CLINICAL STUDY PROTOCOL

Study Title:	Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	Not Available
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Indication:	SARS-CoV2 Infection
Protocol ID:	GS-US-540-5821
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 22 March 2020

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

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CoV	Coronavirus
COVID-19	coronavirus disease-2019
EBOV	Ebola virus
HHS	Health and Human Services
IB	Investigator's Brochure
IV	intravenous
LPV/RTV-IFNb	lopinavir/ritonavir and interferon beta
MARV	Marburg virus
MERS	Middle East respiratory syndrome
MEURI	Monitored Emergency Use for Unregistered Interventions
NHP	nonhuman primates
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PHEIC	public health emergency of international concern
PK	Pharmacokinetic
RDV	Remdesivir
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
SAE	serious adverse event
WHO	World Health Organization

1. BACKGROUND

1.1. General Information

Remdesivir (RDV; GS-5734) is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, Ebola virus [EBOV], Marburg virus [MARV]), coronaviruses (eg, severe acute respiratory syndrome [SARS] coronavirus, Middle East respiratory syndrome [MERS] coronavirus [CoV]), and paramyxoviruses (eg, respiratory syncytial virus [RSV], Nipah virus, and Hendra virus). Remdesivir is being developed by Gilead Sciences, Inc. (Gilead) and is formulated for intravenous (IV) administration.

Provided in this document is an expanded access treatment protocol for use of RDV for the treatment of a patient with coronavirus disease-2019 (COVID-19) resulting from infection of SARS-CoV-2.

1.2. Disease Description

Coronaviruses (CoVs) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. However, over the past two decades, emerging pathogenic CoVs that can cause life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome (SARS) coronavirus {Corman 2015, Hui 2016}, Middle Eastern respiratory syndrome coronavirus (MERS) {Assiri 2013, Choi 2016}, and SARS-CoV-2 {Zhu 2020}. Coronaviruses are known to have high mutation and recombination rates which may allow them to cross species barriers and adapt to new hosts {Lau 2015}. Bats are reservoir hosts for many types of coronaviruses and are thought to have spread emerging CoVs to new species. Cross species transmission to animals and subsequent zoonotic transmission from animals has resulted in disease in humans {De Wit 2020}. Once infection is established in human hosts, these diseases primarily spread through nosocomial transmission to other humans {Al-Abdallat 2014}.

Severe acute respiratory syndrome CoV-2 is identified as the cause of an outbreak of respiratory illness that was first detected in Wuhan, China in December 2019. The virus causes respiratory illness in people and can spread from person to person {Center for Disease Control (CDC) 2020}. Common signs of infection include: fever, cough, shortness of breath, breathing difficulties, and other respiratory symptoms. In severe cases, COVID-19 can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death {World Health Organization (WHO) 2020b}. Since the start of the outbreak, multiple emergency declarations have been made including, but not limited to:

- 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 (PHEIC) {World Health Organization (WHO) 2020c}.

- On 31 January 2020, Health and Human Services (HHS) Secretary Azar declared a public health emergency in the U.S. {U. S. Department of Health & Human Services (DHHS) 2020}.
- On 11 March 2020, the WHO declared COVID-19 a pandemic{World Health Organization (WHO) 2020c}
- On 13 March 2020, the United States (U.S.) president declared COVID-19 a national emergency {FEMA 2020}

The global number of cases, death toll, and mortality rate of COVID-19 as of 17 March 2020 are described in Table 1. Global mortality rates were re-estimated by dividing the number of deaths on a given day by the number of patients with confirmed COVID-19 infection 14 days before (using a 14-day maximum incubation period), which resulted in a higher rate of 5.5 to 5.9% {Baud 2020}.

Table 1. Global Case Number, Death Toll, and Mortality Rate as of 17 March 2020

	WHO[a]	Johns Hopkins[b]
Case Number	179,112	198,155
Death Toll	7,426	7,954
Mortality Rate	3.4%[c,d]	Not reported

a {World Health Organization (WHO) 2020a}
b {Johns Hopkins University and Medicine 2020}
c {World Health Organization (WHO) 2020d}
d As of 03 March 2020, the WHO estimated the mortality rate to be 3.4%. Since the outbreak is ongoing and the number of people infected is unknown, it is too early to make any conclusive statement on the overall mortality rate.

No antiviral treatment is available for CoV infection including SARS-CoV, MERS-CoV, {Rasmussen 2016} and SARS-CoV-2. Treatment of severely ill infected patients is primarily supportive, which may include mechanical ventilation, lung protective ventilation strategies, extracorporeal membrane oxygenation, inotropic support, antimicrobial therapy for secondary infections, and hemodialysis {Bermingham 2012, Guery 2013, Madani 2014}.

A randomized, controlled, open-label trial was conducted to evaluate the efficacy of lopinavir/ritonavir (LPV/RTV) in hospitalized adult patients with severe COVID-19. A total of 199 patients were randomized to receive LPV/RTV (400 mg and 100 mg respectively; N=100) twice a day for 14 days, plus standard care or standard care alone (N=99), for 14 days. No benefit was observed with LPV/RTV treatment beyond standard care. Treatment with LPV/RTV was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72) {Cao 2020}.

There are currently no approved effective therapeutic agents available for the treatment of COVID, and the availability of an effective antiviral agent with a favorable benefit/risk profile would address a serious unmet medical need for the treatment of patients with COVID.

1.3. Rationale for Use of Remdesivir as a Treatment for COVID-19

The recommendation for using RDV as treatment of COVID-19 is based on the in vitro and in vivo activity of RDV against SARS-CoV-2 and other the human highly pathogenic CoVs, MERS-CoV and SARS-CoV.

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

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

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

- The pharmacokinetic (PK) profile of RDV in nonhuman primates (NHPs) and other relevant animal species indicates high and persistent levels of pharmacologically active nucleoside triphosphate metabolite in peripheral blood mononuclear cells (PBMCs), supporting once daily intravenous (IV) administration as a 30-minute infusion.

- Remdisivir has been used in hundreds of patients globally who were infected with SARS-CoV2 under a compassionate use protocol. Data on the safety and efficacy of remdisivir in these patients is limited, but several manuscripts describing some of those clinical cases suggest that remdisivir may have utility in improving the clinical course as well as viral shedding.{Holshue 2020, Kujawski 2020a, Kujawski 2020b, Lescure 2020}

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

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

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

- The target organ identified in the repeat-dose toxicology studies was the kidney in both rats and monkeys. Clinical chemistry, urinalysis, and urine biomarkers were early indicators of the reversible microscopic changes observed in the kidneys.

- 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.

- It is unknown, at present, how the observed efficacy of RDV in animal models of coronavirus infection will translate into clinical efficacy in patients with symptomatic disease.

Reference safety information, an overview of nonclinical experience, an overview of clinical experience, investigator guidance, and physical, chemical, and pharmaceutical information is provided in the RDV IB.

2. DRUG DESCRIPTION AND DOSAGE

Remdesivir is a single diastereomer monophosphoramidate prodrug of a nucleoside analog GS-441524.

2.1. Special Dosing Considerations

Coronavirus infection can progress to the severe life-threatening stage of disease involving severe pneumonia and acute respiratory distress syndrome. In these cases, treatment with RDV might have only limited, if any, impact on the survival of the infected subjects. In order to maximize its impact on viral replication and the chance of a successful outcome, it is important to initiate patient treatment with RDV as soon as possible following the diagnosis of identified CoV infection. Remdesivir may only be administered in accordance with applicable local regulatory requirements.

2.2. Route of Administration

Intravenous (IV) infusion administered over a 30 to 120 minute period.

2.3. Formulation

2.3.1. Solution Formulation, Remdesivir (GS-5734) Injection

The solution formulation of remdesivir is supplied as a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution containing 5 mg/mL remdesivir to be diluted into infusion fluids prior to IV administration. It is supplied as a sterile product in a single-use, clear glass vial with sufficient volume to allow withdrawal of 20 mL (100 mg remdesivir). In addition to the active ingredient, the solution formulation of remdesivir contains the following inactive ingredients: water for injection, sulfobutylether β-cyclodextrin sodium (SBECD), and hydrochloric acid and/or sodium hydroxide.

2.3.2. Lyophilized Formulation, Remdesivir (GS-5734) for Injection

The lyophilized formulation of remdesivir is a preservative-free, white to off-white to yellow, lyophilized solid containing remdesivir to be reconstituted with sterile water for injection and diluted into IV infusion fluids prior to IV administration. It is supplied as a sterile product in a single-use, clear glass vial. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 20 mL (100 mg of remdesivir). In addition to the active ingredient, the lyophilized formulation of remdesivir contains the following inactive ingredients: water for injection, SBECD, hydrochloric acid, and/or sodium hydroxide.

Detailed information regarding study drug administration, reconstitution, and dilution instructions are provided in a pharmacy manual provided to the investigator.

2.4. Dosage for Treatment of Coronavirus Infection

2.4.1. Adult Patient

The proposed regimen for the treatment of established CoV infection, including SARS-CoV, MERS-CoV, and SARS-2-CoV is as follows: single RDV 200 mg IV loading dose on Day 1 of treatment followed by 100 mg IV once-daily maintenance doses on Days 2 - 10. The recommended RDV dosing duration is a total of 10 days.

The proposed dosing regimen is based on clinical safety data in approximately 500 individuals, including healthy volunteers, individuals with acute EBOV infection, individuals exposed to EBOV, as well as Ebola survivors, with supportive data from efficacy studies in MERS-infected rhesus monkeys treated with RDV (Studies PC-399-2037 and PC-399-2038).

In the nonclinical studies, RDV was administered at 10 mg/kg (Study PC-399-2038) or 5 mg/kg (Study PC-399-2037) once daily for 7 days using IV bolus injection beginning either 1 day prior to (10 mg/kg or 5 mg/kg dose) or 12 hours after (5 mg/kg dose only) MERS-CoV inoculation. RDV treatment was efficacious at reducing viral titers in the lung and alleviating clinical disease signs (RDV IB; {De Wit 2020}).

Final results from Studies GS-US-399-1812 and GS-US-399-1954 and preliminary results from Studies GS-US-399-4231 and GS-US-399-5505 indicate that remdesivir is generally safe and well tolerated at a single dose of 3 to 225 mg (Studies GS-US-399-1812 and GS-US-399-4231) and multiple doses of 150 mg once daily for 7 or 14 days (Study GS-US-399-1954) or 200 mg at Day 1 and then 100 mg once daily for 4 or 9 days (GS-US-399-5505).

Transient treatment-emergent elevations in ALT and 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 PT elevations; however, there were no graded changes in INR. Laboratory results for these subjects 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 PALM 1 Ebola therapeutics trial. An additional 221 patients received RDV for acute Ebola virus disease under the Monitored Emergency Use for Unregistered Interventions (MEURI) protocol. Other patients who have received RDV include male Ebola survivors, post exposure prophylaxis, as well as compassionate use for other indications. No significant adverse events or laboratory abnormalities were attributed to RDV.

Toxicology studies in cynomolgus monkeys and rats and safety, pharmacokinetic studies in healthy volunteers and safety data from > 500 individuals support the safety of the proposed dose.

2.4.2. Patients with Renal and/or Hepatic Impairment

There are no specific studies conducted with RDV in patients with renal and/or hepatic impairment. A substantial proportion of patients with acute Ebola virus disease who received treatment with RDV under the PALM and MEURI protocols had moderate to severe liver and renal abnormalities at presentation. No renal or hepatic abnormalities were attributed to RDV. Given the benefit-risk ratio in patients with acute CoV infection, no dose modification is recommended at the present time.

3. OBJECTIVES AND ENDPOINTS

The primary objective of this study is:

- To provide expanded access of RDV for the treatment of SARS-CoV2 infection

The secondary objectives of this study are:

- To evaluate the safety of RDV with respect to incidence of treatment emergent adverse events

3.1. Endpoints

The primary endpoint of this study is:

- The incidence rate of treatment-emergent adverse events

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Up to approximately 5,000 participants may be enrolled

4.2. Inclusion Criteria

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

1) Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age)

2) Age ≥ 18 years

3) Hospitalized with confirmed SARS-CoV2 by PCR or known contact of confirmed case with syndrome consistent with COVID-19 with PCR pending

4) Requiring invasive mechanical ventilation (e.g., via endotracheal intubation or tracheostomy)

5) Adequate renal function with estimated glomerular filtration rate ≥ 30 ml/min by local laboratory measure

6) ALT ≤ 5 x upper limit of normal (ULN) by local laboratory measure

4.3. Exclusion Criteria

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

7) Evidence of multiorgan failure

8) Pressor requirement to maintain blood pressure

9) Renal failure (eGRF < 30 mL/min or dialysis or continuous Veno-Venous Hemofiltration

10) Pregnancy

5. DESCRIPTION OF CLINICAL PROCEDURES, LABORATORY TESTS, OR OTHER MONITORING

Described below are clinical procedures, laboratory tests, and other monitoring necessary to evaluate the effects of the drug and minimize its risks.

5.1. Clinical Procedures

During treatment with RDV, the patient will be admitted as an inpatient at a facility staffed and maintained by the requesting physician. A peripheral IV line or other venous catheter will be maintained. Fluid resuscitation will be available if necessary in the event of signs of renal failure or hypotension. Fever will be treated with acetaminophen (up to maximum allowable daily dose) and antibiotics as indicated. It is recommended that use of nonsteroidal anti-inflammatory medications and other nephrotoxic agents be avoided, if possible.

5.2. Laboratory Tests

The following laboratory tests will be performed daily during RDV therapy: serum chemistries-including electrolytes, renal function tests (creatinine, CrCL, BUN), liver function tests (including ALT, AST, total bilirubin, and alkaline phosphatase), hematology (complete blood count and prothrombin time) and urinalysis. CoV PCR, if available, should be performed at regular intervals to monitor response to RDV therapy and to continually weigh the risks and benefits to the patient. Other lab and clinical parameters will be checked at the discretion of the physician.

All available laboratory and clinical results will be shared daily with the study sponsor) electronically through eCRF, and the action plan for adverse events and abnormal laboratory results will be discussed with the medical monitor.

5.3. Other Monitoring

Physical examination and vital signs will be monitored at least once daily.

Concomitant administration of other investigational agents for COVID-19 is not permitted while receiving remdesivir.

The Medical Monitor should be notified prior to study drug discontinuation when medically feasible. Remdesivir should be permanently discontinued in the following conditions:

- Development of ALT levels $\geq$ 5 times the upper limit of normal
- Estimated creatine clearance < 30 mL/min based on the Cockcroft-Gault formula
- For clinical queries please contact the Medical Monitor

6. BENEFIT-RISK ASSESSMENT

There are currently no investigational agents with demonstrated clinical efficacy or approved treatments for acute severe CoV infection. The timely assessment of a safe and effective antiviral agent that works by directly and selectively blocking the virus replication and is broadly efficacious against human pathogenic CoVs would address a serious unmet medical need, benefiting both infected individuals and the affected community.

The pharmacokinetics of a single 5 mg/kg dose in healthy rhesus monkeys and a single dose of 75 mg in healthy adult human volunteers, both administered as 30-min IV infusion using the lyophilized formulation of RDV, demonstrated similar systemic plasma exposures of RDV. Additionally, the intracellular exposures of the active nucleoside triphosphate metabolite GS-443902 observed in rhesus monkey PBMCs were in the range of those observed in human PBMCs. Based on the dose-proportional pharmacokinetics observed in both species, drug exposure from the loading dose of 10 mg/kg in rhesus monkeys is similar to the expected drug exposure from the loading dose of 200 mg in humans. Toxicology studies in cynomolgus monkeys and rats and safety and pharmacokinetic studies in healthy volunteers support the safety of the proposed dose. Overall, RDV has a favorable pharmacokinetic and safety profile that supports evaluation of a 200 mg loading and a 100 mg daily dose that has potential to be efficacious in adult patients infected with coronavirus.

Transient treatment-emergent elevations in ALT and AST (Grade ≤ 2), have been observed after multiple daily RDV administration in Studies GS-US-399-1954 and GS-US-399-5505. To date in human studies, no SAEs have occurred in healthy individuals who have received at least 1 dose of RDV. Remdesivir has been tested in healthy volunteers as a single ascending dose over a dose range of 3 to 225 mg and in a multi-dose study of 150mg for up to 14 days and at 200 mg loading dose followed by 100mg for a total of 10 days. The potential changes in transaminases in CoV-infected patients treated with RDV can be readily monitored by standard clinical chemistry laboratory tests.

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

The 200 mg loading dose with 8 g of sulfobutylether β-cyclodextrin sodium (SBECD) on day 1 will be followed by 100 mg of RDV each day for 4 or 9 days with 4 g of SBECD, which is within the range of daily SBECD administration considered safe in humans. A total of 250 mg/kg/day of SBECD is considered safe by European Medicines Agency and is therefore safe for all adults with weight over 32 kg. The 100 mg dose prepared in 0.9% saline will be hypertonic relative to human serum osmolality but approaches the normal physiological osmolar range for humans. Renal function can be readily monitored by standard clinical chemistry tests.

The PALM 1 Ebola therapeutics study was a randomized, controlled, open label, trial comparing the ZMapp control to three putative Ebola therapeutics— RDV, REGN-EB3, and mAb114—for reductions in 28-day mortality in patients with acute EVD.{Mulangu 2019}. ZMapp, REGN-EB3, and mAb114 are monoclonal-based therapies. One patient receiving RDV had hypotension during administration of the loading dose followed by cardiac arrest. This serious adverse event (SAE) was deemed possibly related to RDV by the pharmacovigilance committee. An additional 221 patients received RDV for acute Ebola virus disease under the MEURI protocol.

PREVAIL IV was double-blind, 1:1 randomized, two-phase, placebo-controlled, Phase II Trial of RDV dosed at100 mg daily for 5 days designed to assess the antiviral activity, longer-term clearance of seminal EBOV RNA, and safety in Liberian and Guinean men with persistent EBOV RNA in semen. The study enrolled 38 of a planned 60-120 participants, of which 20 received RDV. There were no SAEs. The study allowed for blinded dose reductions for transaminase elevations; there was 1 individual dose reduction in the RDV arm and 5 in the placebo arm.

The first confirmed case of COVID-19 in the US was a 35-year-old previously healthy man who returned from Wuhan, China and was admitted to Providence Regional Medical Center in Washington state with a 4-day history of cough and subjective fever {Holshue 2020}. The patient tested positive for SARS-CoV-2 on illness day 4, progressed to pneumonia on illness day 9 and developed atypical pneumonia on illness day 10. The patient was treated with remdesivir, and no AEs were observed in association with its administration. As of illness day 15, the patient was afebrile and all symptoms were resolved, except for the cough, which was resolving.

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

Overall, the toxicology studies in cynomolgus monkeys and rats, and safety and pharmacokinetic studies in healthy human volunteers and patients with EBOV infection support the safety of the RDV proposed dose. In consideration of the information included in this protocol, the overall risks to patients are outweighed by the potential benefits of RDV experimental therapy for the treatment of potentially coronavirus infection.

In conclusion, RDV has a favorable safety profile that supports evaluation of the proposed dosing regimen with a potential to be efficacious in patients infected with CoV.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

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

An AE does not include the following:

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

7.1.2. Serious Adverse Events

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

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

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

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

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

7.3.1. Requirements for Collection Prior to Study Drug Initiation

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

7.3.2. Adverse Events

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

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

7.3.3. Serious Adverse Events

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

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

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

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

7.3.3.1. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data on the applicable eCRFs and record the SAE on the paper SAE reporting form and submit within 24 hours to:

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

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

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

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

7.4. Gilead Reporting Requirements

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

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

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

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

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

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

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

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

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

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

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

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

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

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

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

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

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

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

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

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

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

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

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE. Gilead PVE contact information is as follows: email: Safety_FC@gilead.com and fax: +1 650-522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number +1-650-522-5477 or email Safety_FC@gilead.com.

Refer to Appendix 2 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

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

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

The objective of the study is to provide expanded access of RDV for the treatment of SARS-CoV2 (CoV) infection.

8.1.1. Analysis Objectives

The analysis objective of this study includes:

- To evaluate the safety of RDV with respect to incidence of treatment emergent adverse events

8.1.2. Primary Endpoint

The primary endpoint of this study is:

- The incidence rate of treatment-emergent adverse events

8.2. Planned Analyses

8.2.1. Interim Analysis

No interim analyses are planned.

8.2.2. Final Analysis

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

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. Safety

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who have received at least 1 dose of RDV.

8.3.2. Data Handling Conventions

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

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

8.4. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods. Demographic summaries will include sex, race/ethnicity, and age.

8.4.1. Primary Analysis

8.5. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed will be summarized.

8.5.1. Extent of Exposure

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

8.5.2. Adverse Events

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

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

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

8.5.3. Laboratory Evaluations

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

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

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

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

9.1.2. Financial Disclosure

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

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

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

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

9.1.4. Informed Consent (or Assent)

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

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

9.1.5. Confidentiality

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

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

9.1.6. Study Files and Retention of Records

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

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

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

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

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

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

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

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

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the eCRF Completion Guidelines (eCCGs) provided by the

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

9.1.8. Investigator Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGMENT

Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARSCoV2 (CoV) Infection

Original Protocol 22 March 2020

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

Hal Martin
Name (Printed)
Executive Director

Signature

22 March 2020
Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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

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

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

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

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

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

b. Contraception Requirements for Female Subjects of Childbearing Potential

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

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - — Non-hormonal intrauterine device (IUD)
  - — Hormonal IUD (must be used with a barrier method)
  - — Tubal sterilization
  - — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
  - — Barrier methods
    - ■ Female barriers: Diaphragm with spermicide or Cervical cap with spermicide
    - ■ Male barriers: Male condom (with or without spermicide)
  - — Hormonal methods are restricted to drugs associated with the inhibition of ovulation. Each method must be used with a barrier method, preferably male condom. Hormonally-based contraceptives permitted for use in this protocol are as follows:
    - ■ Oral contraceptives (either combined or progesterone only)
    - ■ Injectable progesterone
    - ■ Subdermal contraceptive implant
    - ■ Transdermal contraceptive patch
    - ■ Contraceptive vaginal ring

Contraceptive methods must be locally approved to be permitted.

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

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

3) Contraception Requirements for Male Subjects

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

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