CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Combined Cross-Discipline Team Leader, Division Director, and ODE Director Summary Review

Date	October 21, 2020
From	Adam Sherwat; Jeffrey Murray; Debra Birnkrant; and John Farley
Subject	Cross-Discipline Team Leader, Division Director, and ODE Summary Review
NDA/BLA # Supplement#	NDA 214787
Applicant	Gilead Sciences, Inc.
Date of Submission	August 7, 2020
PDUFA Goal Date	April 7, 2021
Proprietary Name / Non-Proprietary Name	Veklury/ Remdesivir
Dosage form(s) / Strength(s)	Lyophilized formulation for injection, 100 mg Solution formulation for injection, 5 mg/mL
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Veklury is indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

1. Benefit-Risk Assessment

We agree with the detailed Benefit-Risk Assessment provided by Dr. Kirk Chan-Tack in his Clinical Review. The following abbreviated Benefit-Risk Assessment highlights the key issues.

Benefit-Risk Summary and Assessment

Coronavirus disease 2019 (COVID-19) is a viral respiratory infection caused by SARS-CoV-2. Clinical severity ranges widely, from asymptomatic infection to critical illness associated with respiratory failure, multi-organ failure, and death. An urgent need exists for safe and effective drugs to treat patients hospitalized with COVID-19. Remdesivir (RDV), a direct acting antiviral drug that inhibits viral RNA synthesis, is one such product.

RDV demonstrated efficacy in the NIAID-sponsored, pivotal Phase 3 trial designated ACTT-1. This double-blind, randomized, placebo-controlled trial, compared 10 days of treatment with RDV to 10 days of treatment with placebo in patients hospitalized with mild, moderate or severe disease. ACTT-1 demonstrated a significantly faster time to recovery in the RDV group compared to the placebo group; the median days to recovery was 10 days in the RDV group versus 15 days in the placebo group. The key secondary endpoint of odds of improvement at Day 15 also significantly favored RDV over placebo. There was a numeric difference in all-cause mortality favoring RDV, but this difference was not statistically significant. Clinical virology data was not submitted for the ACTT-1 trial.

Two Gilead-sponsored Phase 3 trials, GS-US-540-5773 and GS-US-540-5774, provided supportive evidence of efficacy. GS-US-540-5773 was a randomized, open-label trial that evaluated the safety and efficacy of 5 days versus 10 days of RDV in hospitalized patients with severe COVID-19. The trial was designed to assess for superiority of the 10-day regimen over the 5-day regimen. Superiority was not demonstrated, and the results were suggestive of a similar treatment effect with 5-day and 10-day regimens; however, absence of a standard-of-care alone arm limited the interpretability of the data. GS-US-540-5774 was a randomized, open-label trial that evaluated the safety and efficacy of 5 days versus 10 days of RDV compared to standard-of-care in hospitalized patients with moderate COVID-19. This trial demonstrated a statistically significant difference in the odds of improvement at Day 11 favoring the 5-day (but not the 10-day) treatment group over standard of care. Despite the inherent limitations of its open-label design, this trial provided supportive evidence for the efficacy of RDV in patients hospitalized with COVID-19 of moderate severity (i.e., patients hospitalized but not requiring supplemental oxygen). Clinical virology data was not submitted for either GS-US-540-5773 or GS-US-540-5774.

RDV has an acceptable safety profile for the indicated patient population. The major safety issues identified were hepatotoxicity and hypersensitivity reactions. Hepatotoxicity, manifested as an elevation in transaminase levels, was well-characterized in Phase 1 trials in healthy subjects and appears to be related to both increasing dose and longer duration of administration. In healthy subjects, the transaminase elevations do not demonstrate a clear association with other adverse events, and transaminase values returned to baseline levels after stopping the drug. No clear difference in graded transaminase levels between the RDV and placebo arms was demonstrated in the ACTT-1 trial. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been reported during and following administration of RDV. Signs and symptoms included hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering.

There remains uncertainty surrounding the optimal use of RDV in pediatric patients, pregnant patients, and in patients with renal or hepatic impairment. Similarly, in the absence of a dedicated QT study and clinical DDI studies, the potential for clinically significant QT prolongation or drug-drug interactions cannot be entirely excluded. These limitations result, in part, from the important public health priority of expediting the review of a safe and effective therapeutic in the setting of an unmet medical need and will be addressed post-approval. Post marketing requirements (PMRs) will be issued for the conduct of clinical trials in pediatric patients and in patients with renal or hepatic impairment. PMRs will also be issued for the conduct of a DDI trial with rifampin and a dedicated QT trial. A post marketing commitment (PMC) will be issued for a clinical trial to collect PK and safety data in pregnant patients.

The overall benefit-risk profile of RDV is favorable to support an indication for adults and pediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Areas of uncertainty include the optimal duration of therapy, the impact of RDV on virologic parameters, and the optimal dosing of RDV in pediatric patients, pregnant patients, and patients with renal or hepatic impairment. In our decision to approve RDV, we considered the available safety and efficacy data, and the recommendation for approval by all review disciplines.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	COVID-19 is a viral respiratory infection caused by SARS-CoV-2. Clinical severity ranges widely, from asymptomatic infection to critical illness. Risk factors for more severe disease requiring hospitalization include age > 65 years, hypertension, obesity, diabetes, cardiovascular disease, and chronic lung disease.	COVID-19 can cause severe disease resulting in pneumonia, respiratory failure, multi-organ failure, and death.
Current Treatment Options	There are no FDA-approved drugs for the treatment of COVID-19. On May 1, 2020, the FDA issued an Emergency Use Authorization (EUA) for RDV for the treatment of suspected or laboratory confirmed COVID-19 in adult and pediatric patients hospitalized with severe disease. On August 28, 2020, the FDA expanded the scope of the EUA to include the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adult and pediatric patients irrespective of disease severity.	There is an unmet medical need for safe and effective treatment options for patients with COVID-19.
Benefit	The efficacy of RDV was assessed in three Phase 3 clinical trials in hospitalized patients. The pivotal Phase 3 trial was a NIAID-sponsored trial designated ACTT-1. This double-blind, randomized, placebo-controlled trial compared 10 days of	RDV demonstrated efficacy in treating hospitalized patients with COVID-19. There remains uncertainty surrounding: 1) the optimal duration of therapy for patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment with RDV to 10 days of treatment with placebo. ACTT-1 demonstrated a significantly faster time to recovery in the RDV group compared to the placebo group; median days to recovery was 11 days in the RDV group versus 15 days in the placebo group. The key secondary endpoint of odds of improvement at Day 15 also significantly favored RDV over placebo. All-cause mortality was 11% with remdesivir and 15% with placebo, but this difference was not statistically significant. GS-US-540-5773 was a Gilead-sponsored, supportive Phase 3 trial. This randomized, open-label trial evaluated the safety and efficacy of 5 days versus 10 days of RDV in hospitalized patients with severe COVID-19. The trial was designed to assess for superiority of the 10-day regimen over the 5-day regimen. Superiority was not demonstrated, and the results were suggestive of a similar treatment effect with 5-day and 10-day regimens. However, the absence of a standard-of-care alone arm limits the interpretability of the data. GS-US-540-5774 was a Gilead-sponsored, supportive Phase 3 trial. This randomized, open-label trial evaluated the safety and efficacy of 5 days versus 10 days of RDV compared to standard-of-care in hospitalized patients with moderate COVID-19. This trial demonstrated a statistically significant difference in the odds of improvement at Day 11 favoring the 5-day (but not the 10-day) treatment group over standard of care. Despite the inherent limitations of its open-label design, this trial provided supportive evidence for the efficacy of RDV in patients hospitalized with COVID-19 of moderate severity (i.e., patients hospitalized but not requiring supplemental oxygen). Clinical virology data was not submitted for ACTT-1, GS-US-540-5773 or GS-US-540-5774.	hospitalized with COVID-19 and; 2) the impact of RDV on virologic parameters
Risk	The major safety issue identified was hepatotoxicity, manifested as an elevation in transaminase levels. Hepatic safety issues with RDV were well-characterized during the Phase 1 development program and appear to be related to both dose and duration of treatment. Notably, in Phase 1 trials in healthy subjects using the proposed to-be-marketed dosages, graded elevations in ALT were reported with the 10-day, but not the 5-day regimen. No clear	RDV has an acceptable safety profile for the indicated patient population. The major safety signals identified were hepatotoxicity and hypersensitivity reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	difference in graded transaminase levels between the RDV and placebo arms was demonstrated in the ACTT-1 trial. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been reported during and following administration of RDV. Signs and symptoms included hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. The nature and frequency of other significant safety events (deaths, serious adverse events, and discontinuations due to adverse events) reported in the Phase 3 trials largely reflect the patient population targeted for enrollment, i.e., patients hospitalized with COVID-19. To date, the Applicant has not conducted a hepatic impairment study, renal impairment study, dedicated QT study, or any clinical drug-drug interaction (DDI) studies. A trial in pediatric patients is ongoing, and a trial in pregnant patients is planned.	There remains uncertainty surrounding the optimal dosing of RDV in pediatric patients, pregnant patients, and in patients with renal or hepatic impairment. Similarly, in the absence of a dedicated QT study and clinical DDI studies, the potential for clinically significant QT prolongation or drug-drug interactions cannot be entirely excluded.
Risk Management	Warnings for hepatotoxicity and hypersensitivity reactions will be included in the RDV prescribing information (PI). The Applicant has agreed to conduct additional clinical trials to better characterize the safety, pharmacokinetics and pharmacodynamics of RDV.	The risk for hepatotoxicity and hypersensitivity reactions will be appropriately highlighted in the PI. Post marketing requirements (PMRs) will be issued for the conduct of clinical trials in pediatric patients and in patients with renal or hepatic impairment. PMRs will also be issued for the conduct of a dedicated QT trial and a DDI trial with rifampin. A post marketing commitment (PMC) will be issued for a clinical trial to collect PK and safety data in pregnant patients.

2. Background

On February 4, 2020, the Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug, and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel coronavirus (CoV) first detected in Wuhan City, Hubei Province, China in 2019. The virus, now named SARS-CoV-2, causes the illness Coronavirus disease 2019 (COVID-19). On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic.

SARS-CoV-2 can cause severe disease resulting in pneumonia, respiratory failure, multi-organ failure, and death. Globally, as of October 21, 2020, approximately 40,455,651 confirmed cases of COVID-19 have been reported, including an estimated 1,119,431 deaths[1]. In the US, as of October 21, 2020, approximately 8,188,585 cases of COVID-19 have been reported, including 219,499 deaths[2].

The predominant signs and symptoms of COVID-19 include fever, cough, and shortness of breath. Clinical severity ranges widely, from asymptomatic infection to critical illness. Risk factors for hospitalization include, but are not limited to, age > 65 years, hypertension, obesity, diabetes, cardiovascular disease, and chronic lung disease.[3]

Signs and symptoms of COVID-19 in children may be similar to those observed in common viral respiratory infections and other childhood illnesses. Complications of COVID-19 may be less common among children than adults, but severe complications (e.g., acute respiratory distress syndrome, septic shock, and Multisystem Inflammatory Syndrome in Children [MIS-C]) have been reported in children of all ages.[4,5]

This New Drug Application, submitted by Gilead Sciences Inc., contains information to support the approval of Veklury (remdesivir [RDV]) for the treatment of patients with COVID-19 requiring hospitalization. RDV, a direct acting antiviral drug that inhibits viral RNA synthesis, would be the first drug approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19.

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[1] World Health Organization -- Coronavirus disease (COVID-19) pandemic – https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed on October 21, 2020.
[2] CDC – Cases and Deaths in the U.S. -- https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/us-cases-deaths.html. Accessed on October 21, 2020.
[3] COVID-NET: COVID-19-Associated Hospitalization Surveillance Network, CDC. https://gis.cdc.gov/grasp/COVIDNet/COVID19_5 html. Accessed on September 26, 2020.
[4] Feldstein, L.R., Rose, E.B, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *NEJM*. June 29, 2020. DOI: 10.1056/NEJMoa2021680.
[5] CDC – Information for Pediatric Healthcare Providers – https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp html. Accessed on September 26, 2020.

RDV was initially studied under IND 125566, which was opened in 2015, for the treatment of Ebola Virus Disease. In 2016, IND 125566 was placed on partial clinical hold due to a hepatotoxicity safety signal in a clinical trial in healthy participants. In February 2020, IND 147753 for the treatment of COVID-19 was opened. Milestone regulatory events for IND 147753 included the granting of Fast Track designation in March 2020, Rolling Review in April 2020, and Emergency Use Authorization in May 2020.

This review will present the major findings and key issues from the NDA review of RDV. For a more comprehensive assessment, the reader is referred to the discipline-specific reviews for the RDV NDA.

3. Product Quality

The Product Quality review team recommends approval of this NDA based on their review of the submitted data. Please refer to the Product Quality reviews for additional details.

Formulations

- RDV for injection, 100 mg, is a sterile, preservative-free white to off-white to yellow lyophilized powder that requires reconstitution and dilution prior to administration by intravenous (IV) infusion. RDV for injection, 100 mg, vials should be stored below 30°C until required for use.

- RDV Injection, 5 mg/mL, is a sterile, preservative-free, clear, colorless to yellow aqueous-based solution that requires dilution prior to administration by IV infusion. RDV injection, 5 mg/mL vials should be stored at refrigerated temperatures (2°C to 8°C) until required for use.

General product quality considerations

According to the Quality Assessment review, the data presented in the NDA application and amendments are adequate to ensure that the composition, manufacturing processes, and specifications for RDV are appropriate. The expiration dating period of 30 months for the lyophilized powder (RDV for injection) and 12 months for the solution (RDV injection), when stored at recommended temperatures, is supported by adequate data. No product quality microbiology issues were identified that would preclude approval. The specified impurities were reviewed by Dr. John Dubinion and deemed acceptable from a pharmacology/toxicology perspective. The prescribing information (PI) is adequate from the product quality perspective.

Facilities review/inspection

The proposed facilities have a satisfactory Current Good Manufacturing Practices (cGMP) history and related operation experience. The facilities are considered adequate to support this NDA.

4. Nonclinical Pharmacology/Toxicology

Dr. John Dubinion recommended approval of this NDA based on his review of the nonclinical safety information provided in the submission. Please refer to the Pharmacology/Toxicology review by Dr. Dubinion for additional details.

General nonclinical pharmacology/toxicology considerations

Nonclinical safety studies were conducted in rats and cynomolgus monkeys for up to 4 weeks. The kidney was identified as the target organ of toxicity in animals. Findings included increased serum creatinine, proteinuria, increased kidney weight, and proximal tubular epithelial necrosis. Additional adverse effects were noted on appetite, body weight gain, and respiratory rate (increased).

The vehicle control for RDV, 12% sulfobutylether-β-cyclodextrin (SBECD), is a known renal toxicant deemed safe for use in patients > 32 kg (250 mg/kg/day by EMA). It is known to cause vacuolation of the kidney tubular cells without loss/change of kidney function in animals. In monkeys, RDV exacerbated SBECD-related effects at 10 mg/kg where functional changes of the kidney were noted. Exposure at 10 mg/kg in monkeys is 2.7 times the exposure in humans at the recommended human dose (RHD). SBECD exposure in infants <2 (<40 kg) is supported by DMF #14364.

Reproductive toxicology

A complete reproductive and development toxicity program has not identified any risks for pregnant mothers or their off-spring. Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at nontoxic doses in pregnant animals. During organogenesis, exposures to the predominant circulating metabolite (GS-441524) were 4 times higher (rats and rabbits) than the exposure in humans at the RHD. In a pre/postnatal development study, exposures to the predominant circulating metabolite of remdesivir (GS-441524) were similar to the human exposures at the RHD.

Genetic toxicology and carcinogenicity

RDV is not considered a potential mutagen or clastogen based on a battery of in vitro and in vivo studies performed to assess its genotoxic potential.

Carcinogenicity studies with RDV are not being conducted given the intended treatment duration and lack of a specific cause for concern.

Special studies

In vitro examinations showed little to no potential of cytotoxicity or mitochondrial toxicity of RDV or its major metabolites.

5. Clinical Pharmacology

The Office of Clinical Pharmacology reviewed the clinical pharmacology information submitted and considers the NDA approvable from their perspective. Please refer to the clinical pharmacology review by Dr. Mario Sampson for additional details.

General clinical pharmacology considerations

Absorption, Distribution, Metabolism, and Excretion

- RDV is a prodrug that is metabolized to GS-704277 and GS-441524
- GS-441524 is a nucleoside analog that is intracellularly phosphorylated to the active nucleoside triphosphate GS-443902
- The pharmacokinetic (PK) properties of RDV and its metabolites are provided in Table 1.

Table 1: Pharmacokinetic properties of RDV and metabolites (GS-441524 and GS-704277) in healthy adult subjects

	RDV	**GS-441524**	**GS-704277**
Absorption			
T_{max} (h)[a]	0.67-0.68	1.51-2.00	0.75-0.75
Distribution			
% bound to human plasma proteins	88-93.6[b]	2	1
Blood-to-plasma ratio	0.68-1.0	1.19	0.56
Elimination			
$t_{1/2}$ (h)[c]	1	27	1.3
Metabolism			
Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	Not significantly metabolized	HINT1
Excretion			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine[d]	10	49	2.9
% of dose excreted in feces[d]	ND	0.5	ND

Source: FDA's Office of Clinical Pharmacology Review

HINT1 = Histidine triad nucleotide-binding protein 1, also known as adenosine 5'-monophosphoramidase. ND = not detected.

a. RDV administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.
b. Range of protein binding for RDV from 2 independent experiments show no evidence of concentration-dependent protein binding for RDV.
c. Median (Study GS-US-399-4231).
d. Mean (Study GS-US-399-4231).

PK Parameters

The PK of RDV and its metabolites were not evaluated in the Phase 3 studies of patients hospitalized with COVID-19. The single and multiple dose PK parameters of RDV and metabolites in healthy adults administered RDV for 5 or 10 days are provided in Table 2.

Table 2: Multiple Dose PK Parameters[a] of RDV and Metabolites (GS-441524 and GS-704277) Following IV Administration of RDV 100 mg to Healthy Adults

Parameter Mean (CV%)	**RDV**	**GS-441524**	**GS-704277**
C_{max} (nanogram per mL)	2229 (19.2)	145 (19.3)	246 (33.9)
AUC_{tau} (nanogram•h per mL)	1585 (16.6)	2229 (18.4)	462 (31.4)
C_{trough} (nanogram per mL)	ND	69.2 (18.2)	ND

Source: draft RDV USPI
CV=Coefficient of Variation; ND=Not detectable (at 24 hours post-dose)
a. RDV administered as a 30 minute IV infusion (Study GS-US-399-5505).

Critical intrinsic factors potentially affecting elimination

Renal/Hepatic Impairment:

There were no dedicated studies conducted in patients with renal or hepatic impairment. Currently, there is insufficient evidence to conclude that hepatic or renal impairment will not affect PK of RDV. Post marketing requirements (PMRs) will be issued to conduct studies in patients with renal and hepatic impairment (see Section 13).

Demographic/Host Factors:

PK has not been evaluated in patients with COVID-19 or in other specific populations (e.g., pediatrics, pregnant women). A PMR will be issued to conduct a study in pediatric patients with COVID-19 (see Section 10), and a post marketing commitment (PMC) will be issued to conduct a study in pregnant patients with COVID-19 (see Section 13).

Drug-drug interactions (DDIs)

The antiviral activity of RDV was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher RDV EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of RDV triphosphate in normal human bronchial epithelial cells. It is anticipated that a similar antagonistic effect on RDV would occur in a SARS-CoV-2 cell culture model. A warning will be included in the PI to assist in risk mitigation (see Section 12), and a PMR will be issued for the results of the assessment of the effect of chloroquine/hydroxychloroquine on the antiviral activity of RDV against SARS-CoV-2 in human lung cells (see Section 13).

In vitro, RDV is a substrate for drug metabolizing enzyme CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, RDV is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1. GS-704277 is a substrate for OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established.

RDV is not a substrate for CYP1A1, 1A2, 2B6, 2C9, 2C19, or OATP1B3. GS-704277 and GS-441524 are not substrates for CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, or 3A5. GS-441524 is also not a substrate for CYP2C19 or 3A4. GS-704277 and GS-441524 are not substrates for OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2k. GS-441524 is also not a substrate for OATP1B1 or OATP1B3.

Clinical DDI studies have not been performed with RDV. A PMR will be issued to conduct a drug interaction trial to evaluate the PK of RDV when coadministered with rifampin, a broad-spectrum inducer of enzymes/transporters (see Section 13).

Pharmacodynamic Considerations

QT assessment:

Prior to completing the NDA submission, the Applicant requested a waiver for a thorough QT (TQT) study based on data submitted from trial GS-US-399-1954, a randomized, blinded, placebo-controlled, single center study with 24 healthy subjects in 2 sequential dose cohorts. The data were reviewed by the QT-IRT and the QT-IRT concluded that the data are not adequate as a substitute for a TQT study per ICH E14 Q&A (R3) 5.1.

Although a large mean increase in QTc was not observed in a concentration-QTc assessment, the QT-IRT was reluctant to conclude absence of small mean increases in QTc interval for the following reasons:

- There was no positive control or large exposure margin. The highest dose tested in this QT assessment covers approximately 75% of the parent drug and

approximately 150% of the major metabolites at the highest recommended therapeutic dose (i.e., 200 mg on Day 1 and 100 mg once daily for up to 9 days, as a 30-min intravenous [IV] infusion).

- There were unexplained increases in QTc of approximately 10 msec observed on day 14 with data from 8 subjects.
- RDV has the potential to directly block the hERG current at therapeutic exposure. The in vitro hERG study does not provide a large safety margin for the major metabolites at the therapeutic exposure.

A PMR will be issued for the conduct of a TQT study (see Section 13).

6. Clinical Microbiology

Dr. Eric Donaldson recommended approval of this NDA based on his review of the virology information provided in the application. Please refer to the virology review by Dr. Donaldson for a detailed assessment of the virology data.

RDV is a nucleotide prodrug that is intracellularly metabolized into its active form GS-441524, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis.

RDV exhibited cell culture antiviral activity against SARS-CoV-2

- The 50% effective concentration (EC_{50}) of RDV against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells was 9.9 nM after 48 hours post-treatment.
- The EC_{50} values of RDV against SARS-CoV-2 grown in Vero cells was 137 nM at 24 hours and 750 nM at 48 hours post-treatment.
- The EC_{50} value of RDV against a recombinant chimeric virus expressing the RdRp gene (nsp12) of SARS-CoV-2 in a backbone of SARS-CoV with a fluorescent reporter protein in Huh7 cells was 3.5 nM.

Preliminary data from a study of RDV in non-human primates (NHPs) with SARS-CoV-2 suggests proof-of-concept antiviral activity for post-exposure prophylaxis in a nonlethal NHP animal model.

Clinical virology data was not submitted in support of this application. PMCs and PMRs will be issued for additional nonclinical and clinical virology information (see Section 13).

7. Clinical/Statistical - Efficacy

This section summarizes the efficacy analyses conducted by the review team of the key trials supporting an indication for RDV for the treatment of COVID-19 in patients requiring hospitalization. The NDA application is supported by three Phase 3 clinical trials in hospitalized patients of varying disease severity. The study designs, subject characteristics, and key efficacy results from each of these trials are summarized below.

For additional details on the Phase 3 trials, please refer to the Clinical Review by Dr. Kirk Chan-Tack and the Statistical Review by Dr. Daniel Rubin.

Study designs, baseline characteristics, and key efficacy results

ACTT-1 (Sponsor: National Institute of Allergy and Infectious Diseases [NIAID])

ACTT-1 was a Phase 3, multi-national, randomized, double-blind, placebo-controlled trial, which evaluated the safety and efficacy of RDV in hospitalized patients with mild, moderate, or severe COVID-19. A total of 1062 eligible subjects were randomized in a 1:1 ratio to receive RDV at a dose of 200 mg on Day 1, followed by 100 mg on Days 2-10 in single daily intravenous infusions. Treatment with RDV was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

Randomization was stratified by study site and disease severity at enrollment. Mild/moderate disease was defined as $SpO_2 > 94\%$ and respiratory rate < 24 breaths/minute without supplemental oxygen. Severe disease was defined as participants meeting one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an $SpO_2 \leq 94\%$ on room air, or tachypnea (respiratory rate ≥ 24 breaths per minute).

Inclusion criteria specified that patients must be males or non-pregnant females ≥ 18 years of age who had laboratory-confirmed SARS-CoV-2 infection as determined by reverse transcription polymerase chain reaction (RT-PCR) assay. Patients could have illness of any duration. For inclusion, patients were to have at least one of the following: radiographic infiltrates by imaging, $SpO_2 \leq 94\%$ on room air, requirement for supplemental oxygen, or requirement for mechanical ventilation. Exclusion criteria disallowed enrollment of patients with ALT or AST > 5 times the upper limit of normal or an estimated glomerular filtration rate (eGFR) < 30 mL/min.

The primary efficacy endpoint was time to recovery through Day 29. Recovery was defined by being in category 1, 2, or 3 in the following 8-point ordinal scale:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities and/or requiring home oxygen
3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care
4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
5. Hospitalized, requiring supplemental oxygen
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices
7. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8. Death

Patients who died before recovering were censored in the analysis at Day 29, corresponding to failing to recover through the entire follow-up period. The time to recovery analysis was based

on an estimated hazard ratio from a Cox proportional hazards model, log-rank test, and comparison of median days to recovery between the RDV and placebo groups. The pre-specified primary efficacy analysis was conducted in an intention-to-treat population of all randomized patients.

A pre-specified key secondary efficacy analysis was an analysis of the above ordinal scale at Day 15 using a proportional odds model. All-cause mortality at Day 14 and 29 were also pre-specified secondary endpoints.

Because the primary efficacy endpoint was a time to event endpoint, this trial was powered as an event driven study that would reach the final analysis after 400 patients had met recovery criteria. This was planned to provide 85% power for detecting a hazard ratio of 1.35 (on a scale where values greater than 1.00 corresponded to faster recovery in the RDV group).

This was a multi-national trial with approximately 80% of patients enrolled at sites in North America, 15% in Europe, and 5% in Asia. The mean age of patients was 59 years, and 64% were male. Overall, 53% of patients were white, 21% were black, 13% were Asian, and 14% were designated as other or not reported. Twenty-four percent of the patients were Hispanic or Latino. The median time from symptom onset to randomization was 9 days. Most patients (79%) had one or more pre-specified coexisting conditions at enrollment; the most common coexisting conditions were hypertension (51%), obesity (45%), and type 2 diabetes mellitus (31%). Most patients (90%) had severe disease (as defined above) at enrollment, with 27% of patients on mechanical ventilation or ECMO at the time of enrollment. The trial arms were generally well balanced for demographic and other baseline characteristics.

In the intent-to-treat population of all randomized patients, the time to recovery was significantly faster in the RDV group than the placebo group. Median days to recovery was 10 days in the RDV group versus 15 days in the placebo group. The estimated hazard ratio (on a scale with values greater than 1.00 favoring RDV) was 1.29 with a 95% confidence interval for the hazard ratio from 1.12 to 1.49, and a two-sided p-value < 0.001. Figure 1 displays the results for the primary analysis of time to recovery for the ITT population.

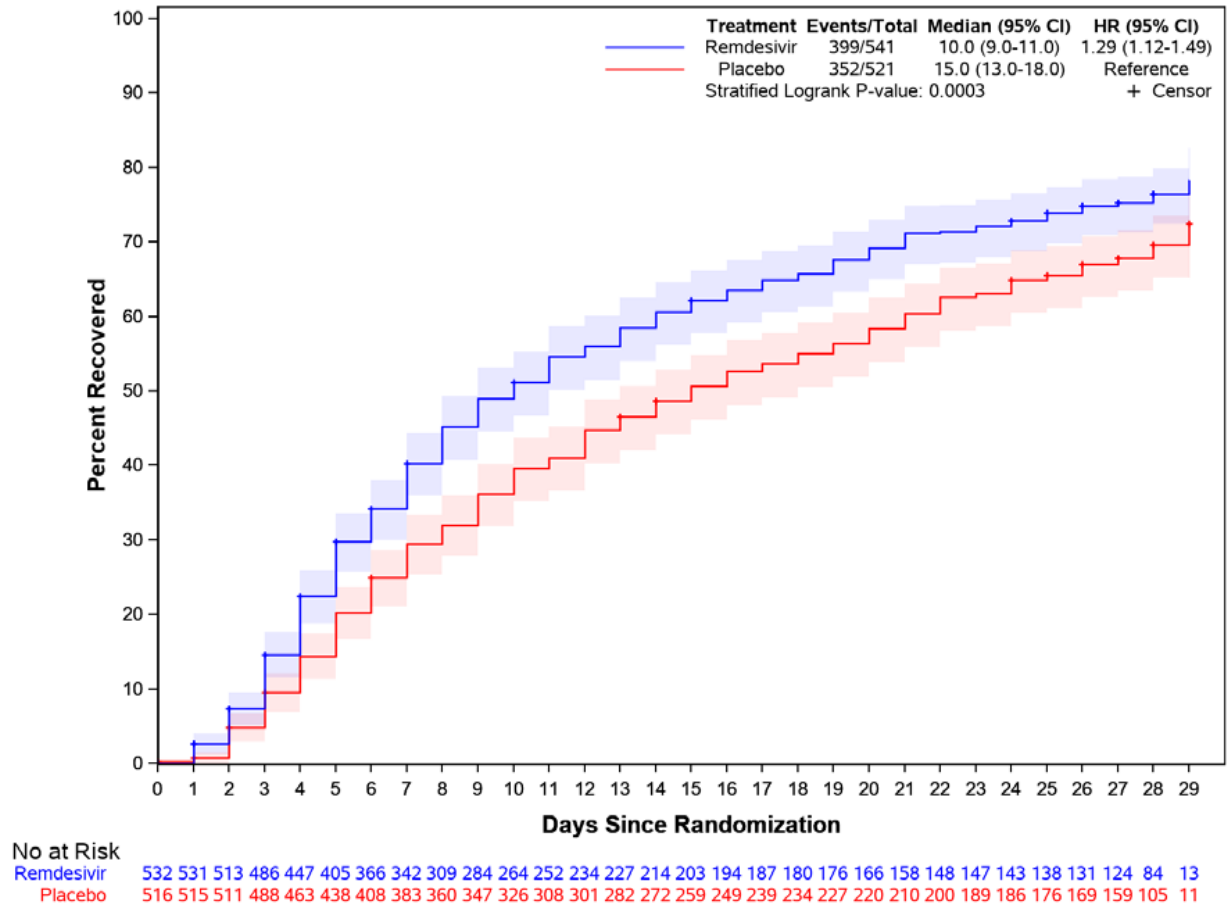

Figure 1: ACTT-1 Kaplan-Meier results for the primary analysis of time to recovery (ITT population)

Abbreviations: ITT = intent-to-treat; CI = confidence interval; HR = recovery rate ratio.
Source: Analytics and informatics reviewer and ACTT-1 Final Clinical Study Report (Table 14 and Figure 3).

Among subjects with mild/moderate disease, the median time to recovery was 5 days in both the RDV and placebo groups (recovery rate ratio 1.22 [95% CI 0.82 to 1.81]). Among subjects with severe disease at enrollment, the median time to recovery was 11 days in the RDV group compared to 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52]). Figures 2 and 3 display the Kaplan-Meier results for the mild/moderate and severe disease strata, respectively.

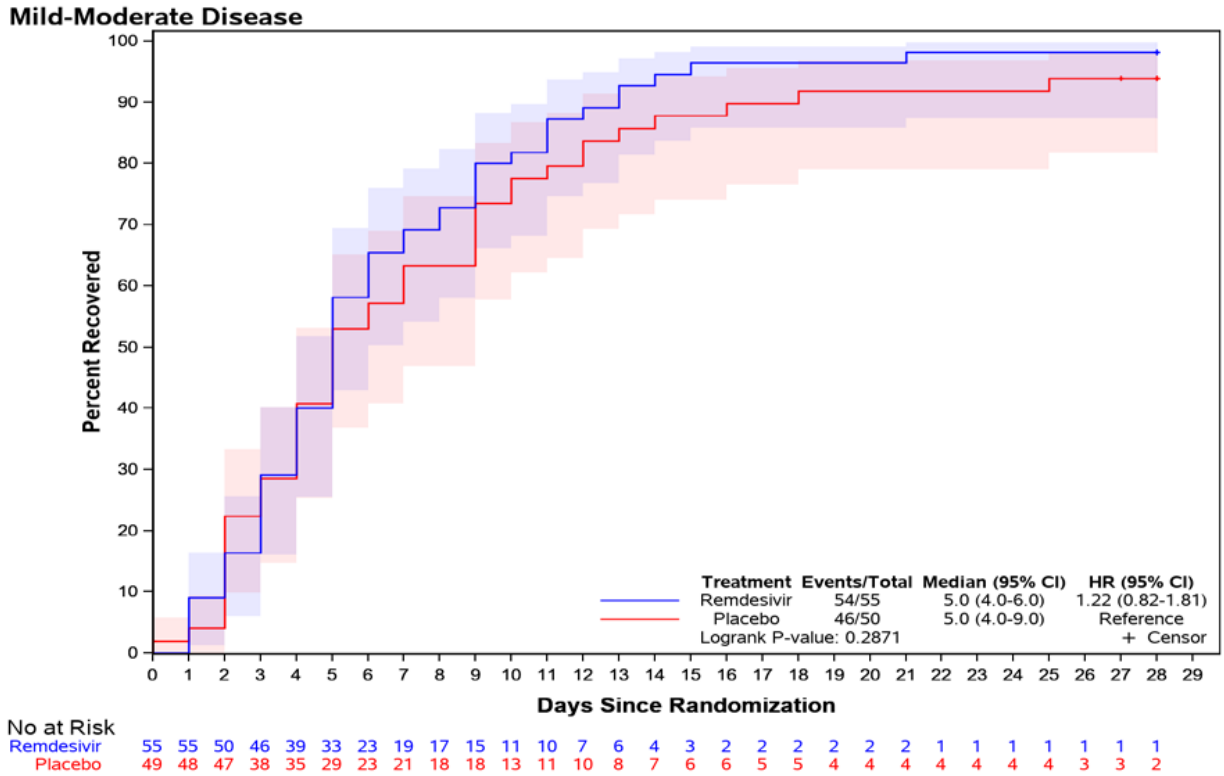

Figure 2: ACTT-1 Kaplan-Meier results for the primary analysis of time to recovery in the mild-moderate disease strata (ITT population)

Abbreviations: ITT = intent-to-treat; CI = confidence interval; HR = recovery rate ratio.
Source: Analytics and informatics reviewer

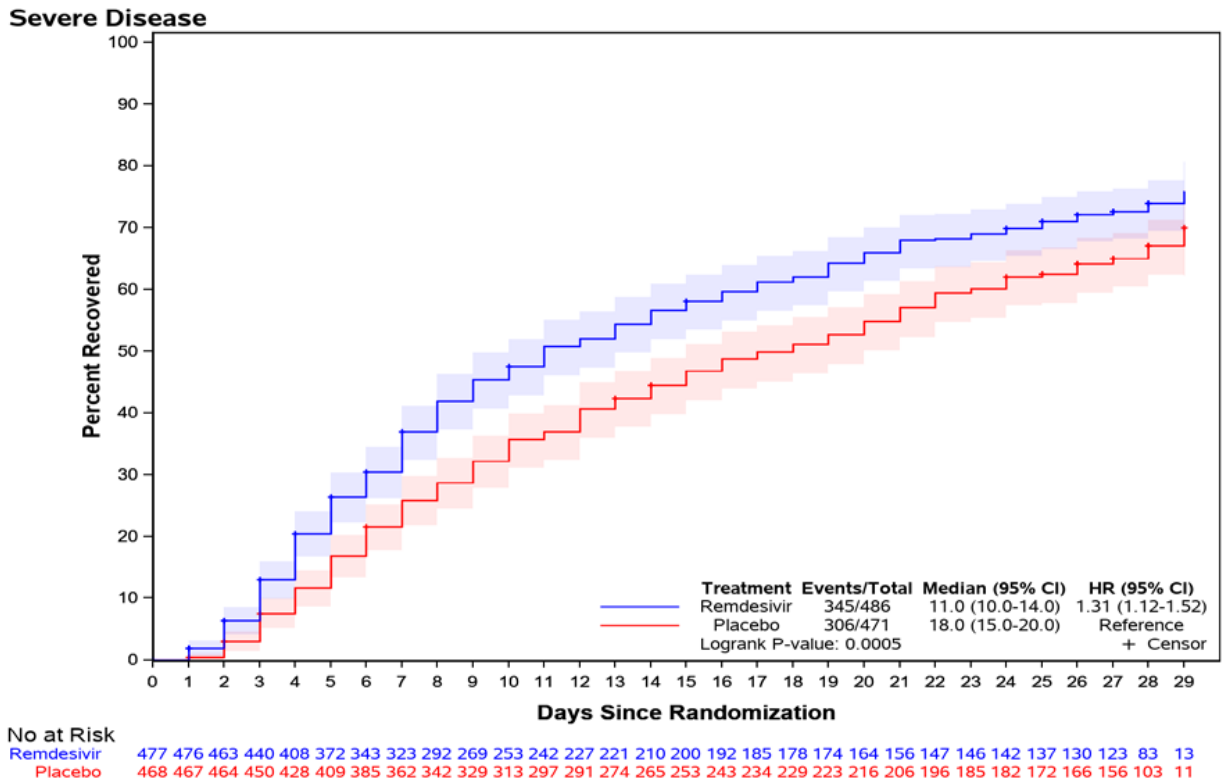

Figure 3: ACTT-1 Kaplan-Meier results for the primary analysis of time to recovery in the severe disease strata (ITT population)

Abbreviations: ITT = intent-to-treat; CI = confidence interval; HR = recovery rate ratio.
Source: Analytics and informatics reviewer

The key secondary endpoint of odds of improvement at Day 15 based on the ordinal scale favored RDV over placebo. An analysis from a proportional odds model estimated an odds ratio (on a scale with values greater than 1.00 favoring RDV) of 1.54 [95% CI 1.25 to 1.91]. Among subjects with mild/moderate disease at enrollment, the odds ratio was 1.46; [95% CI, 0.71 to 2.97]; among subjects with severe disease at enrollment, the odds ratio was 1.56; [95% CI, 1.24 to 1.95].

Mortality was numerically lower in the RDV group compared to the placebo group, however the difference was not statistically significant. Overall, 29-day mortality was 11% for the RDV group vs 15% for the placebo group (hazard ratio 0.73 [95% CI 0.52 to 1.03]).

Trial GS-US-540-5773 (Sponsor: Gilead)

GS-US-540-5773 was a Phase 3, multi-national, randomized, open-label trial, which evaluated the safety and efficacy of 5 days versus 10 days of RDV in hospitalized patients with severe COVID-19. A total of 401 eligible subjects were randomized in a 1:1 ratio to receive RDV at a dose of 200 mg on Day 1, followed by 100 mg on Days 2-5 or Days 2-10 in single daily intravenous infusions. Treatment with RDV was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

Inclusion criteria specified that patients must be males or non-pregnant females ≥ 12 years of age who had laboratory-confirmed SARS-CoV-2 infection as determined by reverse transcription polymerase chain reaction (RT-PCR) assay. Additional inclusion criteria required radiographic evidence of pulmonary infiltrates and either $SpO_2 \leq 94\%$ on room air or a requirement for supplemental oxygen. Exclusion criteria disallowed enrollment of patients who required mechanical ventilation or ECMO[6], patients with signs of multi-organ failure, and patients with ALT or AST > 5 times the upper limit of normal or an estimated creatinine clearance < 50 mL/min.

The primary efficacy endpoint was clinical status assessed via a 7-point ordinal scale on Day 14 using a proportional odds model. The trial was designed to provide greater than 85% power to detect an odds ratio for improvement of 1.75, using a two-sided significance level of 0.05.

The ordinal scale consisted of the following categories:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (related or not to COVID-19)
6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than that specified in the protocol for RDV administration)
7. Not hospitalized

Exploratory end points included the time to clinical improvement (defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale), the time to recovery (defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7), the time to modified recovery (defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7), and death from any cause.

A total of 401 patients were randomized in a 1:1 ratio to the 5-day and 10-day RDV groups. The sponsor excluded 4 patients who were randomized but not treated, and the primary analysis set included 200 patients in the 5-day group and 197 patients in the 10-day group.

Baseline characteristics appeared relatively well balanced between treatment groups in terms of demographics and comorbidities. Patients in this trial had a median age of 61 years; 64% were male; 12% were Black, 12% were Asian, and 22% were Hispanic or Latino. In terms of baseline comorbidities, 22% of patients had diabetes, 22% had hyperlipidemia, 47% had hypertension, and 12% had asthma. Regarding baseline oxygen support status, a higher proportion of patients randomized to receive 10 days versus 5 days of RDV were receiving

[6] The exclusion criterion related to mechanical ventilation and ECMO was subsequently amended to allow enrollment of patients who were mechanically ventilated (including V-V ECMO) for < 5 days.

invasive mechanical ventilation or ECMO (5% vs. 2%, respectively) or were receiving non-invasive ventilation or high flow oxygen (30% vs. 25%, respectively).

After adjusting for between-group differences at baseline, subjects 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]). There were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups 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. Overall, results in this trial were suggestive of similar treatment effects with 5-day and 10-day regimens in this patient population.

It is possible that the open-label trial design influenced the differences in outcomes demonstrated in this trial, with numerical trends favoring the 5-day RDV group over the 10-day RDV group. Virtually all patients in the 5-day group received ≤5 days of therapy, while almost half of patients in the 10-day group received the full 10 days of therapy. Hence, discharge decisions may have been influenced by the patients' treatment assignment, which could potentially impact the overall results.

Additional limitations of this trial impacting its interpretability include its lack of a standard-of-care comparator group, high degree of imputed discharge outcomes for the primary endpoint, and the Applicant's submission of the statistical analysis plan following the release of trial results.

Trial 5774 (Sponsor: Gilead)

GS-US-540-5774 was a Phase 3, multi-national, randomized, open-label trial, which evaluated the safety and efficacy of 5 days versus 10 days of RDV compared to standard of care in hospitalized patients with moderate COVID-19. A total of 584 eligible subjects were randomized in a 1:1:1 ratio to receive standard of care or RDV at a dose of 200 mg on Day 1, followed by 100 mg on Days 2-5 or Days 2-10 in single daily intravenous infusions. Treatment with RDV was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

Inclusion criteria specified that patients must be males or non-pregnant females ≥ 12 years of age who had laboratory-confirmed SARS-CoV-2 infection as determined by reverse transcription polymerase chain reaction (RT-PCR) assay. Additional inclusion criteria required radiographic evidence of pulmonary infiltrates and an SpO_2 > 94% on room air at screening. Exclusion criteria disallowed enrollment of patients with ALT or AST > 5 times the upper limit of normal or an estimated creatinine clearance < 50 mL/min.

The primary efficacy endpoint was clinical status assessed via a 7-point ordinal scale on Day 11 using a proportional odds model. The trial was designed to provide greater than 85% power to detect an odds ratio of 1.8, using a two-sided significance level of 0.05 for comparing each RDV group to the standard of care group.

The ordinal scale consisted of the following categories:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (related or not to COVID-19)
6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than that specified in the protocol for RDV administration)
7. Not hospitalized

A total of 596 patients were randomized in a 1:1:1 ratio to the standard of care, 5-day and 10-day RDV groups. The primary analysis set of randomized and treated subjects included 200 patients in the standard of care group, 191 patients in the 5-day group and 193 patients in the 10-day group.

Baseline characteristics appeared relatively well balanced between treatment groups in terms of demographics and comorbidities. Patients in this trial had a median age of 57 years; 61% were male; 19% were Black, 19% were Asian, and 18% were Hispanic or Latino. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalization prior to first dose of RDV were similar across treatment groups.

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 standard of care (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 standard of care were not statistically significant (odds ratio 1.31; [95% CI 0.88 to 1.95]). All-cause mortality at Day 28 was ≤ 2% in all treatment groups.

Although this trial was by design a study of moderate COVID-19, it included a nontrivial fraction of patients (15%) who required some degree of oxygen supplementation at baseline. If efficacy was driven by results in these patients, this trial would provide less compelling supportive evidence for RDV as a treatment of moderate disease. However, subgroup results by baseline severity show that the RDV 5-day group appeared more effective than the standard of care group even when restricting to the moderate disease patients who required medical care without oxygen supplementation (odds ratio, 1.62; [95% CI, 1.02 to 2.56]).

It is possible that the open-label trial design influenced the differences in outcomes demonstrated in the RDV 5-day and RDV 10-day groups. Virtually all patients in the 5-day group received ≤5 days of therapy, while over a third of patients in the 10-day group received the full 10 days of therapy. Hence, discharge decisions may have been influenced by the patients' treatment assignment which could potentially impact the overall results.

Additional limitations of this trial were the high degree of imputed discharge outcomes for the primary endpoint, and the Applicant's submission of the statistical analysis plan following the release of trial results.

Conclusions on effectiveness

ACTT-1, with its rigorous trial design, large sample size, and broad patient population, provides the most objective assessment of efficacy, and is the key Phase 3 trial supporting the approval of RDV for the treatment of COVID-19 in patients requiring hospitalization. ACTT-1 demonstrated a highly statistically significant difference in the primary endpoint of time to recovery as well as the key secondary endpoint of odds of improvement at Day 15. These endpoints were prespecified in the Sponsor's statistical analysis plan (SAP) and agreed upon with the Agency. There was a numeric difference in mortality favoring RDV over placebo; however, this difference was not statistically significant.

The interpretability of Trial 5773 was limited by its open-label design and lack of a standard of care control arm. Nevertheless, its results were suggestive of a similar treatment effect with 5-day and 10-day regimens in the trial population studied (i.e., patients hospitalized and requiring supplemental oxygen but not mechanical ventilation or ECMO).

The interpretability of Trial 5774 was similarly limited by its open-label design; however, it did include a standard of care control arm and demonstrated a statistically significant difference in the odds of improvement at Day 11 for the 5-day (but not the 10-day) treatment group over standard of care. Overall, Trial 5774 provided supportive evidence for the efficacy of RDV in patients hospitalized with COVID-19 of moderate severity (i.e., patients hospitalized but not requiring supplemental oxygen).

Based on the totality of data, RDV will be approved for the treatment of patients with COVID-19 requiring hospitalization. The data support a 5 to 10-day treatment duration for hospitalized patients who do not require mechanical ventilation or ECMO. The flexibility in the recommendation regarding treatment duration reflects an attempt to balance efficacy and safety considerations. The limitations inherent in the design of Trial 5773 and 5774 preclude a definitive recommendation for a 5-day treatment course based on these trials; however, in Phase 1 trials in healthy patients, the risk of hepatic injury appears to strongly correlate with longer durations of treatment (see Section 8, Safety, for details). Adopting a flexible approach to the duration of treatment will allow providers more latitude in tailoring treatment for their patients. For hospitalized patients who require mechanical ventilation or ECMO, a treatment course of 10 days will be recommended. The paucity of patients enrolled into Trial 5773 who required mechanical ventilation or ECMO at baseline precludes the ability to recommend a treatment duration of RDV apart from that studied in ACTT-1 (i.e., 10 days).

8. Safety

This section will provide a summary of safety focusing on the Phase 3 trials. As detailed in Section 7 of this review, ACTT-1 was a multi-national, randomized, double-blind, placebo-controlled, Phase 3 trial. ACTT-1, with its rigorous trial design, provides a more objective assessment of safety than either Trial 5773 or 5774. The interpretability of Trial 5773 and 5774 is limited by their open-label design, and in the case of Trial 5773, the lack of a standard of care control arm; however, the salient safety findings from each of these trials will be

summarized. Additionally, safety findings from Phase 1 clinical trials in healthy subjects will be summarized as these trials provide the greatest insight into the hepatotoxicity signal of RDV. For a complete description of the Agency's safety assessment for RDV, please refer to the Clinical Review performed by Dr. Kirk Chan-Tack.

Adequacy of the safety database, Applicant's safety assessments, and submission quality

The safety database at the time of NDA submission included phase 3 clinical trial data from 1,313 hospitalized patients with COVID-19, phase 1 clinical trial data from 131 healthy adults, and data from subjects with COVID-19 who received RDV under the Emergency Use Authorization (EUA) or in a compassionate use program. The Agency deemed the safety database adequate to support the NDA.

The Sponsor provided a basic assessment of safety as a component of the NDA submission; however, additional requests for safety-related information and analyses were required to complete the review. No substantive issues with data integrity were identified.

Key safety results from the Phase 3 trials, including deaths, serious adverse events (SAEs), discontinuations due to AEs, and results of laboratory tests

ACTT-1

Please refer to Section 7 (Efficacy) for a description of the ACTT-1 trial design and patient demographics.

The mortality rate in ACTT-1 was higher in the placebo group (15%) compared to the RDV group (11%), and all deaths were assessed as unrelated to study drug by the study investigators.

The collection of adverse event data in this trial was limited to severe (Grade 3) or potentially life-threatening (Grade 4) adverse events, serious adverse events, adverse events leading to study drug discontinuation, and moderate (Grade 2) severity or higher hypersensitivity reactions. A summary of adverse reaction (ADR) rates in ACTT-1 is provided in Table 3. For the purpose of this section, ADRs are defined as adverse events judged related to study drug by the investigator.

Table 3: Summary of Adverse Reaction Rates in Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1

n (%)	**RDV (N=532)**	**Placebo (N=516)**
Adverse reactions, Grade ≥ 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), ALT increased and AST increased (n=1), GFR decreased (n=2), acute kidney injury (n=3).
Source: Draft USPI

A summary of laboratory abnormalities (≥ Grade 3) is provided in Table 4.

Table 4: Laboratory Abnormalities (Grades 3-4) Reported in ≥ 3% of Subjects Receiving RDV in 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%

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.
Source: Draft USPI

Trial 5773

Please refer to Section 7 (Efficacy) for a description of the trial design and patient demographics.

The mortality rate was comparable in the RDV 5-Day group (12%) and the RDV 10-Day group (14%), and all deaths were assessed as unrelated to study drug by the study investigators.

A summary of adverse reaction (ADR) rates in Trial 5773 is provided in Table 5. For the purpose of this section, ADRs are defined as adverse events judged related to study drug by the investigator. The most common adverse reactions occurring in at least 5% of subjects in either the RDV 5-day or 10-day group, respectively, were nausea (5% vs 3%), aspartate aminotransferase increased (3% vs 6%), and alanine aminotransferase increased (2% vs 7%).

Table 5: Summary of Adverse Reaction Rates in Subjects with Severe COVID-19 in Study 5773

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

a. Transaminases increased (n=3).
b. Transaminases increased (n=2), hepatic enzyme increased (n=1), hypertransaminasaemia (n=1).
c. Transaminases increased (n=4), hepatic enzyme increased (n=2), liver function test increased (n=2), hypertransaminasaemia (n=1), ALT increased (n=1), ALT increased and AST increased (n=2), injection site erythema (n=1), rash (n=1).

Source: Draft USPI

A summary of laboratory abnormalities (≥ Grade 3) is provided in Table 6.

Table 6: Laboratory Abnormalities (Grades 3-4) Reported in ≥ 3% of Subjects Receiving RDV in Trial 5773

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

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.

Source: Draft USPI

Trial 5774

Please refer to Section 7 (Efficacy) for a description of the trial design and patient demographics.

The mortality rates were low across all arms of the trial (1% in the RDV 5-Day and RDV 10-Day groups; 2% in the standard-of-care group), and all deaths were assessed as unrelated to study drug by the study investigators.

A summary of adverse reaction (ADR) rates in Trial 5774 is provided in Table 7. For the purpose of this section, ADRs are defined as adverse events judged related to study drug by the investigator. The most common adverse reaction occurring in at least 5% of subjects in the RDV groups was nausea (7% in the 5-day group, 4% in the 10-day group).

Table 7: Summary of Adverse Reaction[a] Rates in Subjects with Moderate COVID-19 in Study 5774

n (%)	RDV 5 Days (N=191)	RDV 10 Days (N=193)
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. ALT increased (n=2), ALT increased and AST increased (n=1), hypertransaminasaemia (n=1), blood alkaline phosphatase increased (n=1), rash (n=2), heart rate decreased (n=1)
Source: Draft USPI

A summary of laboratory abnormalities (≥ Grade 3) is provided in Table 8.

Table 8: Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Subjects Receiving RDV in Trial 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	2%	5%	8%
Glucose increased	4%	3%	2%
Hemoglobin decreased	3%	1%	6%

SOC=Standard of care.
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.
Source: Draft USPI

Submission-specific safety issues

Nephrotoxicity:

A renal safety signal was identified in nonclinical studies (see Section 4); however, no evidence of renal toxicity was demonstrated in early phase clinical trials in healthy volunteers. In ACTT-1, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were lower in the RDV group compared to the placebo group. Trial 5773 did demonstrate a higher rate of renal AEs and Grade 3/4 renal laboratory abnormalities in the 10-day group compared to the 5-day group; however, the open label design and lack of a standard of care group limited the interpretability of these findings. In GS-US-540-5774, the rates of renal AEs were low (~2%) in all groups. Rates of Grade 3/4 renal laboratory abnormalities were higher in the 10-day RDV group compared to the 5-day RDV group; however, rates of Grade 3/4 renal laboratory abnormalities were higher in the standard of care group than in either RDV group.

Based on our review of the available data, no clear renal safety signal was apparent in either healthy volunteers or COVID-19 patients. The nonclinical renal findings will be described in the PI and routine pharmacovigilance will be in place to detect post-marketing safety signals.

Hepatotoxicity:

A hepatic safety signal, manifested as transaminase elevations, was demonstrated in Study GS-US-399-1954, a Phase 1 multi-dose trial in healthy subjects. Subjects received either 7 or 14 days of RDV at a daily dose of 150 mg via IV infusion. The preliminary safety results demonstrated transaminase elevations in 2 of 8 healthy subjects in the 7-day cohort and 6 of 8 subjects in the 14-day cohort. Alanine Aminotransferase (ALT) elevations were up to 10 times the subjects' baseline values. The onset of these adverse events (AEs) occurred as early as day 5 in subjects. Notably, there was no associated increase in bilirubin, and transaminase elevations resolved in all subjects during follow-up. These findings lead to the institution of a partial clinical hold in March 2016.

A multi-dose trial, GS-US-399-5505, was subsequently performed in healthy subjects to assess the safety and PK of an RDV regimen consisting of a 200 mg loading dose followed by 100 mg daily IV infusions for a total duration of 5 or 10 days. No graded increases in ALT were reported in the 5-day cohort which consisted of 9 subjects receiving RDV and 2 subjects receiving placebo; however, a trend towards increasing ALT in the RDV group was noted. In the 10 day-cohort, graded increases in ALT were reported in 9 of 20 subjects in the RDV group and 0 of 5 subjects in the placebo group. The ALT elevations in the nine subjects were Grade 1 (8/9) or Grade 2 (1/9) in severity, were asymptomatic, and resolved in all subjects during follow-up. The mechanism of hepatotoxicity of RDV is currently unknown.

Hepatic safety data from trials in COVID-19 are difficult to evaluate as hepatic injury is a common feature of COVID-19. In ACTT-1, Trial 5773, and Trial 5774, no clear evidence of a hepatic safety signal based on adverse reactions or laboratory indices was demonstrated; however, the underlying disease may have limited the ability to discriminate a safety signal.

Given the findings in the Phase 1 trials, a warning for hepatotoxicity will be included in the PI to assist in risk mitigation (see Section 12). The warning will include a recommendation to perform hepatic laboratory testing on all patients before starting RDV and while receiving RDV as clinically appropriate. Recommendations will also be provided to consider discontinuing RDV if ALT levels increase to greater than 10 times the upper limit of normal and to discontinue RDV if ALT elevation is accompanied by signs or symptoms of liver inflammation.

Hypersensitivity Reactions

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, were reported during and following administration of RDV in clinical trials and under the EUA. Signs and symptoms included hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. A

warning related to hypersensitivity reactions will be included in the PI to assist in risk mitigation (see Section 12).

Prothrombin time (PT) elevation:

In the Phase 3 ACTT-1 trial, a disproportionate percentage of PT elevations occurred in the RDV group as compared to the placebo group. As subjects may benefit from closer monitoring of coagulation parameters while receiving RDV, the PI will include a recommendation to determine PT in all patients prior to starting RDV and to monitor PT as clinically appropriate (see Section 12). No increased risk of clinically significant hemorrhagic adverse events was detected in clinical trials.

9. Advisory Committee Meeting

As there were no issues identified that would benefit from discussion by an Advisory Committee, an Advisory Committee was not convened for this application.

10. Pediatrics

The Applicant submitted an initial Pediatric Study Plan (iPSP) for RDV in advance of the NDA submission. The document was reviewed by the Division of Pediatrics and Maternal Health (DPMH), the Division of Antivirals, and the Pediatric Review Committee (PeRC). The Agency's recommendations for revisions were conveyed to the Applicant. The Applicant accepted the Agency's recommendations, and the Agency issued a formal notice of agreement in July 2020.

The proposed pediatric development plan comprises a broad range of pediatric patients including the following: 1) preterm neonates and infants 0 days to < 56 days old; 2) term neonates 0 days to < 28 days old and; 3) pediatric patients ≥ 28 days to < 18 years old. Patients in all age ranges will be enrolled in parallel, except for preterm neonates and infants < 56 days old and a subset of term neonates. At the time of this review, the pediatric clinical trial (based on the plan outlined in the iPSP) is ongoing.

The initial indication will include patients 12 years of age and older and weighing at least 40 kg. The inclusion of this pediatric sub-population in the indication is supported by the following: 1) the systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after accounting for the effect of body size on pharmacokinetics;[7] 2) using physiologically-based pharmacokinetic (PBPK) modeling and population pharmacokinetic (popPK) modeling, the to-be-marketed dosing regimen is expected to result in comparable steady-state plasma exposures of RDV and metabolites in patients 12 years of age and older and weighing at least 40 kg as observed in healthy adults; 3) the safety profile in adult subjects

[7] Momper JD, Mulugeta Y, Green DJ, et al. Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. *JAMA Pediatr*. 2013;167(10):926-932. doi:10.1001/jamapediatrics.2013.465

weighing 40-50 kg in clinical trials is comparable to adult subjects weighing greater than 50 kg and; 4) thirty-nine pediatric patients 12 years and older and weighing at least 40 kg received RDV in a compassionate use program; however, the available clinical data from these patients are limited. Importantly, confirmatory PK and safety information will be collected in patients 12 to 17 years of age in the ongoing RDV pediatric trial.

Due to limitations of the current PBPK and popPK models and the absence of PK data in the pediatric population, the initial indication for RDV will not include pediatric patients younger than 12 years of age or weighing < 40 kg. The Applicant requested, and the Agency granted, a deferral of pediatric studies for patients younger than 18 years of age or weighing < 40 kg on the basis that the drug is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act). A pediatric clinical trial which will enroll children across a broad age range is currently ongoing.

11. Other Relevant Regulatory Issues

- *Financial disclosures*

Financial disclosures were provided and reviewed for investigators involved in ACTT-1, GS-US-540-5773, and GS-US-540-5774. There were no financial disclosures of significant concern, individually or collectively. Please refer to the Clinical Review for additional details.

- *Other Good Clinical Practice (GCP) issues*

The clinical trials discussed in this review were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

- *Office of Scientific Investigations (OSI) audits*

Inspection sites were selected from the pivotal trial, ACTT-1, as well as the supportive Phase 3 trials, GS-US-540-5773 and GS-US-540-5774. Five U.S. sites were selected. Three of the sites enrolled participants exclusively in ACTT-1; the two other sites enrolled participants in both GS-US-540-5773 and GS-US-540-5774. These sites were chosen based on the enrollment of large numbers of trial participants. In addition to the inspection of the clinical sites, the sponsors of the Phase 3 clinical trials (NIAID for ACTT-1; Gilead Sciences, Inc. for GS-US-540-5773 and GS-US-540-5774) were also inspected.

Per OSI's assessment, the deviations noted at the clinical sites were infrequent, generally minor, and would not have significant impact on safety or efficacy considerations; therefore, the data generated by these sites and submitted by the Applicant appeared acceptable to support the application. Similarly, the inspection of NIAID and Gilead Sciences, Inc. did not produce any findings that would impact the integrity or interpretability of the clinical trials' data.

Please refer to the OSI Consult Review for further details.

12. Labeling

Prescribing Information

The summary that follows reflects the major changes to the prescribing information (PI) that have been proposed by the Agency and accepted by the Applicant. Please refer to the individual FDA reviews from each of the review disciplines for additional details.

- INDICATIONS AND USAGE section:

The indication for Veklury [redacted] (b) (4) to one consistent with the hospitalized patient population studied in the Phase 3 trials supporting the NDA (ACTT-1, GS-US-540-5773, and GS-US-540-5774). [redacted] (b) (4)

The INDICATIONS and USAGE section will include the following language: Veklury is indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

Patients determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) capable of providing acute care comparable to inpatient hospital care are within the scope of the indication. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19. Skilled nursing facilities, long-term care facilities, or other similar healthcare settings not meeting the criteria above remain outside the scope of the indication.

- DOSAGE AND ADMINISTRATION section

Given the disproportionately higher rates of prothrombin time (PT) elevations with RDV compared to placebo in ACTT-1, the PI will recommend that PT be determined in all patients prior to starting RDV and monitored while receiving RDV as clinically appropriate (see Section 8).

- CONTRAINDICATIONS section

RDV will be contraindicated for patients with a history of clinically significant hypersensitivity reactions to RDV or any components of the product (see Section 8).

- WARNINGS AND PRECAUTIONS section

Warnings will be included in the PI to describe the hepatotoxicity and hypersensitivity safety signals and to provide recommendations for management (see Section 8).

A warning will be included in the PI recommending against the concomitant use of RDV with chloroquine or hydroxychloroquine due to the risk of reducing RDV's antiviral activity (see Section 5).

- ADVERSE REACTIONS section:

In accordance with FDA guidance, the listing of adverse events was limited to those events for which there was at least a possible causal relationship with the drug (i.e., adverse reactions).

A section titled "Less Common Adverse Reactions" was added to include information about less common, but still clinically significant, adverse reactions observed in clinical trials

A section titled "Emergency Use Authorization Experience in Patients with COVID-19" was added to include information about adverse reactions reported under the EUA.

- USE IN SPECIFIC POPULATIONS section

The available data supporting the indication for pediatric patients ≥ 12 years of age and ≥ 40 kg was described (see Section 10).

Statements were included indicating that the pharmacokinetics of RDV have not been evaluated in patients with renal or hepatic impairment

- CLINICAL STUDIES section:

(b) (4)

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Based on the overall safety profile of RDV, a REMS is not recommended.

Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

To date, the Agency has determined that the following PMRs and PMCs should be issued:

- PMR to assess safety, pharmacokinetics, and efficacy of RDV in pediatric subjects ages 0 to < 18 years of age with COVID-19
- PMR to evaluate the pharmacokinetics and safety of RDV in subjects with moderate and severe hepatic impairment to inform appropriate dosage recommendations in patients with COVID-19 with impaired hepatic function

- PMR to evaluate the pharmacokinetics and safety of RDV in subjects with mild, moderate, and severe renal impairment to inform appropriate dosage recommendations in patients with COVID-19 with impaired renal function
- PMR to conduct a thorough QT study to evaluate the effect of RDV on the QTc interval.
- PMR to conduct a drug interaction trial to evaluate the pharmacokinetics of RDV when coadministered with rifampin
- PMR to conduct a study to select for RDV resistant SARS-CoV-2 variants in cell culture and characterize several independent isolates phenotypically and genotypically
- PMR to submit all SARS-CoV-2 viral shedding and viral load data from ACTT-1, GS-540-5773, and GS-US-5774 assessing RDV including quantitation of viral shedding and viral load for any subject samples that have not been completed to date
- PMC to submit all sequencing data from ACTT-1, GS-540-5773, and GS-US-5774 assessing RDV including sequencing of any subject samples that have not been completed to date
- PMC to submit a comprehensive resistance study reports from ACTT-1, GS-US-540-5773, and GS-54-5774 describing all resistance assessments performed for RDV
- PMC to submit a complete study report for the assessment of the antagonistic effect of chloroquine/hydroxychloroquine on the antiviral activity of RDV against SARS-CoV-2 in human lung cells
- PMC to conduct a study to evaluate the pharmacokinetics and safety of RDV in pregnant individuals with COVID-19
- PMC to submit the remdesivir drug substance batch release data for two additional registration batches manufactured at (b) (4)
- PMC to submit the remedesivir drug substance stability data for batches manufactured at (b) (4) and (b) (4)
- PMC to submit the drug product batch release data for drug product manufactured with remdesivir drug substance from (b) (4) and (b) (4)
- PMC to submit additional stability data for drug product manufactured on different lines at the manufacturing sites listed in the NDA
- PMC to submit additional stability data for drug product manufactured with different stoppers listed in the NDA
- PMC to evaluate the leachables data at multiple time points through expiry for both remdesivir for injection and remdesivir injection
- PMC to evaluate the stability data for remdesivir injection at pH (b) (4)

14. Recommended Comments to the Applicant

There are no additional comments to be conveyed to the Applicant at this time.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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