Tanner III	enlargement of penis, first mainly in length; further growth of testes and scrotum (11.5-14)
Tanner IV	increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin (13.5-15)
Tanner V	genitalia adult in size and shape
3. Breasts (female)	
Tanner I	no glandular tissue: areola follows the skin contours of the chest
Tanner II	breast bud forms, with small area of surrounding glandular tissue; areola begins to widen
Tanner III	breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
Tanner IV	increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
Tanner V	breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla

Appendix 5. Blood Volume Tables for Clinical Laboratory Studies

The smallest possible blood vials, such as microtainer tubes, must be used for participants weighing < 15 kg.

Lab tests done within 48 h prior to screening may be used for Screening results.

Cohort 1, 2, and 8: ≥ 20 kg

Lab Assessment	Screening	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Total (mL)[a,b,c]
CBC	1.2		1.2			1.2			1.2		1.2	
Chemistry 14	1.1		1.1			1.1			1.1		1.1	
PT/aPTT	1.8		1.8			1.8			1.8		1.8	
Inflammatory Markers	5.2		5.2			5.2			5.2		5.2	
SARS-CoV-2 serology	1					1					1	
PK			2	2		2						
ESR	5		5			5			5		5	
CCI [redacted]												
Total (mL/day)[a,b,c]	15.3	1-2	16.3	2	1-2	17.3			14.3		15.3	80.5-82.5

a Cohort 1 blood volume limits (maximum blood for 40 kg participant): 80 mL for 24-hour maximum and 160 mL for 30-day maximum.

b Cohort 2 blood volume limits (20 kg to < 40 kg participant): 40 mL to ≤ 80 mL for 24-hour maximum and 80 mL to ≤ 160 mL for 30-day maximum.

c Cohort 8 blood volume limits (maximum blood for 41 kg participant): 82 mL for 24-hour maximum and 164 mL for 30-day maximum

d CCI [redacted]

Cohort 3: 12 kg to < 20 kg

Lab Assessment	Screening		D1	D2		D3	D4	D5		D6	D7	D8		D9	D10		Total (mL)[e]	
CBC[f]	1.2	0.3		1.2	0.3			1.2	0.3			1.2	0.3		1.2	0.3		
Chemistry 14[f]	1.1	0.8		1.1	0.8			1.1	0.8			1.1	0.8		1.1	0.8		
PT/aPTT[f]	1.8	1.3		1.8	1.3			1.8	1.3			1.8	1.3		1.8	1.3		
Inflammatory Markers[g]	5.2	0		5.2	0			5.2	0			5.2	0		5.2	0		
SARS-CoV-2 serology	1							1							1			
PK				2		2		2										
ESR[f]	5	0.5		5	0.5			5	0.5			5	0.5		5	0.5		
Total (mL/day)[e]	15.3	3.9		16.3	4.9	2		17.3	5.9			14.3	2.9		15.3	3.9	80.5	23.5

e Cohort 3 blood volume limits (for 12 kg to < 20 kg participant): 24 mL to ≤ 40 mL for 24-hour maximum and 48 mL to ≤ 80 mL for 30-day maximum.

f Smaller volumes for CBC, Chemistry 14, PT/aPTT and ESR reflect collection in a minimum volume tube such as a microtainer tube if participant weighs < 15 kg; the choice of tube/volume should be based on the participants' screening weight and using the following blood volume calculations: Maximum 24-hour blood volume: Wt (kg) × 80 mL/kg × 0.025
Maximum 30-day blood volume: Wt (kg) × 80 mL/kg × 0.050

g For smaller volumes, Inflammatory markers (ferritin, qCRP, procalcitonin, and IL-6) will be batched with Chemistry 14 testing and D-dimer with PT/aPTT.

Cohort 4: 3 kg to < 12 kg

Lab Assessment	Screening	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Total (mL)[h]
CBC	0.3		0.3			0.3			0.3		0.3	
Chemistry 14	0.8		0.8			0.8			0.8		0.8	
PT/aPTT	1.3		1.3			1.3			1.3		1.3	
Inflammatory Markers[j]	0		0			0			0		0	
PK			1	1		1						
ESR[i]	0.5		0.5			0.5			0.5		0.5	
Total (mL/day)[h]	2.9		3.9	1		3.9			2.9		2.9	17.5

h Cohort 4 blood volume limits (for 3 kg to < 12 kg participant): 6 mL to ≤ 24 mL for 24-hour maximum and 12 mL to ≤ 48 mL for 30-day maximum.

i Participants weighing ≤ 4 kg can omit ESR.

j Inflammatory markers (ferritin, qCRP, procalcitonin, and IL-6) will be batched with Chemistry 14 testing and D-dimer with PT/aPTT.

Cohorts 5 and 6: ≥ 2.5 kg

Lab Assessment	Screening	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Total (mL)[k]
CBC	0.3		0.3			0.3			0.3		0.3	1.5
Chemistry 14	0.8		0.8			0.8			0.8		0.8	4.0
PT/aPTT[m]	1.3										1.3	2.6
Inflammatory Markers[l]	0		0			0			0		0	0
PK			1.0	1.0								1.0
Total (mL/day)[k]	2.4		2.1	1.0		1.1			1.1		2.4	9.1

k Cohorts 5 and 6 blood volume limits (for 2.5 kg to < 3.5 kg participant): 5 mL to ≤ 7 mL for 24-hour maximum and 10 mL to ≤ 14 mL for 30-day maximum. If a participant weights ≤ 4 kg, please contact the medical monitor to further discuss the participant's schedule. Total reflects 2 PK samples collected on either Day 2 OR Day 3.

l Inflammatory markers (ferritin, qCRP, procalcitonin, and IL-6) will be batched with Chemistry 14 testing and D-dimer with PT/aPTT.

m PT/aPTT to occur on screening and Day 10 OR Discharge whichever comes first.

Cohort 7: ≥ 1.5 kg

Lab Assessment	Screening	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	Total (mL)[n]
CBC	0.3		0.3			0.3			0.3		0.3	1.5
Chemistry 14	0.8		0.8			0.8			0.8		0.8	4.0
PT/aPTT[p]	1.3										1.3	2.6
Inflammatory Markers[o]	0		0			0			0		0	
PK			1.0	1.0								1.0
Total (mL/day)[n]	2.4		2.1	1.0		1.1			1.1		2.4	9.1

n Cohort 7 blood volume limits (for 1.5 kg participant): 3 mL for 24-hour maximum and 6 mL for 30-day maximum. If a participant weights ≤ 4 kg, please contact the medical monitor to further discuss the participant's schedule. Total reflects PK sample collection on Day 2 or Day 3.

o Inflammatory markers (ferritin, qCRP, procalcitonin, and IL-6) will be batched with Chemistry 14 testing and D-dimer with PT/aPTT.

p PT/aPTT to occur on screening and Day 10 OR Discharge whichever comes first.

Appendix 6. 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 drug supplies to participants and sites:

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

      Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study 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 visit 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 adverse events (AEs)/serious adverse events (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.

   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.

c) Participants may be unable or unwilling to attend the study visit to sign an updated informed consent form (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) Monitors may be unable to carry out source data review (SDR) or source data verification (SDV), or study 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. 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 [study drug(s)] in study participants remains unchanged.