JOINT CDTL, CLINICAL, CLINICAL VIROLOGY, CLINICAL PHARMACOLOGY, STATISTICS, AND DIVISION DIRECTOR REVIEW

Application Type	Supplemental New Drug Application (sNDA), S-10
Application Number(s)	214787
Priority or Standard	Priority
Submit Date(s)	October 21, 2021
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Division/Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)	Division of Antivirals Yodit Belew, MD, Associate Director for Therapeutics Kimberly Struble, PharmD, CDTL Kirk Chan-Tack, MD, Medical Officer William Ince, PhD, Virology Reviewer Jules O'Rear, PhD, Virology Team Leader Division of Biometrics IV/Office of Biostatistics Daniel Rubin, PhD, Statistics Reviewer Thamban Valappil, PhD, Statistics Team Leader Dionne Price, PhD, Deputy Director of the Office of Biostatistics Division of Infectious Disease Pharmacology /Office of Clinical Pharmacology/Office of Translational Sciences Mario Sampson, PharmD, Clinical Pharmacology Reviewer Vikram Arya, PhD, Associate Director for Therapeutic Review
Review Completion Date	January 14, 2022
Established Name	Remdesivir (RDV)
(Proposed) Trade Name	Veklury®
Applicant	Gilead Sciences, Inc.
Formulation(s)	Lyophilized formulation for injection, 100 mg Solution formulation for injection, 5 mg/mL
Dosing Regimen	Single intravenous (IV) loading dose of remdesivir 200 mg on Day 1, followed by 100 mg IV once-daily maintenance doses on Days 2 and 3, for a total of 3 days of dosing
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are: • Nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death • Hospitalized for COVID-19

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Glossary

AE	adverse event
ACTT-1	adaptive COVID-19 treatment trial 1
ADR	adverse drug reaction
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CG	Cockcroft-Gault
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CQ	chloroquine
CrCl	creatinine clearance
CUP	compassionate use program
DAIDS	Division of AIDS
EAP	expanded access program
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	health care provider
HCQ	hydroxychloroquine
IDMC	independent data monitoring committee
IMV	invasive mechanical ventilation
IUFD	intrauterine fetal demise
IV	intravenous
IVDU	intravenous drug use
MAV	medically attended visit
NDA	new drug application
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PBO	placebo
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PT	prothrombin time
RdRp	RNA-dependent RNA polymerase
RDV	remdesivir
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set

sNDA	supplemental new drug application
SNF	skilled nursing facility
SOC	system organ class
U.S.	United States
VOC	variant of concern
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Veklury® (remdesivir, 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 ribonucleic acid (RNA) synthesis. Veklury is approved for use in 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. For this hospitalized patient population, the recommended dosage is a single loading dose of Veklury 200 mg on Day 1 via intravenous (IV) infusion followed by once-daily maintenance doses of Veklury 100 mg from Day 2 via IV infusion.

- The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation (IMV) and/or extracorporeal membrane oxygenation (ECMO) is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
- The recommended total treatment duration for hospitalized patients requiring IMV and/or ECMO is 10 days.

In this supplemental new drug application (sNDA), the Applicant's proposed indication is (b) (4)

- The Applicant's recommended dosage for nonhospitalized patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who are at high risk for progression to COVID-19, including hospitalization or death, is a single loading dose of Veklury 200 mg on Day 1 via IV infusion followed by once-daily maintenance doses of Veklury 100 mg on Days 2 and 3 via IV infusion.
- The Applicant's recommended total treatment duration for nonhospitalized patients with confirmed SARS-CoV-2 infection who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from the GS-US-540-9012 Phase 3 trial included in this application provides substantial evidence of effectiveness as required by law 21 Code of Federal Regulations (CFR) 314.126(a)(b) to support approval of RDV for treatment of nonhospitalized adults and pediatric patients 12 years of age and older and weighing at least 40 kg with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

In Study GS-US-540-9012, treatment with RDV for 3 days was superior to placebo (PBO) for the primary endpoint which is a composite of COVID-19-related hospitalization or all-cause mortality through Day 28. Of the 562 nonhospitalized subjects who are at high risk for

progression to severe COVID-19, two (1%) subjects in the RDV group experienced COVID-19-related hospitalizations compared to 15 (5%) subjects in the PBO group (hazard ratio 0.13 [95% confidence interval (CI): 0.03 to 0.59]; p=0.008). No deaths were observed through Day 28 in either group. These data support use of RDV for the treatment of COVID-19 in nonhospitalized adults and pediatric patients 12 years of age and older and weighing at least 40 kg with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

Cumulatively, data from the Study GS-US-540-9012 Phase 3 trial included in this sNDA support use of RDV for treatment of nonhospitalized adults and pediatric patients 12 years of age and older and weighing at least 40 kg with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Remdesivir (RDV) is an intravenous (IV) antiviral drug approved for use in 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. 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 ribonucleic acid (RNA) synthesis.

COVID-19 is a potentially serious or life-threatening disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. Globally, according to the World Health Organization, 281,808,270 confirmed cases of COVID-19 have been reported as of December 29, 2021, including 5,411,759 deaths. In the United States, according to the Centers for Disease Control and Prevention, approximately 53,795,407 cases of COVID-19 have been reported with 820,355 deaths as of December 29, 2021. RDV is currently the only approved treatment for COVID-19.

In this supplemental new drug application (sNDA), the Applicant's proposed indication is (b) (4) . The Applicant's proposed expansion of the indication is based on the results from Study GS-US-540-9012, a Phase 3 randomized, double-blind, placebo- (PBO-) controlled clinical trial which evaluated 562 nonhospitalized adult and adolescent subjects with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. Treatment with RDV for 3 days was superior to PBO for the primary endpoint which is a composite of COVID-19-related hospitalization or all-cause mortality through Day 28. Overall, two (1%) subjects in the RDV group experienced COVID-19-related hospitalizations compared to 15 (5%) subjects in the PBO group (hazard ratio 0.13 [95% confidence interval: 0.03 to 0.59]; p=0.008). No deaths were observed through Day 28 in either group. These data support RDV for treatment of mild-to-moderate COVID-19 in nonhospitalized adult and adolescent subjects who are at high risk for progression to severe COVID-19, including hospitalization or death.

The overall safety profile in nonhospitalized subjects is consistent with the known safety profile of RDV. Nausea was the most commonly reported adverse drug reaction.

In Study GS-US-540-9012, higher rates of creatinine elevations and decreases in creatinine clearance occurred with RDV compared to PBO. This information will be described in labeling. Of note, at the time of the original NDA approval, the labeling outlines that renal function should be determined before starting RDV and monitored while receiving RDV.

Approval of RDV for treatment of nonhospitalized adults and pediatric patients (≥12 years of age and weighing ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is supported by the available efficacy and safety data. The recommended dosage is a single loading dose of RDV 200 mg on Day 1 via IV infusion followed by once-daily maintenance doses of RDV 100 mg on Days 2 and 3 via IV infusion.

Table 1. Benefit-Risk Framework

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td><u>Analysis of Condition</u></td><td>• Coronavirus disease 2019 (COVID-19) is a potentially serious or life-threatening disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 can cause severe disease which can result in pneumonia, respiratory failure, multi-organ failure, and death.
• Globally, 281,808,270 confirmed cases of COVID-19 have been reported as of December 29, 2021, including 53,795,407 people in the United States.
• Globally, 5,411,759 deaths due to COVID-19 have been reported as December 29, 2021, including 820,355 deaths in the United States.</td><td>The ongoing COVID-19 pandemic is a significant and ongoing public health concern, one that affects a large population in the United States and worldwide. When infected with SARS-CoV-2, patients can experience symptoms that are severe, debilitating, and can be fatal.</td></tr>
<tr><td><u>Current Treatment Options</u></td><td>• There are no approved COVID-19 treatments for nonhospitalized patients.
• The following products are authorized for emergency use for the treatment of mild-to-moderate COVID-19 in the following nonhospitalized patient populations:
<table>
<tr><th>Patient Population</th><th>Emergency Use Authorization</th></tr>
<tr><td>Adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death</td><td>Paxlovid
Sotrovimab
Casirivimab and imdevimab</td></tr>
<tr><td>Adults and pediatric patients, including neonates, with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death</td><td>Bamlanivimab and etesevimab</td></tr>
<tr><td>Adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options authorized by the U.S. Food and Drug Administration are not accessible or clinically appropriate</td><td>Molnupiravir</td></tr>
</table>
• Due to the mortality and severe morbidity associated with COVID-19, there is an urgent need to develop effective treatments.</td><td>An unmet medical need exists for effective antiviral regimens for nonhospitalized patients who develop COVID-19.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of remdesivir (RDV) in nonhospitalized adult and adolescent subjects was established in a Phase 3 clinical trial which evaluated 562 subjects. – Study GS-US-540-9012: Randomized, double-blind, placebo- (PBO-) controlled, multicenter trial assessing the safety and efficacy of 3 days of intravenous RDV for the treatment of unvaccinated, nonhospitalized subjects with COVID-19, with risk factors for progression to severe disease. • The primary efficacy endpoint was COVID-19-related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28. • Treatment with RDV for 3 days was significantly superior to PBO for the primary endpoint which is a composite of COVID-19-related hospitalization or all-cause mortality through Day 28. Overall, two (1%) subjects in the RDV group experienced COVID-19-related hospitalizations compared to 15 (5%) subjects in the PBO group (hazard ratio 0.13 [95% confidence interval: 0.03 to 0.59]; p=0.008). No deaths were observed through Day 28 in either group. Overall, results from this randomized, double-blind, PBO-controlled trial provided reliable and statistically persuasive evidence of benefit for RDV for the treatment of nonhospitalized adult and adolescent subjects with mild-to-moderate COVID-19 who are at high risk for progression to severe disease, including hospitalization or death. • Overall, demographic factors did not impact efficacy outcomes in these trials.	The clinical trial provides substantial evidence of effectiveness for RDV, administered for3 days for treatment of nonhospitalized adult and pediatric patients (≥12 years and ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. RDV fills an important unmet medical need for nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.
Risk	• The safety database for RDV includes 279 subjects from the aforementioned clinical trial and is considered adequate; the obseved safety profile during Study GS-US-540-9012 is consistent with the known safety profile of RDV. • The overall safety pool from other registrational trials encompasses 1,313 hospitalized adult subjects with COVID-19 treated with 5 to 10 days of RDV. • The safety of RDV in Study GS-US-540-9012 was compared to PBO. • The safety assessment of RDV when administed outside of health care facilities is constrained due to limited available data; only 44 subjects received RDV via home health, and only eight subjects received RDV at a skilled nursing facility. – The safety of RDV in subjects who received RDV in the home health setting was overall comparable to subjects who received RDV at an outpatient facility, but the assessment is based on limited data. • Nausea was the most commonly reported adverse drug reaction (ADR) reported in the trial. All other ADRs occurred at similar or lower rates compared to PBO.	RDV demonstrated an overall favorable safety profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The RDV prescribing information will include the following safety information: – Section 5 of the approved RDV labeling includes a warning regarding the risk of hypersensitivity reactions, including infusion-related and anaphylactic reactions, and recommends postinfusion monitoring as part of the risk mitigation strategy. This warning was revised to describe that most of these events occurred within one hour postinfusion and specifies the recommended duration of at least one-hour postinfusion. – In Study GS-US-540-9012, higher rates of creatinine elevations and decreases in creatinine clearance occurred in RDV-treated subjects compared to PBO-treated subjects. This information will be described in labeling. Of note, at the time of the original NDA approval, the labeling outlines that renal function should be determined before starting RDV and monitored while receiving RDV.	Safety concerns associated with RDV will be adequately addressed in product labeling.

1.4. Patient Experience Data

Table 2 contains a summary of patient experience data relevant to this application.

Table 2. Patient Experience Data Relevant to This Application

√	The patient experience data that were submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient-reported outcome (PRO)	
		□	Observer-reported outcome (ObsRO)	
		□	Clinician-reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	√	Other: (Expanded Access)		8.8.2, 8.8.3
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data were not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

COVID-19 can result in pneumonia, respiratory failure, multi-organ failure, and death (Berlin et al. 2020; Gandhi et al. 2020; Puelles et al. 2020; Centers for Disease Control and Prevention 2021a; Centers for Disease Control and Prevention 2021b; Centers for Disease Control and Prevention 2022; World Health Organization 2022).

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Globally, according to the WHO, 281,808,270 confirmed cases of COVID-19 have been reported as of December 29, 2021, including 5,411,759 deaths (World Health Organization 2022). In the United States, according to the Centers for Disease Control and Prevention,

approximately 53,795,407 cases of COVID-19 have been reported with 820,355 deaths as of December 29, 2021 (Centers for Disease Control and Prevention 2022).

Patients with symptomatic SARS-CoV-2 infection, or COVID-19, can experience a wide range of clinical manifestations. Mild illness is defined by the presence of symptoms without shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe and critical illness are defined as worsening pulmonary status requiring hospitalization, supplemental oxygen, noninvasive ventilation, high-flow oxygen devices, IMV, or ECMO.

The progression of SARS-CoV-2 infection to severe COVID-19 can occur in adults of any age, but the risk increases with age. Per the Centers for Disease Control and Prevention, over 80% of COVID-19 deaths occur in adults aged 65 years and older, and more than 95% of COVID-19 deaths occur in adults aged 45 years and older. Irrespective of age, certain underlying comorbidities or conditions, including but not limited to cancer, chronic kidney disease, chronic lung disease, obesity, diabetes, pregnancy, and immunocompromised states, increase the risk for progression to severe COVID-19. People who have experienced long-standing systemic health and social inequities, such as many racial and ethnic minorities and those with disabilities, are also at increased risk of worse outcomes (Centers for Disease Control and Prevention 2021b).

There are currently no approved therapies for treatment of COVID-19 in nonhospitalized patients who are at high risk for progression to severe COVID-19, including hospitalization or death (COVID-19 Treatment Guidelines Panel 2021; Feburary 2021; Bhimraj et al. 2022). RDV would provide an approved antiviral drug to address this unmet medical need.

2.2. Analysis of Current Treatment Options

RDV is currently the only approved antiviral treatment regimen for COVID-19 caused by SARS-CoV-2. Approved on October 22, 2020, RDV is indicated for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization (Gilead Sciences 2021b). The original NDA approval is based on efficacy and safety data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19 treated with 5 to 10 days of RDV (Beigel et al. 2020; Goldman et al. 2020; Spinner et al. 2020). At the time of this review, RDV remains authorized for emergency use for treating suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg (Hinton 2020).

There are other COVID-19 treatments authorized for emergency use (COVID-19 Treatment Guidelines Panel 2021). Baricitinib, a Janus kinase inhibitor, is authorized for emergency use for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplementary oxygen, IMV, or ECMO (Eli Lilly and Company 2021b). Tocilizumab, an interleukin-6 inhibitor, is authorized for emergency use for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age and older who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO (Genentech 2021).

Several monoclonal antibodies are currently authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Casirivimab 1200 mg and imdevimab 1200 mg were authorized to be administered together on November 21, 2020 (Regeneron Pharmaceuticals 2021). Bamlanivimab 700 mg and etesevimab 1400 mg were authorized to be administered together on February 9, 2021 (Eli Lilly and Company 2021a). Of note, bamlanivimab 700 mg as monotherapy was authorized for emergency use on November 9, 2020, and was subsequently revoked on April 16, 2021, due to a sustained increase in variants resistant to bamlanivimab alone resulting in the increased risk for treatment failure. Sotrovimab (500 mg) was authorized on May 26, 2021 (GlaxoSmithKline 2021).

Of note, on December 3, 2021, bamlanivimab 700 mg and etesevimab 1400 mg Emergency Use Authorization (EUA) was expanded to include treatment of mild-to-moderate COVID-19 in adults and pediatric patients, including neonates, with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death (Eli Lilly and Company 2021a).

There are two oral drugs authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adults. Paxlovid is authorized for adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid (300 mg [i.e., two 150-mg tablets] of nirmatrelvir with one 100-mg tablet of ritonavir, given twice daily for 5 days) was authorized on December 22, 2021 (Pfizer 2021). Molnupiravir (800 mg [i.e., four 200 mg capsules] twice daily for 5 days) is authorized for adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options authorized by the U.S. Food and Drug Administration (FDA) are not accessible or clinically appropriate. Molnupiravir was authorized on December 23, 2021 (Merck & Co 2021).

On December 23, 2021, the National Institutes of Health COVID-19 Treatment Guidelines issued a statement that the Omicron (B.1.1.529) variant of concern (VOC) has become the dominant variant in many parts of the United States. The Panel outlined that, the Omicron variant, which includes numerous mutations in the spike protein, is predicted to have markedly reduced susceptibility to several anti-SARS-CoV-2 monoclonal antibodies (mAbs), especially bamlanivimab plus etesevimab and casirivimab plus imdevimab. The Panel noted sotrovimab appears to retain activity against the Omicron variant. The Panel stated that, with the rapid rise in the prevalence of the Omicron VOC, it is anticipated there will be a limited supply of therapeutic agents that are active against the Omicron variant (e.g., the anti-SARS-CoV-2 mAb sotrovimab and small molecule antiviral agents, Paxlovid and molnupiravir) for patients who are at high risk of progression to severe COVID-19 and who might benefit from these therapies. The Panel described Study GS-US-540-9012 topline results and noted RDV is expected to be active against the Omicron VOC (COVID-19 Treatment Guidelines Panel 2021).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

RDV was first approved on October 22, 2020, for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization (Gilead Sciences 2021b).

3.2. Summary of Presubmission/Submission Regulatory Activity

This section summarizes and focuses only on the notable events that directly impacted this RDV sNDA. The clinical protocol and development plan were reviewed by the Division of Antivirals throughout the RDV development program, with feedback provided regarding issues of efficacy endpoints, dose selection, treatment duration, treatment regimen, and clinical trial population. The final Phase 3 protocol design later submitted to the Division of Antivirals was determined to be acceptable.

The Applicant submitted this sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate, and the material was reviewable as submitted. According to the applicant, the pivotal trial was conducted in conformance with Good Clinical Practice (GCP) standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. These standards are consistent with the requirements of the U.S. CFR Title 21, Part 312 (21CFR312).

3.3. Foreign Regulatory Actions and Marketing History

At the time this review was finalized, RDV is approved in the following countries:

Table 3. Summary of Foreign Regulatory Actions

Country	COVID-19 Patient Population
European Economic Area[1], Argentina, Australia, Brazil, Canada, Great Britain[2], Israel, Switzerland	Treatment of adults and adolescents (≥12 years with body weight ≥40 kg) with pneumonia requiring supplemental oxygen
Hong Kong, India, Iraq, Japan, Lebanon, United Arab Emirates	Treatment of SARS-CoV-2 infection in adults and pediatric population with body weight ≥40 kg and in pediatric population with body weight between 3.5 kg and <40 kg
Russia	Treatment of adults with pneumonia requiring supplemental oxygen
Singapore	Treatment of SARS-CoV-2 infection in adult patients with SpO_2≤94% on room air, or those requiring oxygen inhalation, under IMV, or under ECMO

Country	COVID-19 Patient Population
South Korea, Taiwan	Treatment of patients[3] with COVID-19 confirmed by PCR test; hospitalized patients[3] with severe disease following at least one condition among below: SpO_2≤94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation or requiring ECMO

Source: Development Safety Update Report 6 (reporting period: August 7, 2020 – May 6, 2021)
[1] Includes Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom (Northern Ireland).
[2] Includes England, Wales, and Scotland.
[3] Adults and pediatric population with body weight ≥40 kg and in pediatric population with body weight between 3.5 kg and <40 kg
Abbreviations: ECMO, extracorporeal membrane oxygenation: IMV, invasive mechanical ventilation; SpO_2, oxygen saturation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Three sites were selected from the large number of GS-US-540-9012 sites based on enrollment. All selected sites for inspection were domestic, based on logistical considerations during the ongoing pandemic and 94% of subjects were enrolled in the United States. The three sites comprised approximately 20% of all enrollment in the trial.

The final reports from the clinical site inspections were completed. Per Office of Scientific Investigations (OSI) 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. Please refer to the OSI consult review for further details.

4.2. Clinical Microbiology

4.2.1. Nonclinical Virology

RDV is a nucleotide prodrug that is intracellularly metabolized into its active form GS-443902, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis. Key nonclinical and clinical virology characteristics, including mechanism of action, antiviral activity, and resistance mechanisms in cell culture have been reviewed and described previously (refer to the clinical virology review of the original NDA by E. Donaldson, PhD, reference ID in DARRTS: 4672246).

Biochemical studies have demonstrated that the nucleoside triphosphate GS-443902 acts as an analog of ATP and competes with the natural ATP substrate to selectively inhibit viral RNA-dependent RNA polymerase (RdRp) by two mechanisms. One mechanism of inhibition is the incorporation of the nucleoside triphosphate GS-443902 into nascent RNA chains by RdRp,

which results in delayed (position i+3) RNA chain termination and inhibition of viral RNA replication (Gordon et al. 2020a; Gordon et al. 2020b). A secondary mechanism of viral replication inhibition is template-dependent inhibition of RdRp due to hindered incorporation of uracil triphosphate that would be complementary to GS-443902 incorporated into the template RNA; however, this may also lead to misincorporation of a complementary nucleotide and mutagenesis of the second strand (Tchesnokov et al. 2020).

Cell culture antiviral activity for RDV against SARS-CoV-2 Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Epsilon (B.1.429) variants has been evaluated. In plaque reduction assays against authentic virus in Vero-TMPRSS2 cells, fold-changes in RDV EC_{50} values relative to the wild type (WA1) reference strain for Delta and Epsilon variants were 0.5 and 0.4, respectively. In an antinucleoprotein ELISA assay against authentic virus in A549-ACE2-TMPRSS2 cells, the fold-changes in RDV EC_{50} values relative to the reference WA1 strain against Alpha, Beta, Gamma, and Delta virus were 1.5-, 1.0-, 0.7-, and 0.4-fold, respectively (refer to the clinical virology review for NDA 214787, supplement 9 (SDN 182) by E. Donaldson, PhD, reference ID in DARRTS: 4916770).

Preliminary antiviral activity of RDV and GS-441524 against a representative of the Omicron variant has been evaluated along with representative Alpha, Beta, Gamma, and Delta variants in an authentic virus inhibition assay in Vero E6 cells. The preliminary data indicate that RDV and GS-441524 retain activity against each variant evaluated (EC_{50} value range: 0.048 to 0.077μM). While a wild type control virus was not included in the reported results, EC_{50} values against Omicron were within 2-fold those of variants previously evaluated, which have been shown to be susceptible relative to wild type (WA1). The nsp12 gene of Omicron is commonly distinguished from wild type virus (WA1) by a single substitution, P323L, which is also shared by other variants that have been evaluated and which does not appear to impact RDV activity in cell culture. Together, these data indicate that RDV is not expected to have reduced activity against the evaluated variants in cell culture, including Delta and Omicron variants (refer to the clinical virology review for NDA 214787, supplement 10 (SDN 190) by W. Ince, PhD, reference ID in DARRTS: 4920462).

4.2.2. Clinical Virology

Clinical virology data from Study GS-US-540-9012 submitted to support this supplement include longitudinal quantitative nasopharyngeal viral RNA data and preliminary baseline and postbaseline sequence data for subjects who progressed to COVID-19-related hospitalization or all-cause death by Day 28 (primary endpoint) or who had evaluable viral RNA at Day 14.

Of the 562 subjects included in the full analysis set (FAS), a total of 431 subjects were included in the Virology Analysis Set [RDV (n=217); PBO (n=214)], which included all subjects who (1) were randomized into the study, (2) received at least one dose of study treatment, and (3) were SARS-CoV-2 viral RNA positive at baseline based on the central lab assay (result of “No SARS-CoV-2 detected” was considered negative; results of “Inconclusive,” “<2228 copies/mL SARS-CoV-2 detected,” and numerical results were considered positive). (For additional details regarding methodology and analyses, refer to the clinical virology review for NDA 214787, supplement 10 (SDN 190) by W. Ince, PhD, reference ID in DARRTS: 4920462.)

Viral RNA Shedding

Nasopharyngeal swabs were collected at baseline (Day 1) and Days 2, 3, 7, and 14. Quantitative reverse transcription polymerase chain reaction (RT-PCR) was carried out on viral RNA extracted from nasopharyngeal swabs. There was no significant impact of RDV treatment relative to placebo on the change from baseline in viral RNA at each study Day or on time to viral RNA negativity as measured by RT-PCR.

Resistance Analyses

Preliminary sequence analysis reports were submitted as summaries without additional raw sequence data or phenotypic analyses, which precluded an independent and in-depth analysis of potential resistance. Whole viral genome sequencing was attempted on baseline and post baseline samples for subjects in the FAS who met the following criteria:

- A: Progressed to COVID-19-related hospitalization or all-cause death by Day 28 (N=17)

AND/OR

- B: Nasopharyngeal viral RNA above the limit of detection of the sequencing assay at Day 14 (n=71)

Of the 88 subjects who met either of the criteria above (50 in the RDV arm and 38 in the PBO arm), 80 subjects (46 in the RDV arm and 34 in the PBO arm) had available sequence data. Among these subjects, the most common SARS-CoV-2 variant represented was B.1.2 (n=23), followed by WHO-designated Alpha (n=14) and Epsilon (n=9) variants. Other variants were represented by three or fewer subjects in this sequence analysis subset. These limited data indicate that the Delta variant was not significantly represented in the trial, consistent with the trial enrollment time period. This trial predated the emergence of the Omicron variant. Data were inadequate to draw a conclusion regarding the association between the treatment effect or clinical outcome and the SARS-CoV-2 genotype due to biased sequencing criteria and small sample sizes for individual variants.

Baseline and postbaseline nsp12 sequence data were available for 18 subjects in the RDV arm and 14 subjects in the PBO arm. Overall, there was one subject [Subject ID (b) (6)] in the RDV arm identified as having a treatment-emergent substitution (in ≥15% of sequencing reads): A376V in nsp12 at Day 14; this subject did not meet the primary endpoint (i.e., COVID-19–related hospitalization [defined as at least 24 hours of acute care] or all-cause death by Day 28), but symptoms were not resolved by Day 14. Viral RNA kinetics for the subject with the A376V substitution were not clearly distinguished from other subjects with sequence data. Nsp12 sequence analysis data were not available at Day 7 for RDV-treated subjects. For subjects who met sequencing criterion B, sequencing was attempted for subjects who had evaluable viral RNA at Day 14, when potential treatment-emergent substitutions may have been below the threshold of reporting or detection as a result of the host immune response. Based on the viral RNA kinetics observed in the trial, this approach is inadequate to detect potential treatment-emergent resistant variants that may have been present at earlier time points when viral RNA rebound peaked at a high level on Day 7 in some subjects. Sixteen subjects in the RDV treatment arm in Study GS-US-540-9012 who exhibited apparent viral RNA rebound and had high viral RNA levels at Day 7 potentially indicative of treatment-emergent resistance were identified for additional sequence analyses at Day 7 (see Section 12). (For additional details regarding

methodology and analyses refer to the clinical virology review for NDA 214787, supplement 10 (SDN 190) by W. Ince, PhD, reference ID in DARRTS: 4920462.)

Additional key nonclinical and clinical virology characteristics, including mechanism of action, antiviral activity, and resistance mechanisms in cell culture and in clinical trials have been reviewed and described previously (refer to the clinical virology review of the original NDA by E. Donaldson, PhD, reference ID in DARRTS: 4672246).

4.3. Product Quality

The commercial RDV drug product is summarized below:

- Lyophilized powder: Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and diluted into 0.9% saline prior to administration by IV infusion. Remdesivir for injection, 100 mg, is supplied in a single-dose clear glass vial. The appearance of the lyophilized powder is white to off-white to yellow.
- Remdesivir injection, 5 mg/mL, is a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution that is to be diluted into 0.9% saline prior to administration by IV infusion. Remdesivir injection, 5 mg/mL, is supplied in a single-dose clear glass vial.

Changes to the commercial product were not made in this sNDA. Please refer to the Office of Product Quality reviews of the original NDA for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for RDV.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical safety studies for RDV were reviewed previously to support the original NDA approval. Please refer to Dr. John Dubinion's pharmacology/toxicology review of the original NDA for full details.

4.5. Clinical Pharmacology

General pharmacology and clinical pharmacokinetics (PK) have been reviewed for the original NDA. Please refer to Dr. Mario Sampson's clinical pharmacology review of the original NDA for full details.

4.5.1. Mechanism of Action

RDV is an inhibitor of the SARS-CoV-2 RdRp, which is essential for viral replication.

4.5.2. Human Dose Selection

The Applicant's rationale for the proposed dosing regimen is summarized below:

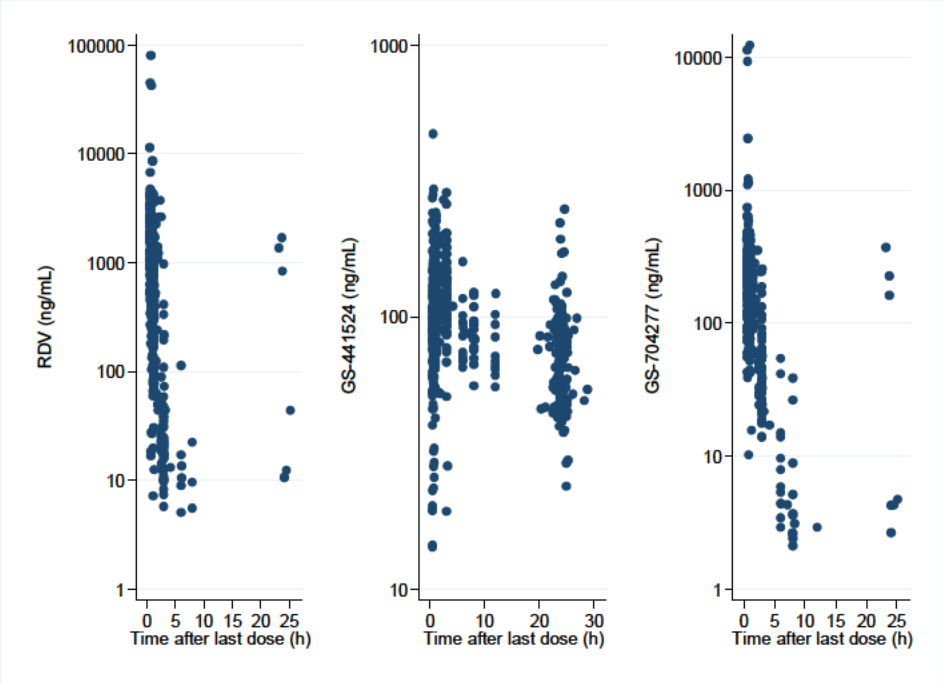
- The Applicant postulated that early antiviral treatment in subjects with early stage COVID-19 not requiring hospitalization or oxygen supplementation may prevent disease progression and may also facilitate shorter courses of treatment.
- The Applicant cited an RCT in nonhospitalized patients with influenza to support the concept that, in early viral infection, shorter courses of antivirals may be effective in preventing disease progression (Nicholson et al. 2000).
- In Study GS-US-540-5774, treatment with 5 days of RDV resulted in significantly greater odds of improved clinical status on Day 11 compared to standard of care in hospitalized subjects with moderate COVID-19. Of the 191 subjects randomized to receive 5 days of RDV, 35 subjects (18%) were discharged prior to completion of 5 days of RDV (Spinner et al. 2020; Gilead Sciences 2021b).
- Consequently, for Study GS-US-540-9012, the Applicant proposed to evaluate 3 days of RDV in subjects with early stage COVID-19 not requiring hospitalization or oxygen supplementation with the goal of preventing disease progression.
- Based on PK modeling and simulation, the adult dosing regimen is expected to result in comparable exposures of RDV and metabolites in children 12 years of age and older and weighing at least 40 kg as compared to adults.

4.5.3. Pharmacokinetics

While PK datasets were submitted for Study GS-US-540-9012, the Applicant did not submit PK or exposure-response analyses and did not propose inclusion of the results of such analyses in the label. The Applicant is planning (b) (4)

Using the PK data from Study GS-US-540-9012, we conducted exploratory PK and exposure-response analyses. In Study GS-US-540-9012, sparse PK was collected from subjects at participating sites on Day 2: end of infusion and optional 2 hours after end of infusion and Day 3: predose (within 30 minutes of dosing) and end of infusion. Intensive PK was collected from subjects at selected sites on Day 1 and Day 3, at the following time points relative to the start time of infusion: 0 (predose), 0.5, 0.75, 3, 6, 8, 12 (optional), and 24 hours. In the RDV arm, sparse and/or intensive PK data were collected for 148 of 279 subjects, all of whom were adults. Intensive PK was collected for seven subjects (Figure 1).

Figure 1. RDV and Metabolite Plasma Concentration-Time, Study GS-US-540-9012



Source: Plotted by reviewer from population PK dataset (NDA 214787 SDN 208).
Abbreviations: RDV, remdesivir

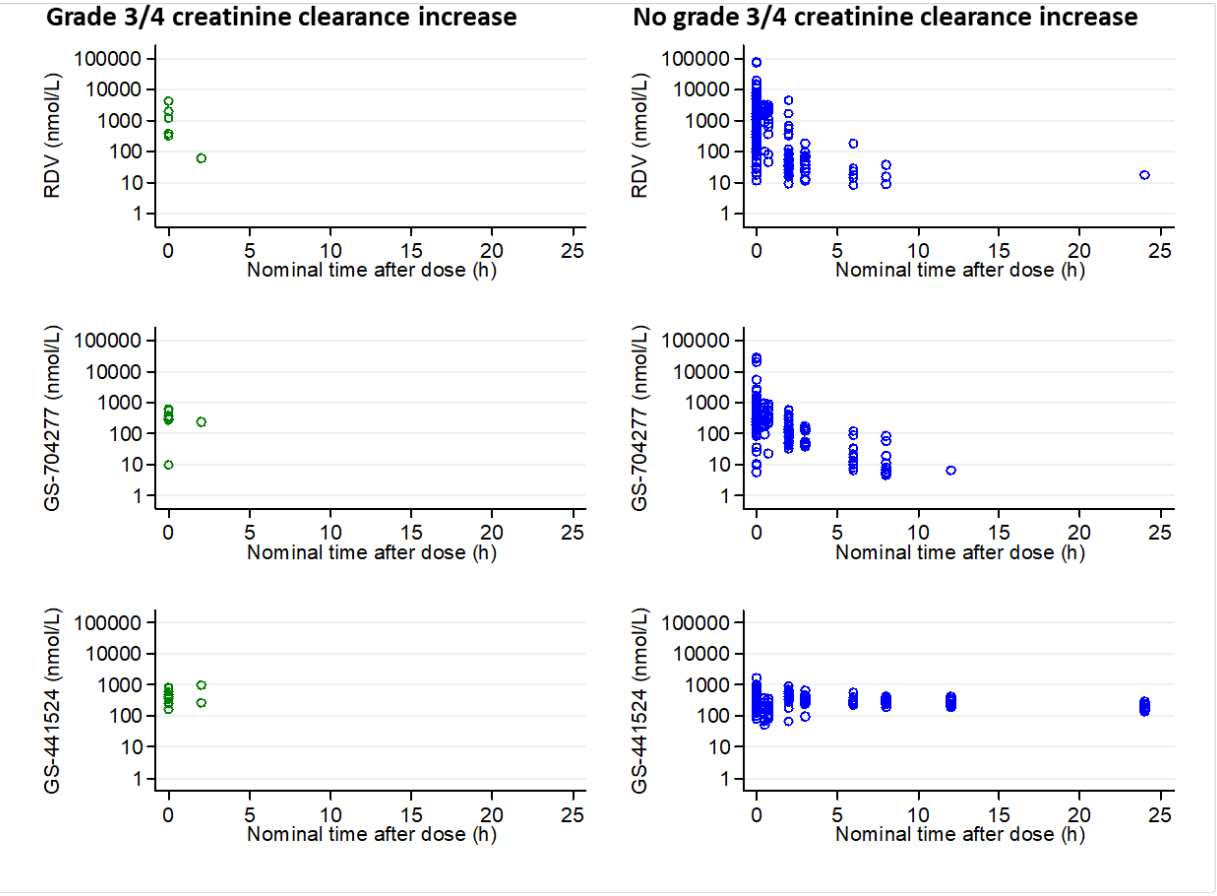
Exposure-Response for Efficacy

No PK data of RDV, GS-704277, and GS-441524 were collected from the two subjects in the RDV arm who had an event as defined in the primary endpoint (hospitalization or death). Thus, exposures of RDV, GS-704277, and GS-441524 in those with or without an event could not be compared.

Exposure-Response for Safety

As detailed in Section 8.5.10 of this review, Grade 3/4 renal laboratory parameters were of interest in Study GS-US-540-9012. Fifteen subjects in the RDV group had Grade 3/4 creatinine clearance decreased; PK data of RDV, GS-704277, and GS-441524 were collected in five of these subjects. PK data of RDV, GS-704277, and GS-441524 were collected in 143 out of the 264 RDV recipients who did not have Grade 3/4 creatinine clearance decreased. Overlapping exposures of RDV, GS-704277, and GS-441524 were observed in those RDV recipients with versus without Grade 3/4 renal creatinine clearance decreased (Figure 2).

Figure 2. Plasma Concentration-Time Data of RDV and Metabolites in Subjects With Vs. Without Grade 3/4 Renal Creatinine Clearance Decreased, Study GS-US-540-9012



Source: plotted by reviewer using Study GS-US-540-9012 pc dataset.
Abbreviations: RDV, remdesivir

No PK data were collected in the eight adolescent subjects (RDV [n=3], PBO [n=5]) in Study GS-US-540-9012. However, simulations from the physiologically based PK model indicate that in children ≥40 kg, administration of the proposed regimen results in exposures of RDV and its metabolites, GS-704277 and GS-441524, generally within the range of exposures observed in adults, therefore supporting extrapolation of efficacy observed in adults to pediatrics weighing ≥40 kg.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4 contains a summary of the Phase 3 trial that was submitted with this application.

Table 4. Summary of Clinical Trial Relevant to This Supplemental NDA

Trial Identity	NCT No.	Phase	Trial Design	Regimen	Study Population	No. of Patients Enrolled	Study Endpoint	No. of Centers and Countries
Studies to Support Efficacy and Safety								
GS-US-540-9012	04501952	3	Randomized, double-blind, PBO-controlled trial with 1:1 randomization	RDV 3 days[1] or PBO 3 days	Nonhospitalized adults and adolescents with COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death	562 in total: 279 RDV_3 283 PBO	COVID-19-related hospitalization (defined as at least 24 hours of acute care) or all-cause mortality through Day 28 and Safety	64 sites, 4 countries[2]

Source: Reviewer analysis
[1] RDV_3, RDV for 10 days (200 mg IV on Day 1, followed by 100 mg IV QD Days 2 to 3
[2] Study GS-US-540-9012 was implemented in a total of 105 sites and five countries; subjects were enrolled in a total of 64 sites and four countries.
Abbreviations: IV, intravenous; PBO, placebo; QD, once daily; RDV, remdesivir; NCT, national clinical trial

5.2. Review Strategy

The single trial reviewed to assess efficacy and safety was Study GS-US-540-9012, as this was the only completed randomized, placebo-controlled trial evaluating IV RDV for the treatment of nonhospitalized adult and adolescent subjects with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. This design and analysis of this trial will be discussed in the following section of this review.

6. Review of Relevant Individual Trials Used To Support Efficacy

Compliance With Good Clinical Practices

Study GS-US-540-9012 was conducted under a U.S. investigational new drug application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for GCP and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the U.S. CFR Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The trial protocols, amendments and informed consent forms were reviewed and approved by independent ethics committees or institutional review boards before trial initiation. Investigators (or designees) were responsible for obtaining written informed consent from each individual prior to undertaking any study-related procedures. The FDA OSI inspected selected clinical sites, and the inspection reports were completed at the time this review was finalized (see Section 4.1). A detailed discussion of the OSI audit will be available in the Clinical Inspection Summary.

Data Quality and Integrity: Applicant's Assurance

The review team considered the Applicant's methods for assuring data quality and integrity to be adequate. These methods included investigator and study center staff training on the trial protocols and study-specific procedures, study site monitoring in accordance with International Conference on Harmonization GCP guidelines, compliance audits of investigative sites, use of electronic case report forms (eCRFs), and use of data validation specifications along with manual data review. The Applicant reviewed eCRF data to verify protocol and GCP adherence, and to verify the data against source documentation. The Applicant confirmed that missing data, selected protocol deviations and other data inconsistencies were addressed prior to database finalization. Clinical laboratory data were transferred electronically to the Applicant using defined transfer specifications. The Applicant's lead clinical data associate completed the database.

6.1. Study GS-US-540-9012

6.1.1. Study Design

Overview and Objectives

Study GS-US-540-9012 (clinicaltrials.gov identifier NCT04501952) was a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to assess the safety and efficacy of 3 days of IV RDV for the treatment of mild-to-moderate COVID-19 in nonhospitalized, unvaccinated patients with risk factors for progression to severe disease. The primary objectives of the trial in nonhospitalized patients with early stage COVID-19 were to evaluate the efficacy of RDV in reducing the rate of COVID-19-related hospitalization or all-cause death, and to evaluate the safety of RDV administered in an outpatient setting. The first subject was screened on September 18, 2020, and the last subject completed a follow-up visit for the primary endpoint on May 6, 2021. A total of 562 subjects were randomized and treated. Subjects were enrolled across 55 centers in the United States, five in Denmark, two in Spain, and two in the United Kingdom.

Trial Design

Adults and adolescents with laboratory-confirmed SARS-CoV-2 infection and at least one risk factor for progression to hospitalization were randomized in a 1:1 ratio in a double-blind manner to receive either intravenously administered RDV or matching PBO for 3 days. A placebo-controlled trial design was chosen because no approved regimens existed for this patient population. Study drug was given intravenously daily for up to a total of 3 days of treatment. The dose of RDV was 200 mg on the first day and 100 mg on the second and third days. Subjects were treated at outpatient facilities, through home health care, or in skilled nursing facilities (SNFs).

Inclusion criteria specified that subjects were to be males and nonpregnant females aged ≥12 years weighing ≥40 kg who had laboratory-confirmed SARS-CoV-2 infection (as determined by RT-PCR or antigen testing) ≤4 days prior to screening, and at least one of the following pre-existing risk factors for progression to hospitalization:

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

- Current cancer
- Sickle cell disease

OR

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

Other inclusion criteria are summarized below:

- Presence of ≥1 symptom(s) consistent with COVID-19 for ≤7 days prior to randomization (such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia)
- Did not receive, require, or expect to require supplemental oxygen
- Did not require hospitalization (hospitalization defined as ≥24 hours of acute care)

Exclusion criteria disallowed subjects with any of the following:

- Participation in any other clinical study of an experimental treatment and prevention for COVID-19
- Prior hospitalization for COVID-19 (hospitalization defined as ≥24 hours of acute care)
- Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 or administration of any SARS-CoV-2 (or COVID-19) vaccine
- Use of hydroxychloroquine (HCQ) or chloroquine (CQ) ≤7 days prior to screening
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5x upper limit of normal at screening or within 90 days of screening (Note: If per local practice only ALT was routinely measured, this exclusion criterion was evaluated on ALT alone.)
- Creatinine clearance <30 mL/min at screening or within 90 days of screening using the Cockcroft-Gault (CG) formula in subjects ≥18 years of age or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 at screening or within 90 days of screening using the Schwartz formula in subjects <18 years of age
- Breastfeeding (nursing) woman
- Known hypersensitivity to the study drug, the metabolites, or formulation excipient
- Use or planned use of exclusionary medications

Randomization was stratified by residence in an SNF, age (<60 years versus ≥60 years), and region (United States versus ex-United States).

Follow-up visits occurred on Day 2, Day 3, Day 7±1, Day 14±1, and Day 28±5. Measurements at these study visits were to include vital signs, respiratory status, SARS-CoV-2 quantitative RT-PCR testing, COVID-19 symptoms, adverse events (AEs), concomitant medications, and information on medically attended visits (MAVs) including hospitalizations.

Study Endpoints

The primary efficacy endpoint was the composite of COVID-19–related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28. The endpoint was derived by combining the available all-cause death and COVID-19-related hospitalization reported by the

site. The first COVID-19-related hospitalization was used for the proportion of COVID-19-related hospitalization or all-cause death.

Reviewer Comment: The primary endpoint was considered appropriate from a clinical and statistical standpoint, and highly meaningful for a trial of high risk COVID-19 nonhospitalized patients.

Secondary efficacy endpoints included the composite of COVID-19-related MAVs, defined as medical visits attended in person by the subject and a health care professional, or all-cause death through Day 28; all-cause mortality at Day 28; hospitalization by Day 28; the composite of COVID-19-related hospitalization or all-cause mortality by Day 14; the composite of COVID-19-related MAVs or all-cause death by Day 14; progression to requirement for oxygen supplementation by Day 28; time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7; and time to alleviation of baseline COVID-19 symptoms. The time to symptom alleviation endpoint was defined through Day 14, was based on an adapted inFLUenza Patient-Reported Outcome Plus (FLU-PRO Plus) questionnaire, and defined alleviation at the first day baseline symptoms were mild or absent.

Statistical Analysis Plan

The primary efficacy analysis was performed using the FAS, which included all randomized subjects who received at least one dose of study medication.

Secondary efficacy endpoints were also to be analyzed in the FAS, with several exceptions. The composite endpoints based on COVID-19-related MAVs or all-cause death was analyzed using the modified FAS. This analysis set included randomized and treated subjects enrolled under protocol amendment 2 or later, which had defined these endpoints and specified the requisite data capture. Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7 was analyzed in the Virology Analysis Set, which included subjects in the FAS who had positive SARS-CoV-2 viral load at baseline.

Safety was to be assessed in the safety analysis set (SAS), which was defined identically to the FAS except that subjects were grouped according to treatment received rather than treatment randomized. In this trial the FAS and SAS happened to completely coincide.

The primary endpoint of COVID-19-related hospitalization or all-cause death by Day 28 was analyzed through a Cox proportional hazards model with the randomization stratification factors used as covariates. This was a superiority trial, and thus the null hypothesis was that the hazard ratio was equal to 1. If a subject prematurely discontinued from the study prior to Day 28 or the hospitalization status was missing, the subject was censored at the date of last contact. If a subject had a COVID-19-related hospitalization first and then died, then the date of the COVID-19-related hospitalization and status was used for the primary analysis for this subject. If a subject had a non-COVID-19-related hospitalization first and then died without experiencing a COVID-19-related hospitalization, then date of the death and status was used for the primary analysis for this subject. Results for the primary endpoint were to be reported through the estimate and 95% confidence for the hazard ratio, p-value, and Kaplan-Meier estimates of the event rate by Day 28 in each treatment group.

The statistical analysis plan specified a sensitivity analysis for the primary endpoint based on conducting a Cochran-Mantel-Haenszel test adjusting for the randomization stratification factors. For this analysis censored subjects were considered to have not experienced a COVID-19-related

hospitalization or all-cause death by Day 28. The Applicant stated that this analysis was conducted to examine robustness of results to proportional hazards assumptions.

Similar time-to-event analyses as for the primary endpoint were specified for the secondary endpoints of COVID-19-related MAVs or all-cause death by Day 28, COVID-19-related hospitalization or all-cause death by Day 14, COVID-19-related MAVs or all-cause death by Day 14, COVID-19-related hospitalization by Day 28, and time to symptom alleviation. The dichotomous secondary endpoints of all-cause mortality by Day 28 and progression to oxygen supplementation requirements by Day 28 were analyzed using Fisher's exact test. Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7 was summarized by treatment groups and compared between treatment groups using an analysis of covariance (ANCOVA) model with baseline viral load as covariate. No formal multiplicity corrections were implemented for the analyses of secondary endpoints.

Subgroup analyses of the primary endpoint were to be performed in the FAS for exploratory purposes. The subgroups prespecified for analyses were based region (US and ex-US), age (<18 years, 18 to 59 years, and ≥60 years), skilled nursing home residence (yes and no), sex at birth (male and female), race (Asian, black, white, and other), and presence or absence of the baseline risk factors for disease progression that were used for inclusion criteria.

The planned sample size was 1264 subjects (632 in each group with 1:1 randomization). The Applicant estimated that this would achieve >90% power to detect a ratio of 0.55 (RDV to PBO) in proportion of COVID-19-related hospitalization or all-cause death, which is equal to a hazard ratio: [HR] of 0.534) using a 2-sided significance level of 0.05 assuming the overall COVID-19-related hospitalization or all-cause death rate is 9.3% (12% in the PBO group and 6.6% in the RDV IV for 3 days group) and a 5% drop out rate. The Applicant further estimated this sample size would provide approximately 80% power to detect a smaller treatment effect size with a ratio of 0.60 (RDV to PBO), assuming a 2-sided significance level of 0.05 and the overall COVID-19-related hospitalization or all-cause death rate is 9.6% (12% in the PBO group and 7.2% in the RDV group) and a 5% drop out rate. The Applicant cited a study evaluating bamlanivimab monotherapy and combination therapy with bamlanivimab and etesevimab in nonhospitalized subjects with mild-to-moderate COVID-19 in which the proportion of patients with COVID-19-related hospitalizations or emergency department visits was 13.5% in high-risk patients (age ≥65 or BMI ≥35) who received placebo (Gottlieb et al. 2021a). Consequently, the Applicant assumed a 12% event rate for Study GS-US-540-9012 to account for decrease in hospitalization rate in recent months since the trial's initiation.

The statistical analysis plan prespecified one interim analysis to be conducted by an independent data monitoring committee (IDMC) to review the progress of the study and to perform interim reviews of the efficacy, futility, and safety. The IDMC analysis was scheduled to occur when approximately 50% of the total 1264 planned subjects completed the Day 28 assessment.

The IDMC analysis was not performed due to the Applicant's decision to stop study enrollment on April 8, 2021, after less than 50% of the total 1264 planned subjects were randomized. The Applicant's reasons for stopping enrollment were administrative in nature, including rapidly declining COVID-19 case rates, increasing availability of single-infusion monoclonal antibody therapies under EUAs, and increasing vaccination rates among high-risk subjects. At the time of enrollment cessation, a total of 584 subjects were randomized. Hence, the final sample size was considerably smaller than the planned sample size. Due to the administrative nature of the halted

enrollment, no interim adjustments were made to the two-sided 0.05 significance level for hypothesis testing in the primary efficacy analysis.

Protocol Amendments

Four protocol amendments were made, none of which significantly impact the conduct of this double-blinded trial. Key changes in these amendments are summarized below.

Amendment 1 (dated August 11, 2020)

- Removed the 30% cap on enrolling subjects from SNFs.
- Incorporated enrollment of adolescents (≥12 years and weighing ≥40 kg) with pre-existing risk factors for progression to hospitalization.
- Under inclusion criteria, revised the risk factor "Chronic kidney disease: any stage" to "Chronic mild or moderate kidney disease."
- Revised the renal exclusion criterion for clarity (i.e., Creatinine clearance should be calculated using the Cockcroft-Gault formula in subjects ≥18 years of age or the Schwartz formula in subjects <18 years of age).
- Under RDV discontinuation criteria, added the following: Infusion-related systemic reactions ≥ Grade 2 or infusion-related localized reactions ≥ Grade 3
- Added the recommended duration of RDV infusion (i.e., over 30 to 120 minutes).
- Added sputum samples for SARS-CoV-2 quantitative RT-PCR viral load testing and possible resistance testing.
- Number of sites: Increased from 100 to 150 globally.

Amendment 2 (dated November 6, 2020)

- This amendment was not implemented. Amendment 2 was submitted to the Agency on November 9, 2020. On November 10, 2020, the Applicant informed the Agency that a correction is being made to the protocol and that the updated protocol (Amendment 3) would be submitted for review.

Amendment 3 (dated November 12, 2020)

- Primary endpoint was revised as follows:
  - From: Composite endpoint of hospitalization or death from any cause by Day 14
  - To: Composite endpoint of all-cause MAVs (medical visits attended in person by the subject and a health care professional) or death by Day 28
- The total sample size was revised to approximately 1264 subjects, including 60 subjects enrolled in the study at that time, and the number of subjects needed for the new primary endpoint under the protocol amendment (n=1204).
- The endpoint of time to alleviation of baseline COVID-19 symptoms was returned back to secondary from exploratory.

- Revised the renal exclusion criterion to incorporate the following: eGFR <30 mL/min/1.73m^2.

Amendment 4 (dated January 14, 2021)

- Primary endpoint was revised as follows:
  - From: Composite endpoint of all-cause MAVs (medical visits attended in person by the subject and a health care professional) or death by Day 28
  - To: Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or death by Day 28

The Applicant stated that, at time Amendment 4 was finalized, 172 subjects were enrolled.

- The composite endpoint of all-cause MAVs (medical visits attended in person by the subject and a health care professional) or death by Day 28 was revised from being the primary endpoint to being one of the secondary endpoints.
- The following secondary endpoint was added: Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 14
- The following secondary endpoint was revised:
  - From: Composite endpoint of all-cause MAVs (medical visits attended in person by the subject and a health care professional) or death by Day 14
  - To: Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the subject and a health care professional) or all-cause death by Day 14
- Previous receipt of a SARS-CoV-2 vaccine was added as an exclusion criterion.
- The following exclusion criterion was removed (use of HCQ or CQ ≤7 days prior to screening) for consistency with the revision to Section 5.4 of the protocol.
  - Section 5.4 (Prior and Concomitant Medications) was revised to state concomitant use of HCQ or CQ for any indication is prohibited in subjects receiving RDV.

Reviewer Comment: There were two major changes during study conduct. First, the study was terminated for administrative reasons after only 562 of the planned 1264 patients had been enrolled. The Applicant communicated to the Agency that there was less need for a 3-day IV regimen due to decreasing rates of hospitalizations; increasing availability of single-infusion monoclonal antibodies under EUA for nonhospitalized high-risk patients with COVID-19; and increasing vaccination rates among high-risk individuals (Gottlieb et al. 2021a). The Applicant assessed that continuing to conduct a randomized placebo-controlled study with a multiple-day infusion treatment in such an environment had become increasingly difficult given the evolving epidemiology and therapeutic landscape (Gilead Sciences 2021a). The Applicant noted several study sites described ongoing challenges with patient recruitment in recent months given these therapeutic advances and study enrolment was significantly slower than expected with the changing epidemiology. The Applicant assessed that Study GS-US-540-9012 may not reach the enrolment threshold to perform the primary endpoint analysis.

The first formal interim analysis had not yet occurred as this was planned after reaching 50% enrolment. No bias was expected to be introduced from this early termination as it was not related to unblinded interim results.

The second major midstream change was to the primary endpoint. Originally this was based on Day 14 hospitalization or all-cause death, was modified to Day 28 COVID-19-related MAVs or all-cause death, and finally was changed to Day 28 COVID-19-related hospitalization or all-cause death. This modification also was not expected to introduce any bias because the endpoint change was made while the sponsor was blinded to results by treatment group.

6.1.2. Study Results

Patient Disposition

Of the 630 subjects who were screened, 562 were randomized to treatment groups and received at least one dose of study medication, and consequently were included in the FAS. There were 279 subjects in the RDV group and 283 subjects in the PBO control group. Over 96% of subjects in the FAS completed the 3-day treatment course, with the most common reasons for treatment discontinuation being adverse events and subject decisions. Approximately 96% in the FAS also completed planned study assessments, with the most common reasons for noncompletion being withdrawal of consent and loss to follow-up. In this study, the FAS used for efficacy assessments exactly coincided with the SAS.

Table 5. Subject Disposition, Study GS-US-540-9012

Disposition	RDV IV for 3 Days	PBO	Total
Subjects screened			630
Subjects not randomized			46
Subjects randomized	292	292	584
Subjects randomized and never treated	13	9	22
Subjects randomized and treated (full analysis set)	279	283	562
Subjects completed study drug	273 (97.8)	269 (95.1)	542 (96.4)
Subjects prematurely discontinuing study drug	6 (2.2)	14 (4.9)	20 (3.6)
Adverse event	1 (0.4)	6 (2.1)	7 (1.2)
Protocol violation	1 (0.4)	1 (0.4)	2 (0.4)
Noncompliance with study drug	0 (0)	1 (0.4)	1 (0.2)
Subject decision	3 (1.1)	5 (1.8)	8 (1.4)
Investigator's discretion	1 (0.4)	1 (0.4)	2 (0.4)
Subjects completed study	266 (95.3)	272 (96.1)	538 (95.7)
Subjects prematurely discontinuing from study	13 (4.7)	11 (3.9)	24 (4.3)
Protocol violation	1 (0.4)	1 (0.4)	2 (0.4)
Withdrew consent	5 (1.8)	4 (1.4)	9 (1.6)
Lost to follow-up	7 (2.5)	2 (0.7)	9 (1.6)
Adverse event	0 (0)	3 (1.1)	3 (0.5)
Investigator's discretion	0 (0)	1 (0.4)	1 (0.2)

Source: Study GS-US-540-9012 Clinical Study Report, Table 6.
Notes: The denominator for percentages is the number of subjects in the full analysis set.
Abbreviations: IV, intravenous; RDV, remdesivir; PBO, placebo

Protocol Violations/Deviations

A total of 26 important protocol deviations occurred (RDV [n=13], PBO [n=13]) in 23 subjects. These events were evenly distributed between treatment groups as approximately 4% of subjects

in each arm had an important protocol deviation. The largest number of protocol deviations (10 of 26) were due to violations of eligibility criteria.

Reviewer Comment: Rates of important protocol deviations were considered relatively low and noncompliance with study procedures did not impact overall conclusions.

Baseline Characteristics

The table below summarizes baseline demographics. Approximately 30% of subjects were at least 60 years of age, slightly less than 70% of subjects were between 18 and 60 years of age, and only eight subjects were adolescents under 18 years old. Approximately half of subjects were male, and half were female. The majority of subjects (approximately 80%) were white and slightly less than half of subjects were Hispanic or Latino. More than 94% of subjects were enrolled in the United States. Demographics were similar in the RDV and PBO groups.

Table 6. Demographics, Full Analysis Set, Study GS-US-540-9012

Demographics	RDV IV for 3 Days (N=279)	PBO (N=283)
Age category (years) [n (%)]		
<18	3 (1.1)	5 (1.8)
≥18 to <60	193 (69.2)	191 (67.5)
≥60	83 (29.7)	87 (30.7)
Sex at birth [n (%)]		
Male	148 (53.0)	145 (51.2)
Female	131 (47.0)	138 (48.8)
Race category [n (%)]		
Asian	6 (2.2)	7 (2.5)
Black	20 (7.2)	22 (7.8)
White	228 (81.7)	224 (79.2)
Other or not permitted	25 (9.0)	30 (10.6)
Ethnicity [n (%)]		
Hispanic or Latino	123 (44.1)	112 (39.6)
Not Hispanic or Latino	146 (52.3)	158 (55.8)
Not permitted	10 (3.6)	13 (4.6)
Country [n (%)]		
USA	264 (94.6)	267 (94.3)
Outside USA	15 (5.4)	16 (5.7)

Source: Statistical reviewer and Study GS-US-540-9012 Clinical Study Report, Table 8.
Abbreviations: IV, intravenous; RDV, remdesivir; PBO, placebo

The following table (Table 7) displays additional baseline characteristics, which were generally well balanced between the treatment groups. Approximately 85% of subjects were treated at outpatient facilities, with remaining subjects (approximately 13%) were treated through home health care and a small proportion (<3%) were treated at SNFs. Subjects had high rates of baseline risk factors for progression to more severe disease. The most common risk factors were diabetes mellitus (approximately 60% of subjects), obesity (approximately 55% of subjects), and hypertension (slightly less than half of subjects). Subjects in each treatment group had a median of 5 days of symptoms prior to the first dose of study drug. The median time from confirmed SARS-CoV-2 positivity to the first dose was 2 days in the RDV group and 3 days in the PBO group. No subjects in the RDV group and only one subject in the PBO group had been vaccinated for COVID-19.

Table 7. Baseline Characteristics, Full Analysis Set, GS-US-540-9012

Baseline Characteristics	RDV IV for 3 Days (N=279)	PBO (N=283)
Location of first dose [n (%)]		
Skilled nursing facility	8 (2.9)	7 (2.5)
Home health care	36 (12.9)	36 (12.7)
Outpatient facility	235 (84.2)	240 (84.8)
Baseline risk factors [n (%)]		
Chronic lung disease	67 (24.0)	68 (24.0)
Hypertension	138 (49.5)	130 (45.9)
Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)
Diabetes mellitus	173 (62.0)	173 (61.1)
Obesity (BMI ≥30)	154 (55.2)	156 (55.1)
Immunocompromised state	14 (5.0)	9 (3.2)
Chronic mild/moderate kidney disease	7 (2.5)	11 (3.9)
Chronic liver disease	1 (0.4)	1 (0.4)
Current cancer	12 (4.3)	18 (6.4)
Sickle cell disease	0 (0.0)	0 (0.0)
Days of symptoms prior to first dose [median (IQR)]	5 (3 to 6)	5 (4 to 6)
Days from positive SARS-CoV-2 test to first dose [median (IQR)]	2 (1 to 3)	3 (1 to 4)
SARS-CoV-2 viral load [log_{10} copies/mL] [median (IQR)]	6.2 (4.3 to 7.5)	6.3 (4.1 to 7.6)

Source: Statistical reviewer and Study GS-US-540-9012 Clinical Study Report, Tables 9 and req13292.10.
Abbreviations: BMI, body mass index; IQR, interquartile range; IV, intravenous; RDV, remdesivir; PBO, placebo; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Efficacy Results: Primary Endpoint

Results for the primary efficacy analysis of COVID-19-related hospitalization or all-cause death by Day 28 are shown in the table below and RDV was superior to PBO. Events occurred in 2/279 (0.7%) subjects in the RDV group and in 15/283 (5.4%)[1] subjects in the PBO group of the FAS, which led to an estimated hazard ratio of 0.13 (95% CI: 0.03 to 0.59) and represented a statistically significant treatment effect (p=0.008). All events for the composite primary endpoint were COVID-19-related hospitalizations because no deaths occurred in this study by Day 28.

Table 8. Primary Analysis of COVID-19-Related Hospitalization or All-Cause Death by Day 28, Full Analysis Set, Study GS-US-540-9012

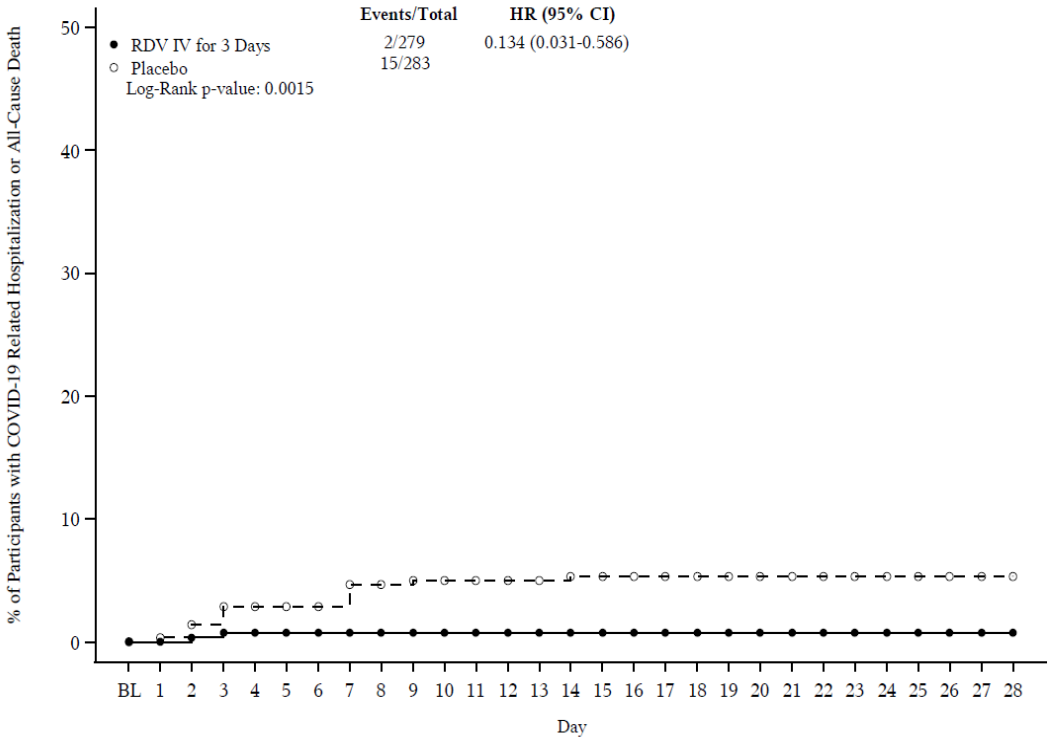
Parameter	RDV IV for 3 Days (N=279)	PBO (N=283)
COVID-19-related hospitalization or all-cause death [n (%)]	2 (0.7)	15 (5.4)
Hazard ratio for RDV vs. placebo	0.13	
95% CI for hazard ratio	0.03 to 0.59	
p-value for hazard ratio	0.008	

Source: Study GS-US-540-9012 Clinical Study Report, Table 12.
Notes: Proportions are based on Kaplan-Meier estimates. The hazard ratio, 95% CI, and two-sided p-value are based on Cox regression with baseline stratification factors as covariates.
No PK data were collected from the two subjects in the RDV arm who had an event as defined in the primary endpoint.
Abbreviations: CI, confidence interval; IV, intravenous; RDV, remdesivir; PBO, placebo

[1] Event rate percentages cited in text for time-to-event efficacy endpoints are based on Kaplan-Meier estimates and may not exactly equal percentages formed by dividing the number of subjects with events by the number of subjects.

The figure below displays Kaplan-Meier curves in the RDV and placebo groups for the cumulative incidence of the primary endpoint. The curves displayed a separation in the first week that was maintained throughout the 28-day follow-up period.

Figure 3. Kaplan-Meier Analysis of COVID-19-Related Hospitalization or All-Cause Death Through Day 28, Full Analysis Set, Study GS-US-540-9012



Source: Study GS-US-540-9012 Clinical Study Report, Figure 15.9.1.1.

One potential issue affecting the primary analysis was missing data, as subjects with unknown hospitalization status were censored at their last study day or Day 28, whichever was earlier. In the FAS there were 51/279 (18.3%) subjects in the RDV group and 41/283 (14.5%) in the placebo group censored before the end of the 28-day follow-up period. However, there were several reasons why this high rate of censoring did not necessarily limit the efficacy conclusions.

- Much of the censoring was likely administrative and related to the Day 28±5-day visit window, as subjects were often censored after completing the visit. Only 21/562 (3.7%) subjects were censored before the Day 23 start of this visit window.
- All of the primary endpoint events had occurred by Day 14. Due to this time course of disease progression, it is unlikely that there was a large number of missing late events.
- Several secondary endpoint results to be discussed below were defined at Day 14, had relatively little missing data (approximately 3% for COVID-19-related hospitalization or all-cause death), and continued to favor RDV compared to PBO.

The Applicant conducted a post hoc analysis in which the primary endpoint was redefined to include all-cause hospitalization rather than COVID-19-related hospitalization. This led to three

additional subjects in each group experiencing events, and results continued to significantly favor RDV compared to PBO. Hence, conclusions from the primary efficacy analysis did not appear to depend on determinations of COVID-19-relatedness.

In addition to the time-to-event primary analysis, the statistical analysis plan prespecified a sensitivity analysis of the primary endpoint. This was based on considering COVID-19-related hospitalization or all-cause death by Day 28 as a binary endpoint, imputing nonevents for censored subjects, and using the Cochran-Mantel-Haenszel to estimate the relative risk with adjustment for the randomization stratification factors. This method does not depend on the proportional hazards assumption used for the primary analysis. Further, the binary endpoint is less sensitive to detecting effects of interventions that delay but do not prevent progression to COVID-19-related hospitalization or death.

The table below shows that results for this sensitivity analysis significantly favored RDV compared to placebo with an estimated relative risk of 0.14 (95% CI: 0.03 to 0.59), p=0.002. In addition, the table displays two other supplemental analyses of this binary endpoint conducted by FDA reviewers. Fisher's exact test was conducted because event rates for the primary endpoint were low and it was unclear if asymptotic approximations used for the prespecified primary analysis were appropriate. Although this exact method is often conservative it continued to significantly favor RDV compared to placebo (p=0.002). An estimate and CI were also constructed for the risk difference as this may be more interpretable for benefit-risk analysis than the hazard ratio. The estimated (RDV – PBO) difference in event rates was -4.6% (95% CI: -7.9% to -2.0%), which corresponded to an estimated number needed to treat of approximately 22 (95% CI: 12 to 50) unvaccinated high risk nonhospitalized patients to prevent one patient from progression to COVID-19-related hospitalization or death. A treatment effect of this magnitude likely represents clinical benefit that would outweigh uncommon drug toxicities.

Table 9. Supplemental Analysis of COVID-19-Related Hospitalization or All-Cause Death by Day 28 as a Binary Endpoint, Full Analysis Set, Study GS-US-540-9012

Parameter	RDV IV for 3 Days (N=279) [n (%)]	PBO (N=283) [n (%)]	Treatment Effect Estimate	95% CI	p-Value
Relative risk (Mantel-Haenszel)			0.14	0.03 to 0.59	0.002
Fisher's exact test	2 (0.7)	15 (5.3)			0.002
Risk difference			-4.6%	-7.9% to -2.0%	

Source: Statistical reviewer and Study GS-US-540-9012 Clinical Study Report, Table 13.
Notes: The relative risk estimate, CI, and two-sided p-value are based on the Mantel-Haenszel method adjusting for baseline stratification factor. The estimate and CI for the risk difference are based on the Miettinen-Nurminen method.
Abbreviations: CI, confidence interval; IV, intravenous; RDV, remdesivir; PBO, placebo

Reviewer Comment: The primary efficacy analysis provided evidence of efficacy for RDV. Conclusions were robust to handling of censored data, determinations of whether hospitalizations were COVID-19-related, and statistical model assumptions used for time-to event data with rare events.

Secondary Endpoints Based on Progression to Severe Disease

For the secondary endpoint of COVID-19-related hospitalization of all-cause death through Day 14 the estimated event rates, hazard ratio, and corresponding confidence interval and p-value

were identical to those for the primary analysis that defined this endpoint through Day 28. This was because all events had occurred by Day 14.

Reviewer Comment: Because only 3% of subjects were censored for the Day 14 analysis, this secondary endpoint was less impacted by missing data than the primary endpoint. Hence, this secondary analysis supported the conclusion that efficacy findings were not artifacts of censoring.

Results for the secondary analysis of COVID-19-related MAVs or all-cause death by Day 28 in the modified FAS favored RDV compared to PBO and are shown in the table below. Events occurred for 4/246 (1.7%) subjects in the RDV group and 21/252 (8.5%) subjects in the PBO, which led to an estimated hazard ratio of 0.19 (95% CI: 0.07 to 0.56) and was statistically significant (p=0.002).

Table 10. Secondary Analysis of COVID-19-Related MAVs or All-Cause Death by Day 28, Modified Full Analysis Set, Study GS-US-540-9012

Parameter	RDV IV for 3 Days (N=246)	PBO (N=252)
COVID-19-related MAVs or all-cause death [n (%)]	4 (1.7)	21 (8.5)
Hazard ratio for RDV vs. PBO	0.19	
95% CI for hazard ratio	0.07 to 0.56	
p-value for hazard ratio	0.002	

Source: Study GS-US-540-9012 Clinical Study Report, Table 14.
Notes: Proportions based on Kaplan-Meier estimates. Hazard ratio, 95% CI, and two-sided p-value based on Cox regression with baseline stratification factors as covariates.
Abbreviations: CI, confidence interval; IV, intravenous; MAV, medically attended visit; RDV, remdesivir; PBO, placebo

Reviewer Comment: As this secondary endpoint of COVID-19-related MAVs or all-cause death by Day 28 had previously been designated as the primary in this trial, results showed that efficacy findings were insensitive to the primary endpoint change.

The secondary analysis of COVID-19-related MAVs or all-cause death by Day 14 in the modified FAS gave similar favorable results for RDV as the secondary analysis defined through Day 28. This was because most events occurred in the first 14 days. Event rates were 2/246 (0.8%) for RDV versus 20/252 (8.0%) for PBO, which led to an estimated hazard ratio of 0.10 (95% CI: 0.02 to 0.43), p=0.002.

There were no deaths in either treatment group for the secondary endpoint of all-cause mortality by Day 28.

Reviewer Comment: Deaths did not occur in this trial.

Because there were no deaths by Day 28, results for the secondary endpoint of COVID-19-related hospitalization by Day 28 were identical to the primary analysis of COVID-19-related hospitalization or all-cause death by Day 28.

For the secondary endpoint of requiring oxygen supplementation by Day 28 there were events recorded for one subject in the RDV group and five subjects in the placebo group. Events were too uncommon to draw statistical conclusions for this endpoint.

Reviewer Comment: Results for secondary endpoints based on progression to more severe disease states were generally consistent with the primary analysis results and provided additional support for the efficacy of RDV.

Secondary Endpoint of Time to Symptom Alleviation

The secondary endpoint of time to symptom alleviation through Day 14 was limited by missing data at baseline. Only 66 subjects in the RDV arm and 60 subjects in the PBO arm had baseline symptoms recorded prior to the first dose of study drug, and thus were included in the Applicant's prespecified analysis. The table below shows that there was numerically faster symptom alleviation in the RDV group than the PBO group, but the difference was not nominally statistically significant. Under 40% of subjects in each arm had achieved alleviation of COVID-19 symptoms (meaning symptoms were absent or mild) by Day 14. The table also displays a post hoc analysis conducted by the Applicant that includes subjects with symptoms recorded at or before the first day of dosing rather than prior to the first dose.

This analysis was less limited by missing baseline data and showed nominally statistically significantly faster time to symptom alleviation in the RDV arm than the PBO arm. This was a post-treatment subgroup analysis (and thus potentially confounded) because subjects were included based on information recorded after dosing. The Applicant does not propose to include symptom alleviation results in labeling.

Table 11. Time to Alleviation (Mild or Absent) of Baseline COVID-19 Symptoms Through Day 14, Full Analysis Set, Study GS-US-540-9012

Subjects with symptoms captured prior to the first dose of study drug				
Time to Alleviation	**RDV IV for 3 Days (N=66)**	**PBO (N=60)**	**Hazard Ratio (95% CI)**	**p-Value**
Symptom alleviation at or before Day 14 [n (%)]	23 (36.6)	15 (28.3)	1.41 (0.73 to 2.69)	0.30
Subjects with symptoms captured prior to or on the first dosing day of study drug				
Time to Alleviation	**RDV IV for 3 Days (N=169)**	**PBO (N=165)**	**Hazard Ratio (95% CI)**	**p-Value**
Symptom alleviation at or before Day 14 [n (%)]	61 (38.9)	33 (22.0)	1.92 (1.26 to 2.94)	0.001

Source: Study GS-US-540-9012 Clinical Study Report, Tables 15.9.2.15 and req13202.8.
Notes: Proportions are based on Kaplan-Meier estimates. The hazard ratio and 95% CI are based on Cox regression with baseline stratification factors as covariates. The p-value is based on a stratified log-rank test with baseline stratification factors as strata.
Abbreviations: CI, confidence interval; IV, intravenous; RDV, remdesivir; PBO, placebo

Reviewer Comment: The secondary analysis of time to symptom alleviation provided supportive evidence for the efficacy as numerical trends generally favored RDV. However, it is appropriate that the Applicant does not propose to include symptom results in labeling. The prespecified secondary analysis was limited by missing data and did not provide statistically conclusive evidence of an RDV treatment effect, the Applicant's additional analysis was post hoc and was based on a post-treatment subgroup, and the optimal definition of a symptom alleviation endpoint is unclear.

Secondary Endpoint of Time-Weighted Average Change From Baseline Viral Load

For the secondary analysis of time-weighted average change from baseline viral load through Day 7 in the virology analysis set there were no observed differences between the RDV and PBO groups. Virologic data (nasopharyngeal SARS-CoV-2 viral load) were available for 211 subjects in the RDV group and 208 subjects in the PBO group for this analysis. The estimated average decrease from baseline was -1.2 $\log_{10}$ copies/mL in each treatment arm.

Table 12. Time-Weighted Average Change From Baseline to Day 7 in Nasopharyngeal Viral Load, Virology Analysis Set, Study GS-US-540-9012

Parameter	RDV IV for 3 Days (N=217)	PBO (N=214)
Time-weighted average change from baseline to Day 7 (log_{10} copies/mL)		
n	211	208
LS mean (SE)	−1.22 (0.06)	−1.16 (0.06)
Median (IQR)	-1.15 (−2.01 to −0.54)	-1.11 (−1.82 to −0.41)
Difference by Day 7		
LS mean	0.07	
95% CI	−0.10 to 0.24	
p-value	0.43	

Source: Study GS-US-540-9012 Clinical Study Report, Table 18.
Notes: The time-weighted average was between the first postbaseline value through the last available value up to Day 7 minus the baseline value in SARS-CoV-2 viral load and was calculated using the trapezoidal rule and the area under the curve. For subjects with data through days prior to Day 7, the time-weighted average change used data up to last available time point. If there was no postbaseline data, the subject was excluded from the analysis. The LS mean (SE), 95% CI, and p-value were calculated from an analysis of covariance model with baseline viral load as a covariate.
Abbreviations: CI, confidence interval; IQR, interquartile range; IV, intravenous; LS, least squares; SE, standard error; PBO, placebo; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Reviewer Comment: Based on the available data, upper respiratory viral load is an inadequate efficacy surrogate for RDV. As this trial provided direct evidence of clinical benefit, the lack of an observed virologic treatment effect does not limit efficacy conclusions but may represent a limitation of nasopharyngeal viral load surrogate endpoints.

Subpopulations

As there were only 17 subjects in the FAS with events recorded for the primary endpoint of COVID-19-related or all-cause death by Day 28, subgroup analyses were limited by low event rates and small sample sizes. Because the hazard ratio method used for the primary analysis may have suboptimal properties with rare events, FDA reviewers analyzed subgroups by considering the primary endpoint as a binary endpoint rather than a time-to-event endpoint and assessing treatment effects through odds ratios with exact confidence intervals and exact p-values. The table below shows that results generally favored RDV compared to PBO across demographic subgroups. However, due to small sample sizes there was a high degree of uncertainty in several demographic subgroups such as subjects <18 years old (no events were recorded in the eight pediatric subjects in the trial), Asian and black subjects, and subjects outside the United States.

Table 13. Analysis of COVID-19-Related Hospitalization or All-Cause Death by Day 28 in Demographic Subgroups, Study GS-US-540-9012

Demographic Category	RDV IV for 3 Days (N=279)	PBO (N=283)	Odds Ratio (95% CI)	p-Value
Age category (years)				
<18	0/3 (0.0%)	0/5 (0.0%)		
≥18 to <60	1/193 (0.5%)	6/191 (3.1%)	0.16 (0.00 to 1.35)	0.067
≥60	1/83 (1.2%)	9/87 (10.3%)	0.11 (0.00 to 0.8)	0.018
Sex at birth				
Male	1/148 (0.7%)	9/145 (6.2%)	0.1 (0.00 to 0.76)	0.010
Female	1/131 (0.8%)	6/138 (4.3%)	0.17 (0.00 to 1.43)	0.121

Demographic Category	RDV IV for 3 Days (N=279)	PBO (N=283)	Odds Ratio (95% CI)	p-Value
Race category				
Asian	0/6 (0.0%)	0/7 (0.0%)		
Black	1/20 (5.0%)	2/22 (9.1%)	0.53 (0.01 to 11.06)	1.00
White	0/228 (0.0%)	12/224 (5.4%)	0.00 (0.00 to 0.34)	<0.001
Other or not permitted	1/25 (4.0%)	1/30 (3.3%)	1.21 (0.01 to 98.00)	1.00
Ethnicity				
Hispanic or Latino	0/123 (0%)	6/112 (5.4%)	0.00 (0.00 to 0.75)	0.011
Not Hispanic or Latino	2/146 (1.4%)	8/158 (5.1%)	0.26 (0.03 to 1.34)	0.106
Not permitted	0/10 (0%)	1/13 (7.7%)	0.00 (0.00 to 50.66)	≥0.99
Country				
USA	2/264 (0.8%)	12/267 (4.5%)	0.16 (0.02 to 0.74)	0.012
Outside USA	0/15 (0%)	3/16 (18.8%)	0.00 (0.00 to 2.49)	0.226

Source: Statistical reviewer and Study GS-US-540-9012 Clinical Study Report, Section 9.4.
Notes: Exact 95% CIs and p-values are based on Fisher's exact test.
Abbreviations: CI, confidence interval; IV, intravenous; RDV, remdesivir; PBO, placebo

The next table (Table 14) displays subgroup analyses by location of treatment, baseline risk factors for progression to severe disease, and days of symptoms prior to dosing. Results in the subgroup first dosed at outpatient treatment facilities mirrored the overall results because all but two primary endpoint events occurred in this group. Due to rare events, there was uncertainty regarding treatment effects in subjects first dosed at SNFs or through home health care. Results generally favored RDV compared to PBO in subgroups defined by baseline risk factors, and were nominally statistically significant in subjects with hypertension, diabetes, and obesity. Subgroup analyses did not suggest treatment effect modification by duration of prior symptoms, but the trial was not powered for this analysis and it is biologically plausible that antivirals may have greater efficacy when given earlier in the disease course.

Table 14. Analysis of COVID-19-Related Hospitalization or All-Cause Death by Day 28 in Baseline Subgroups, Study GS-US-540-9012

Baseline Subgroup	RDV IV for 3 Days (N=279)	PBO (N=283)	Odds Ratio (95% CI)	p-Value
Location of first dose				
Skilled nursing facility	0/8 (0.0%)	0/7 (0.0%)		
Home health care	1/36 (2.8%)	1/36 (2.8%)	1.00 (0.01 to 81)	≥0.99
Outpatient facility	1/235 (0.4%)	14/240 (5.8%)	0.07 (0.00 to 0.46)	0.001
Baseline risk factors				
Chronic lung disease	0/67 (0.0%)	4/68 (5.9%)	0.00 (0.00 to 1.51)	0.119
Hypertension	2/138 (1.4%)	10/130 (7.7%)	0.18 (0.02 to 0.86)	0.017
Cardiovascular or cerebrovascular disease	0/20 (0.0%)	2/24 (8.3%)	0.00 (0.00 to 6.37)	0.493
Diabetes mellitus	2/173 (1.2%)	14/173 (8.1%)	0.13 (0.01 to 0.60)	0.003
Obesity (BMI ≥30)	1/154 (0.6%)	9/156 (5.8%)	0.11 (0.00 to 0.79)	0.020
Immunocompromised state	0/14 (0%)	0/9 (0%)		
Chronic mild/moderate kidney disease	1/7 (14.3%)	1/11 (9.1%)	1.67 (0.02 to 143)	≥0.99
Chronic liver disease	0/1 (0%)	0/1 (0%)		
Current cancer	0/12 (0%)	2/18 (11.1%)	0.00 (0.00 to 8.01)	0.503
Sickle cell disease	0/0	0/0		

Baseline Subgroup	RDV IV for 3 Days (N=279)	PBO (N=283)	Odds Ratio (95% CI)	p-Value
Days of symptoms prior to first dose				
≤3	0/77 (0.0%)	5/69 (7.2%)	0.00 (0.00 to 0.95)	0.022
4	0/61 (0.0%)	3/71 (4.2%)	0.00 (0.00 to 2.8)	0.249
5	1/63 (1.6%)	1/54 (1.9%)	0.85 (0.01 to 68)	≥0.99
≥6	1/78 (1.3%)	6/89 (6.7%)	0.18 (0 to 1.55)	0.123

Source: Statistical reviewer and Study GS-US-540-9012 Clinical Study Report, Section 9.4 and Table req13292.10.
Notes: Exact 95% CIs and p-values are based on Fisher's exact test.
Abbreviations: BMI, body mass index; CI, confidence interval; IV, intravenous; RDV, remdesivir; PBO, placebo

Reviewer Comment: Subgroup analyses did not detect any modification of the treatment effect by baseline factors and did not detect any groups for which RDV may lack efficacy.

At the time of this writing, the Applicant has not provided data allowing subgroup analysis by baseline sequence data that identify variants of the infecting SARS-CoV-2. The Applicant plans to (b) (4) .

At the time of this writing the Applicant is in the process of (b) (4)

Reviewer Comment: Due to the trial design it has not been possible at the time of this writing to directly assess RDV treatment effects on clinical outcomes in subgroups defined by variant of the infecting SARS-CoV-2, baseline serostatus, or subjects with prior COVID-19 vaccination. Based on cell culture antiviral activity data (see Section 4.2), RDV is expected to be active against SARS-CoV-2 variants that have circulated at a high frequency to date.

Overall Efficacy Assessment

The results from this randomized, double-blind, placebo-controlled, multicenter trial provided reliable and statistically persuasive evidence of benefit for RDV in nonhospitalized subjects with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

In Study GS-US-540-9012, treatment with 3 days of IV RDV was significantly superior to PBO for the primary endpoint which is a composite of COVID-19-related hospitalization or all-cause mortality through Day 28. Overall, two (1%) subjects in the RDV group experienced COVID-19-related hospitalizations compared to 15 (5%) subjects in the PBO group (hazard ratio 0.13 [95% CI: 0.03 to 0.59]; p=0.008).

7.1.2. Subpopulations

Overall, demographic factors did not impact efficacy outcomes in Study GS-US-540-9012.

7.1.3. Dose and Dose-Response

Dose-ranging studies were not conducted as part of the Phase 3 development program in nonhospitalized patients. In the original NDA, RDV was evaluated for different durations in Phase 1, as well as in Phase 3 studies, GS-US-540-5773 and GS-US-540-5774.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

The risk of adverse outcomes from COVID-19 increases with age and the presence of underlying comorbidities or conditions, including but not limited to cancer, chronic kidney disease, chronic lung disease, obesity, diabetes, pregnancy, and immunocompromised states (Berlin et al. 2020; Gandhi et al. 2020; Puelles et al. 2020; Centers for Disease Control and Prevention 2021a; Centers for Disease Control and Prevention 2021b; COVID-19 Treatment Guidelines Panel 2021; Feburary 2021; Bhimraj et al. 2022; Centers for Disease Control and Prevention 2022; World Health Organization 2022). The goal of treatment of nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is to reduce morbidity and mortality. Therefore, the Phase 3 study, GS-US-540-9012 was designed to evaluate clinically meaningful primary endpoints, consistent with the guidance for industry COVID-19: Developing Drugs and Biologic Products for Treatment or Prevention (Feburary 2021).

Statistically significant treatment benefit over placebo for the primary endpoint of COVID-19-related hospitalization or all-cause death by Day 28 was observed in Study GS-US-540-9012 when RDV x 3 days was administered to nonhospitalized adult and pediatric patients (≥12 years and ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The 3-day course of IV RDV would provide an approved treatment option for nonhospitalized adult and pediatric patients (≥12 years and ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

The efficacy of RDV for the treatment of nonhospitalized adult and pediatric patients (≥12 years and ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, has been established by the results from the Phase 3 trial, as discussed in Section 6.

Data from Study GS-US-540-9012 demonstrate that for nonhospitalized adult and pediatric patients (≥12 years and ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, treatment with 3 days of RDV yields improved clinical outcomes compared to PBO. The key findings from Study GS-US-540-9012 are as follows:

- The primary efficacy analysis in the overall study population strongly favored RDV:
  - Significantly fewer subjects in the RDV group experienced COVID-19-related hospitalization by Day 28 compared to the PBO group
  - Overall, two (1%) subjects in the RDV group experienced COVID-19-related hospitalizations compared to 15 (5%) subjects in the PBO group
  - Hazard ratio 0.13; 95% CI: 0.03 to 0.59]; p=0.008)
  - No deaths were observed through Day 28 in either group

Overall, results from this randomized, double-blind, placebo-controlled trial provided reliable and statistically persuasive evidence of benefit for RDV for the treatment of nonhospitalized adult and pediatric patients (≥12 years and ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

When Study GS-US-540-9012 was prematurely terminated for administrative reasons after only 562 of the planned 1264 patients were enrolled, the Applicant described there was less need for a 3-day IV regimen due to decreasing rates of hospitalizations; increasing availability of single-infusion monoclonal antibodies under EUA for nonhospitalized high-risk patients with COVID-19; and increasing vaccination rates among high-risk individuals (Gordon et al. 2020b). The Applicant assessed that continuing to conduct a randomized placebo-controlled study with a multiple-day infusion treatment in such an environment had become increasingly difficult given the evolving epidemiology and therapeutic landscape (Tchesnokov et al. 2020). The Applicant

noted several study sites described ongoing challenges with patient recruitment in recent months given these therapeutic advances and study enrollment was significantly slower than expected with the changing epidemiology. At the time of study cessation, the first formal interim analysis had not yet occurred as this was planned after reaching 50% enrollment. No bias was expected to be introduced from early termination of this double-blinded trial as it was not related to accumulating results.

The logistical considerations associated with administering infusions in nonhospitalized patients with COVID-19, including multiple-day infusion regimens such as RDV, are acknowledged (Gottlieb et al. 2021b; Razonable et al. 2021).

From a clinical perspective, based on the results from the Phase 3 trial, the available data support that RDV, administered for days, is effective for the treatment of nonhospitalized adult and pediatric patients (≥12 years and ≥40 kg) with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

8. Review of Safety

8.1. Safety Review Approach

The safety review focused on Study GS-US-540-9012 as this Phase 3 study will be described in labeling. Data were analyzed with JMP Clinical software. Discrepancies between the FDA analyses and the Applicant's analyses were relatively minor and attributable to variable methods of pooling and subgroup analyses.

Hypersensitivity reactions and hepatotoxicity were the major safety issues identified in original NDA review, and these issues were a focus of scrutiny during the safety review of this sNDA.

The safety review also focused on adverse drug reactions (ADRs) of interest, including rash, renal events, hemorrhagic events, seizure events, pancytopenia, rhabdomyolysis, and pancreatitis.

Given the close temporal proximity of the finalized Phase 3 data and the timing of the sNDA submission, the Agency agreed with the Applicant's assessment that a safety update report was not needed.

The EUA outlines mandatory reporting of all medication errors and adverse events (death, serious adverse events) considered to be potentially related to RDV. EUA safety data and postmarketing safety data were reviewed by the Office of Surveillance and Epidemiology (OSE) and key findings are highlighted in the relevant safety sections of this report.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In Study GS-US-540-9012, the maximum duration of exposure to RDV was 3 days. The currently approved label describes safety data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19 treated with 5 to 10 days of RDV. This supplement evaluates 279 nonhospitalized adult and adolescent subjects treated with 3 days of RDV.

Table 15. Safety Population, Size and Denominators, Study GS-US-540-9012

Number of Doses Received	RDV 3 Days (N=279)	PBO (N=283)	Total (N=562)
1	4 (1.4%)	5 (1.8%)	9 (1.6%)
2	2 (0.7%)	8 (2.8%)	10 (1.8%)
3	273 (97.8%)	270 (95.4%)	543 (96.6%)

Source: ADAE dataset, Study GS-US-540-9012
Abbreviations: PBO, placebo; RDV, remdesivir

Reviewer Comment: The 3-day regimen was overall well-tolerated in nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death.

8.2.2. Relevant Characteristics of the Safety Population

Baseline characteristics for Study GS-US-540-9012 are described individually in Section 6.

Approximately 30% of subjects were at least 60 years old, slightly less than 70% of subjects were between 18 and 60 years old, and only eight subjects were adolescents under 18 years old. Approximately half of subjects were male, and half were female. The majority of subjects (approximately 80%) were white and slightly less than half of subjects were Hispanic or Latino. More than 94% of subjects were enrolled in the United States. Demographics were similar in the RDV and PBO groups. Subgroup analyses based on demographic factors will be presented in Section 8.6 of this review.

8.2.3. Adequacy of the Safety Database

The safety database (n=279) is considered adequate to assess the safety of RDV for the proposed indication, dosage regimen, duration of treatment, and patient population (nonhospitalized subjects who are at high risk for progression to severe COVID-19, including hospitalization or death), and is supported by the current labeling with safety data from three, Phase 3 trials in 1,313 hospitalized adult subjects with COVID-19 treated with RDV for 5 to 10 days.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No data quality or data integrity issues were identified. For Study GS-US-540-9012, all narratives for deaths, serious adverse events (SAEs), and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment.

8.3.2. Categorization of Adverse Events

No issues were identified with respect to recording, coding, and categorizing AEs. The Applicant categorized AEs and SAEs in accordance with standard regulatory definitions. In Study GS-US-540-9012, AEs were graded using the Division of AIDS (DAIDS) toxicity grading criteria.

8.3.3. Routine Clinical Tests

In Study GS-US-540-9012, routine clinical evaluation and laboratory testing occurred at prespecified intervals: Screening, Day 1 (Baseline), Days 2, 3, 7, 14; Follow-Up on Day 28. The frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurement, physical examinations, and standard laboratory safety tests. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

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

8.4. Safety Results

Each subsection in this section presents the results from Study GS-US-540-9012.

The SAS was used for all analyses unless otherwise specified; all subjects who received at least one dose of study medication were included in the SAS. Treatment-emergent events were defined in the trial and in this review as any AE with onset date on or after study drug start date and no later than 30 days after permanent study drug discontinuation, or any AE leading to premature study drug discontinuation. For all analyses, subjects who experienced the same treatment-emergent AE on more than once occasion are counted only once, at the highest toxicity grade reported. When a "total" value is included for a column, it represents the total number of subjects included the analysis, rather than the total number of events.

An overall summary of safety events in Study GS-US-540-9012 is presented in Table 16. The reviewer assessments and conclusions are overall similar to the Applicant's.

Table 16. Overview of Adverse Events, Study GS-US-540-9012

Subjects Experiencing Event	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Any AE	118 (42.3%)	131 (46.3%)
Related AE	34 (12.2%)	25 (8.8%)
Any Grade 3 or 4 AE	10 (3.6%)	20 (7.1%)
Related Grade 3 or 4 AE	1 (0.4%)	0 (0%)
SAE	5 (1.8%)	19 (6.7%)
Related SAE	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)
Related deaths	0 (0%)	0 (0%)
Discontinuation of study drug due to AE	2 (0.7%)	5 (1.8%)
Discontinuation of study drug due to related AEs	0 (0%)	0 (0%)

Source: ADAE dataset, Study GS-US-540-9012
Abbreviations: PBO, placebo; RDV, remdesivir; AE, adverse event; SAE, serious adverse event

Reviewer Comment: Higher rates (i.e., cumulative incidence) of SAEs, AEs, Grade 3/4 AEs, and AEs leading to discontinuation were observed with PBO compared to RDV. The majority of AEs were Grade 1 in severity. SAEs, AEs leading to study drug discontinuation, and Grade 3/4 AEs were infrequent. There were no treatment-related deaths. Related Grade 3/4 AEs were infrequent and there were no related SAEs. Among eight adolescents (RDV [n=3], PBO [n=5]) in the study, only one AE (mild fatigue in one placebo recipient) occurred.

8.4.1. Deaths

There was one death, occurring in a PBO recipient on Day 59: Subject (b) (6) was a 69-year-old white male with a history of hypertension, left bundle branch block, hyperlipidemia, obesity, obstructive sleep apnea, diabetes, peripheral vascular disease. This subject received three doses of PBO and developed worsening COVID-19 on Day 7, leading to hospitalization on Day 7. On Day 59, subject died due to worsening COVID-19. The AE of COVID-19was considered Grade 5, fatal, and not related to study drug.

Reviewer Comment: The clinical narrative was reviewed, and I agree with the investigators' assessments that this death was unrelated to study medication.

Overall Assessment: There were no treatment-related deaths in Study GS-US-540-9012.

8.4.2. Serious Adverse Events

SAEs were infrequent overall, occurring in 2% of subjects in the RDV group and 7% of subjects in the PBO group. These SAEs were assessed by investigators as not related to study drug. Table 17 provides a summary of SAEs by system organ class (SOC) and preferred term.

Table 17. Treatment-Emergent SAEs by System Organ Class and Preferred Term, Study GS-US-540-9012

SOC Preferred Term	RDV 3 Days N=279	PBO 3 Days N=283
Cardiac disorders (SOC)	3 (1.1%)	2 (0.7%)
Angina pectoris	1 (0.4%)	1 (0.4%)
Atrial fibrillation	2 (0.7%)	0 (0%)
Cardiac failure congestive	1 (0.4%)	0 (0%)
Acute myocardial infarction	0 (0%)	1 (0.4%)
Mitral valve prolapse	0 (0%)	1 (0.4%)
Infections and infestations (SOC)	3 (1.1%)	12 (4.2%)
COVID-19 pneumonia	0 (0%)	7 (2.5%)
Pneumonia	2 (0.7%)	3 (1.1%)
COVID-19	1 (0.4%)	2 (0.7%)
Viral myocarditis	1 (0.4%)	0 (0%)
Investigations (SOC)	0 (0%)	1 (0.4%)
Fibrin D-dimer increased	0 (0%)	1 (0.4%)
Injury, poisoning and procedural complications (SOC)	0 (0%)	1 (0.4%)
Lumbar vertebral fracture	0 (0%)	1 (0.4%)
Road traffic accident	0 (0%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.4%)	5 (1.8%)
Acute respiratory failure	0 (0%)	1 (0.4%)
Respiratory failure	1 (0.4%)	1 (0.4%)
Dyspnea	0 (0%)	1 (0.4%)
Hypoxia	0 (0%)	3 (1.1%)
Pulmonary embolism	0 (0%)	1 (0.4%)
Vascular disorders (SOC)	1 (0.4%)	0 (0%)
Blood pressure inadequately controlled	1 (0.4%)	0 (0%)
Total subjects	5 (1.8%)	19 (6.7%)

Source: ADAE dataset, Study GS-US-540-9012
Abbreviations: PBO, placebo; RDV, remdesivir; SOC, system organ class

Reviewer Comment: Higher rates of SAEs occurred in the PBO group compared to the RDV group. The clinical narratives were reviewed, and I agree with the investigators' assessments that these SAEs are unlikely to be related to study medication.

Overall Assessment: No specific drug-related safety concern has been identified from the SAEs reported in Study GS-US-540-9012. All narratives were reviewed and did not uncover new concerns. The reviewer assessments and conclusions are similar to the Applicant's.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs were infrequent, occurring in 1% of subjects in the RDV group and 2% of subjects in the PBO group (Table 18 and Table 19). These events were assessed by investigators as not related to study drug.

Table 18. Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term, Study GS-US-540-9012

SOC Preferred Term	RDV 3 Days N=279	PBO 3 Days N=283
Infections and infestations (SOC)	1 (0.4%)	4 (1.4%)
COVID-19	1 (0.4%)	1 (0.4%)
COVID-19 pneumonia	0 (0%)	2 (0.7%)
Pneumonia	1 (0.4%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.4%)	2 (0.7%)
Respiratory failure	1 (0.4%)	0 (0%)
Dyspnea	0 (0%)	1 (0.4%)
Hypoxia	0 (0%)	1 (0.4%)
Total subjects	2 (0.7%)	5 (1.8%)

Source: ADAE, ADSL datasets, Study GS-US-540-9012
Abbreviations: PBO, placebo; RDV, remdesivir; SOC, system organ class

Table 19. Adverse Events Leading to Study Drug Discontinuation, Study GS-US-540-9012

Treatment Arm	Dictionary-Derived Term	Day Start/End of AE	Last Day of Study Drug	# of Doses	SAE	Grade	Outcome	Related
RDV x 3 days								
(b) (6)	COVID-19	2/6	2	2	Yes	3	Resolved	No
	Pneumonia	2/13	2	2	Yes	3	Resolved	No
(b) (6)	Respiratory failure	3/-	3	3[1]	Yes	3	Ongoing	No
PBO x 3 days								
(b) (6)	COVID-19	2/35	1	1	Yes	3	Resolved	No
(b) (6)	COVID-19 pneumonia	2/-	2	2	Yes	3	Ongoing	No
(b) (6)	COVID-19 pneumonia	2/16	2	2	Yes	4	Resolved	No
(b) (6)	Hypoxia	3/11	2	2	Yes	1	Resolved	No
	Pneumonia	3/-	2	2	Yes	1	Ongoing	No
(b) (6)	Dyspnea	1/14	1	1	Yes	4	Resolved	No

Source: ADAE dataset; Study GS-US-540-9012
[1] Although subject (b) (6) received three doses of RDV, subject was hospitalized from Days 3 to 5, had an Emergency Room visit on Day 7, and was hospitalized from Days 8 to 16. These events and medically attended visits were all assessed by investigators as COVID-19 related.
Abbreviations: PBO, placebo; RDV, remdesivir; SAE, serious adverse event

Reviewer Comment: There were low rates of AEs leading to discontinuation (1 to 2%) across treatment groups; rates were slightly higher in the PBO group compared to the RDV group. The clinical narratives were reviewed, and I agree with the investigators' assessments.

Overall Assessment: No specific drug-related safety concern has been identified from the review of AEs leading to study drug discontinuation.

8.4.4. Significant Adverse Events

This section describes Grades 3 and 4 events that occurred in the treatment-emergent period (during treatment and through Day 28 visit).

Adverse events are treatment-emergent and regardless of causality. Adverse drug reactions are treatment-emergent and at least possibly related as assessed by the investigator. Some of these

events were also considered SAEs; hence, there is some overlap between events reported in this section and in Section 8.4.2.

Grade 3/4 AEs were infrequent, occurring 4% of subjects in the RDV group and 7% of subjects in the PBO group (Table 20).

Table 20. Grade 3 or Higher AEs by System Organ Class and Preferred Term, Study GS-US-540-9012

SOC Preferred Term	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Cardiac disorders (SOC)	2 (0.7%)	2 (0.7%)
Angina pectoris	1 (0.4%)	1 (0.4%)
Atrial fibrillation	1 (0.4%)	0 (0%)
Cardiac failure congestive	1 (0.4%)	0 (0%)
Acute myocardial infarction	0 (0%)	1 (0.4%)
Gastrointestinal disorders (SOC)	1 (0.4%)	0 (0%)
Abdominal pain	1 (0.4%)	0 (0%)
Diarrhea	1 (0.4%)	0 (0%)
General disorders and administration site conditions (SOC)	7 (1.3%)	5 (1.0%)
Fatigue	1 (0.4%)	0 (0%)
Injection site thrombosis	1 (0.4%)	0 (0%)
Infections and infestations (SOC)	4 (1.4%)	10 (3.5%)
COVID-19 pneumonia	0 (0%)	6 (2.1%)
Pneumonia	2 (0.7%)	2 (0.7%)
COVID-19	1 (0.4%)	2 (0.7%)
Tooth infection	1 (0.4%)	0 (0%)
Viral myocarditis	1 (0.4%)	0 (0%)
Injury, poisoning and procedural complications (SOC)	0 (0%)	1 (0.4%)
Lumbar vertebral fracture	0 (0%)	1 (0.4%)
Road traffic accident	0 (0%)	1 (0.4%)
Investigations (SOC)	1 (0.4%)	1 (0.4%)
Alanine aminotransferase increased	1 (0.4%)	0 (0%)
Aspartate aminotransferase increased	1 (0.4%)	0 (0%)
Fibrin D-dimer increased	0 (0%)	1 (0.4%)
Metabolism and nutrition disorders (SOC)	1 (0.4%)	0 (0%)
Hypokalemia	1 (0.4%)	0 (0%)
Musculoskeletal and connective tissue disorders (SOC)	0 (0%)	1 (0.4%)
Musculoskeletal chest pain	0 (0%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.4%)	6 (2.1%)
Acute respiratory failure	0 (0%)	1 (0.4%)
Respiratory failure	1 (0.4%)	1 (0.4%)
Dyspnea	0 (0%)	3 (1.1%)
Hypoxia	0 (0%)	1 (0.4%)
Vascular disorders (SOC)	1 (0.4%)	1 (0.4%)
Blood pressure inadequately controlled	1 (0.4%)	0 (0%)
Deep venous thrombosis	0 (0%)	1 (0.4%)
Total subjects	10 (3.6%)	20 (7.1%)

Source: ADAE dataset, Study GS-US-540-9012
Abbreviations: AE, adverse event; PBO, placebo; RDV, remdesivir; SOC, system organ class

The majority of Grade 3/4 AEs were assessed by investigators as not related to study drug. Grade 3/4 AEs that occurred in two or more subjects in each group were:

- RDV: pneumonia (n=2)
- PBO: COVID-19 pneumonia (n=6), dyspnea (n=3), pneumonia (n=2)

Grade 3/4 AEs considered related to study drug by the study investigators (i.e., ADRs) occurred in one subject in the RDV group and no subjects in the PBO group.

- In the RDV group, Subject (b) (6) had Grade 3 AEs of ALT increased and AST increased at Day 9; these AEs were not considered by investigators to be serious and resolved by Day 15 with no further intervention.
  - Baseline: ALT 25 U/L; AST 24 U/L
  - Day 3: ALT 25 U/L; AST 23 U/L
  - Day 8: ALT 272 U/L; AST 219 U/L
  - Day 11: ALT 154 U/L; AST 63 U/L
  - Day 15: ALT 98 U/L; AST 43 U/L

Reviewer Comment: No clear safety signal emerged from the review of the Grades 3 and 4 events.

8.4.5. Treatment-Emergent Adverse Events and Adverse Reactions

Treatment-emergent AEs (TEAEs) occurred in 42% of subjects in the RDV group and 46% of subjects in the PBO group. The majority of these AEs were assessed by investigators as not related to study drug. Table 21 summarizes TEAEs occurring with ≥2% frequency in either group, irrespective of severity or causality.

Table 21. Treatment-Emergent AEs by Preferred Term, All Grade and All Causality, Occurring in ≥1% in Either Treatment Group, Study GS-US-540-9012

Preferred Term	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Nausea	30 (10.8%)	21 (7.4%)
Headache	16 (5.7%)	17 (6.0%)
Cough	10 (3.6%)	18 (6.4%)
Diarrhea	11 (3.9%)	11 (3.9%)
Fatigue	10 (3.6%)	11 (3.9%)
Dyspnea	7 (2.5%)	15 (5.3%)
Ageusia	8 (2.9%)	7 (2.5%)
Anosmia	9 (3.2%)	6 (2.1%)
Dizziness	5 (1.8%)	10 (3.5%)
Chills	6 (2.2%)	8 (2.8%)
Pyrexia	1 (0.4%)	11 (3.9%)
COVID-19 pneumonia	2 (0.7%)	8 (2.8%)
Abdominal pain[1]	6 (2.2%)	4 (1.4%)
Vomiting	4 (1.4%)	4 (1.4%)
Decreased appetite	4 (1.4%)	4 (1.4%)
Back pain	3 (1.1%)	5 (1.8%)

Preferred Term	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Insomnia	3 (1.1%)	5 (1.8%)
Pneumonia	2 (0.7%)	6 (2.1%)
Pruritus	5 (1.8%)	2 (0.7%)
Infusion site pain	4 (1.4%)	3 (1.1%)
Chest discomfort	2 (0.7%)	5 (1.8%)
Rash[2]	6 (2.2%)	1 (0.4%)
Oropharyngeal pain	3 (1.1%)	3 (1.1%)
Lower respiratory tract congestion	3 (1.1%)	2 (0.7%)
Sinus congestion	3 (1.1%)	2 (0.7%)
Palpitations	2 (0.7%)	3 (1.1%)
Hypertension	4 (1.4%)	0 (0%)
Lacrimation increased	3 (1.1%)	1 (0.4%)
Nasal discomfort	3 (1.1%)	1 (0.4%)
Constipation	2 (0.7%)	2 (0.7%)
Alanine aminotransferase increased	1 (0.4%)	3 (1.1%)
Total subjects	118 (42.3%)	131 (46.3%)

Source: ADAE dataset, Study GS-US-540-9012
[1] Includes abdominal pain, abdominal pain upper, abdominal tenderness, abdominal distension, abdominal discomfort, abdominal symptom.
[2] Includes rash, rash macular.
Abbreviations: AE, adverse event; PBO, placebo; RDV, remdesivir

The majority of events were Grade 1 in severity. The three most commonly reported AEs in each group were:

- RDV: nausea (11%), headache (6%), diarrhea (4%)
- PBO: nausea (7%), headache (6%), cough (6%)

Table 22 summarizes treatment-related adverse events (hereafter referred to as ADRs), irrespective of severity. The investigator's determination of causality is the basis for classification. The limitations of this approach to causality assessment are acknowledged.

Table 22. Treatment-Emergent ADRs, Study GS-US-540-9012

Preferred Term	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Nausea	18 (6.5%)	10 (3.5%)
Chills	6 (2.2%)	6 (2.1%)
Vomiting	2 (0.7%)	3 (1.1%)
Alanine aminotransferase increased	1 (0.4%)	3 (1.1%)
Diarrhea	1 (0.4%)	3 (1.1%)
Dizziness	1 (0.4%)	3 (1.1%)
Headache	3 (1.1%)	0 (0%)
Rash[1]	3 (1.1%)	0 (0%)
Pruritus	2 (0.7%)	1 (0.4%)
Tachycardia	1 (0.4%)	2 (0.7%)
Aspartate aminotransferase increased	1 (0.4%)	1 (0.4%)
Blood pressure increased	0 (0%)	2 (0.7%)
Arthralgia	1 (0.4%)	0 (0%)
Dry mouth	1 (0.4%)	0 (0%)

Preferred Term	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Gastroesophageal reflux disease	1 (0.4%)	0 (0%)
Hyperhidrosis	1 (0.4%)	0 (0%)
Hypertension	1 (0.4%)	0 (0%)
Hypotension	1 (0.4%)	0 (0%)
Palpitations	1 (0.4%)	0 (0%)
Abnormal dreams	0 (0%)	1 (0.4%)
Pyrexia	0 (0%)	1 (0.4%)
Tinnitus	0 (0%)	1 (0.4%)
Total subjects	34 (12.2%)	25 (8.8%)

Source: ADAE dataset, Study GS-US-540-9012
[1] Includes rash, rash macular.
Abbreviations: ADR, adverse drug reaction; PBO, placebo; RDV, remdesivir

For nonlaboratory events, the most commonly reported ADRs in each group were:

- RDV: nausea (7%), chills (2%), headache (1%), rash (1%)
- PBO: nausea (4%), chills (2%), diarrhea (1%), dizziness (1%)

Reviewer Comment: Higher rates of ADRs occurred in the RDV group compared to the PBO group (12% versus 9%). Nausea was the only clinical ADR that occurred in ≥5% in the RDV group. Nausea (7% versus 4%) was also the only ADR with a ≥2% risk difference between RDV and PBO.

Overall Assessment: No new or unexpected findings were observed compared to the events noted in the hospitalized trials. Nausea was the most commonly reported ADR in the Phase 3 clinical trial in nonhospitalized patients. Product labeling for the nonhospitalized population will display ADR results for nausea as this ADR occurred with greater frequency compared to PBO.

8.4.6. Laboratory Findings

The tables in this section display treatment-emergent graded laboratory abnormalities for chemistry and hematology parameters in Study GS-US-540-9012. These analyses represent the worst change from baseline per subject.

Graded chemistry results are summarized in Table 23, and hematology results in Table 24.

Table 23. Liver Function Tests and Other Chemistry Lab Results, All Grade, Study GS-US-540-9012

Parameter and Max Analysis Toxicity Grade	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Liver function test		
Increased alanine aminotransferase (U/L)		
Grade 1 (1.25 to <2.5 × ULN)	29 (10.6%)	27 (9.8%)
Grade 2 (2.5 to <5 × ULN)	4 (1.5%)	8 (2.9%)
Grade 3 (5 to <10 × ULN)	1 (0.4%)	2 (0.7%)
Grade 4 (≥10 × ULN)	0 (0%)	0 (0%)
Increased aspartate aminotransferase (U/L)		
Grade 1 (1.25 to <2.5 × ULN)	16 (5.8%)	12 (4.4%)
Grade 2 (2.5 to <5 × ULN)	3 (1.1%)	5 (1.8%)
Grade 3 (5 to <10 × ULN)	1 (0.4%)	1 (0.4%)
Grade 4 (≥10 × ULN)	0 (0%)	0 (0%)
Increased total bilirubin (mg/dL)		
Grade 1 (1.1 to <1.6 × ULN)	3 (1.1%)	5 (1.8%)
Grade 2 (1.6 to <2.6 × ULN)	0 (0%)	0 (0%)
Grade 3 (2.6 to <5 x ULN)	0 (0%)	0 (0%)
Grade 4 (≥5 x ULN)	0 (0%)	0 (0%)
Liver function tests and other chemistry labs		
Increased creatinine (mg/dL)		
Grade 1 (1.1 to 1.3 × ULN)	2 (0.7%)	1 (0.4%)
Grade 2 (>1.3 to 1.8 × ULN *OR* increase to 1.3 to <1.5 x subject's baseline)	15 (5.5%)	10 (3.6%)
Grade 3 (>1.8 to <3.5 x ULN *OR* increase to 1.5 to <2.0 x subject's baseline)	8 (2.9%)	3 (1.1%)
Grade 4 (≥3.5 x ULN *OR* increase of ≥2.0 x subject's baseline)	0 (0%)	0 (0%)
Decreased creatinine clearance (mL/min)		
Grade 1 (NA)	0 (0%)	0 (0%)
Grade 2 (<90 to 60 mL/min *OR* 10 to <30% decrease from subject's baseline)	71 (26.3%)	67 (24.8%)
Grade 3 (<60 to 30 mL/min *OR* 30 to <50% decrease from subject's baseline)	14 (5.2%)	5 (1.9%)
Grade 4 (<30 mL/min *OR* ≥50% decrease from subject's baseline or dialysis needed)	1 (0.4%)	0 (0%)
Increased glucose (mg/dL)		
Grade 1 (116 to 160 mg/dL)	70 (29.8%)	77 (31.4%)
Grade 2 (>160 to 250 mg/dL)	33 (14.0%)	26 (10.6%)
Grade 3 (>250 to 500 mg/dL)	14 (6.0%)	14 (5.7%)
Grade 4 (≥500 mg/dL)	1 (0.4%)	0 (0%)

Source: ADLB dataset, Study GS-US-540-9012
Creatinine Clearance calculated using Cockcroft-Gault formula
Abbreviations: PBO, placebo; RDV, remdesivir; ULN, upper limit of normal

Reviewer Comment: Nonclinical studies in rats and cynomolgus monkeys identified the kidney as the target organ of toxicity, mainly driven by the sulfobutylether-β-cyclodextrin sodium salt excipient. Similar effects were seen in humans in Study GS-US-540-9012, with increased creatinine (3% versus 1%) in the RDV group compared to the PBO group. Additionally, higher rates of Grade 3/4 creatinine clearance decreased (6% versus 2%) were seen in the RDV group compared to the PBO group. These laboratory abnormalities were also noted in the hospitalized

trials but occurred at similar or slightly higher rates in the PBO or SOC groups compared to the RDV group. Please refer to Section 8.5.10 for further details.

Rates of Grade 3/4 transaminase elevations were low (<1%) across treatment groups; Grade 3/4 transaminase elevations occurred at similar or slightly higher rates in the PBO group compared to the RDV group. There were no Grade 3/4 bilirubin elevations in either group.

Table 24. Hematology and Coagulation Laboratory Results, All Grade, Study GS-US-540-9012

Parameter/ Max Analysis Toxicity Grade	RDV 3 Days N=279	PBO 3 Days N=283
Decreased hemoglobin (g/dL)		
Grade 1 (10 to <10.9 g/dL)	5 (1.8%)	6 (2.2%)
Grade 2 (9 to <10 g/dL)	1 (0.4%)	2 (0.7%)
Grade 3 (7 to <9 g/dL)	0 (0%)	0 (0%)
Grade 4 (<7 g/dL)	0 (0%)	0 (0%)
Decreased neutrophils (cells/mm^3)		
Grade 1 (800 to 1000/mm^3)	2 (0.7%)	2 (0.7%)
Grade 2 (600 to 799/mm^3)	0 (0%)	0 (0%)
Grade 3 (400 to 599/mm^3)	1 (0.4%)	0 (0%)
Grade 4 (<400/mm^3)	0 (0%)	0 (0%)
Decreased lymphocytes (cells/mm^3)		
Grade 1 (600 to 650/mm^3)	1 (0.4%)	5 (1.8%)
Grade 2 (500 to <600/mm^3)	1 (0.4%)	2 (0.7%)
Grade 3 (350 to <500/mm^3)	3 (1.1%)	3 (1.1%)
Grade 4 (<350/mm^3)	1 (0.4%)	0 (0%)
Decreased platelets (cells/mm^3)		
Grade 1 (100,000 to <125,000/mm^3)	2 (0.7%)	7 (2.5%)
Grade 2 (50,000 to <100,000/mm^3)	2 (0.7%)	3 (1.1%)
Grade 3 (25,000 to <50,000/mm^3)	0 (0%)	0 (0%)
Grade 4 (<25,000/mm^3)	1 (0.4%)	0 (0%)
Prothrombin time increased		
Grade 1 (1.1 to <1.25 × ULN)	11 (4.4%)	10 (4.1%)
Grade 2 (1.25 to <1.5 × ULN)	0 (0%)	2 (0.8%)
Grade 3 (1.5 to <3 x ULN)	2 (0.8%)	3 (1.2%)
Grade 4 (≥3 x ULN)	0 (0%)	2 (0.8%)

Source: ADLB dataset, Study GS-US-540-9012
Abbreviations: PBO, placebo; RDV, remdesivir; ULN, upper limit of normal

Reviewer Comment: Grade 3/4 prothrombin time (PT) elevations were uncommon; slightly higher rates of Grade 3/4 PT elevations occurred in the PBO group compared to the RDV group (2% versus 1%).

Grade 3/4 hematologic laboratory abnormalities were uncommon. No Grade 3/4 decreased hemoglobin occurred in either group. The other Grade 3/4 hematologic laboratory abnormalities (decreased neutrophils; decreased lymphocytes; decreased platelets) occurred at similar or slightly higher rates in subjects treated with RDV relative to PBO:

- *Grade 3/4 decreased lymphocytes: RDV 1.5% versus PBO 1.1%*
- *Grade 3/4 decreased neutrophils: RDV 0.4% versus PBO 0%*
- *Grade 3/4 decreased platelets: RDV 0.4% versus PBO 0%*

Overall Assessment: The laboratory abnormalities noted were also observed in the hospitalized trials, albeit at a higher frequency in the hospitalized trials. No new or unexpected findings were observed. In Study GS-US-540-9012, the notable laboratory abnormalities were the higher rates of Grade 3/4 creatinine clearance decreased (6% versus 2%) and creatinine increased (3% versus 1%) in the RDV group compared to the PBO group. These findings will be displayed in product labeling. Of note, the approved labeling already outlines that monitoring of renal function is recommended while receiving RDV (see Section 8.5.10 for a summary of renal safety).

8.4.7. Vital Signs

In Study GS-US-540-9012, vital signs were measured at prespecified intervals: Screening; Day 1 (baseline), Days 2, 3, 7, 14; Day 28 follow-up visit (if conducted in-person). On Days 1, 2, and 3, vital signs were measured pre-infusion, postinfusion, and when postinfusion observation was completed. No clinically meaningful changes in vital signs were observed in association with RDV use.

8.4.8. Electrocardiograms

Electrocardiograms were not assessed in the Phase 3 trial unless clinically indicated. No treatment-emergent electrocardiogram abnormalities were reported in Study GS-US-540-9012.

Reviewer Comment: The primary review team concludes that the available reported cardiac data do not require specific safety labeling. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.4.9. QT

Please refer to the review of the original NDA for further details. A thorough QT study will be conducted as a postmarketing requirement (PMR).

8.4.10. Immunogenicity

Because RDV is a small molecule and not a peptide, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials.

8.5. Analysis of Submission-Specific Safety Issues

This section includes analyses conducted to address safety concerns based on nonclinical studies such as renal events, concerns from prior trials such as hepatotoxicity, as well as issues which can be associated with antiviral nucleoside/nucleotide inhibitors, such as cardiac events, rash, and elevations of creatine kinase and lipase.

8.5.1. Hepatotoxicity

- In Study GS-US-540-9012, the only hepatic AEs were laboratory events (see Section 8.4.5):
  - RDV: ALT increased (n=1), AST increased (n=1)
  - PBO: ALT increased (n=3), AST increased (n=1)
- Hepatic ADRs were the same laboratory events outlined above (see Section 8.4.5):
- Grade 3/4 hepatic AEs occurred in one subject (0.4%) in the RDV group and zero subjects in the PBO group (see Section 8.4.4):
  - Subject (b) (6) had Grade 3 AEs of ALT increased and AST increased at Day 9; these were also assessed as Grade 3/4 ADRs (see Section 8.4.4).
- There were no hepatic SAEs (see Section 8.4.2).
- No hepatic AEs or hepatic ADRs led to discontinuation (see Section 8.4.3).
- Grade 3/4 ALT elevations occurred in one subject (0.4%) in the RDV group and two subjects (0.7%) in the PBO group. Grade 3/4 AST elevations occurred in one subject (0.4%) in the RDV group and one subject (0.4%) in the PBO group (see Section 8.4.6).
- No Grade 3/4 transaminase elevations led to discontinuation (see Section 8.4.3).

Overall Assessment: The Warnings and Precautions section for the original product labeling (in hospitalized subjects) clearly describes the hepatotoxicity safety signal that has been observed for RDV and outlines risk mitigation strategies for health care providers to consider. The approved labeling also displays hepatic laboratory data in Section 6, and under Section 2, recommends performing hepatic laboratory testing in all patients before starting RDV and while receiving RDV as clinically appropriate.

As a postmarketing requirement, the Applicant is also conducting a pharmacokinetic and safety study in adults with moderate and severe hepatic impairment to better define potential safety risks and inform dosage recommendations for this subpopulation.

In Study GS-US-540-9012, there were no hepatic AEs other than laboratory abnormalities. There were low rates of Grade 3/4 hepatic laboratory abnormalities (<1%) across treatment groups, with a slightly higher rate in the PBO group compared to the RDV group. Based on these findings, no additional labeling regarding hepatotoxicity is warranted at this time. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.2. Hypersensitivity Reactions

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of RDV. Clinical manifestations have included hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering.

Hypersensitivity or infusion-related reactions occurred in 14 subjects (5%) in the RDV group and 10 subjects (3.5%) in the PBO group. The majority of events were Grade 1 in severity.

- RDV (n=14 [note: subjects could have more than one event]): Grade 1 (n=14), Grade 2 (n=1)
  - Events that were considered related occurred in six subjects (2.2%): rash (n=3), hyperhidrosis (n=1), hypertension (n=1), hypotension (n=1); all of these ADRs were Grade 1 in severity.
- PBO (n=10): Grade 1 [(n=7), Grade 2 (n=3)
  - Events that were considered related occurred in two subjects (0.7%): hypertension (n=2); both of these ADRs were Grade 1 in severity.

No SAEs or Grade 3/4 events were observed in Study GS-US-540-9012 (see Sections 8.4.2 and 8.4.4). No subjects discontinued RDV due to hypersensitivity or infusion-related reactions (see Section 8.4.3).

Overall Assessment: The original product labeling (in hospitalized subjects) includes a Warnings and Precautions section that clearly describes the hypersensitivity reactions, including infusion-related and anaphylactic reactions, that have been observed for RDV and outlines risk mitigation strategies for health care providers to consider. The majority of these events, including those that resulted in the Warning and Precautions occurred within one-hour postinfusion. Of note, the first update to the Warning and Precaution section was implemented on June 15, 2020, with revisions to the EUA fact sheet due to the emergence of new safety findings after the May 1, 2020, initial EUA issuance; this safety information was also subsequently described in the Warning and Precaution section of the original product labeling. Please refer to the OSE review by Kate McCartan, Kimberley Swank, Miriam Chehab, Paolo Fanti, Rachna Kapoor and Ida-Lina Diak for details (Reference ID in DARRTS: 4638219). Hypersensitivity reactions are also included under Less Common Adverse Reactions in the original product labeling.

> **5.1 Hypersensitivity Including Infusion-Related and Anaphylactic Reactions (Approved USPI)**
>
> Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of VEKLURY. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients under close medical supervision for hypersensitivity reactions during and following administration of VEKLURY. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment. The use of VEKLURY is contraindicated in patients with known hypersensitivity to VEKLURY or any components of the product [see Contraindications (4)].

During the original NDA review, a suggested timeframe for postinfusion monitoring was not described because it was encompassed by the level of monitoring commensurate with ongoing, inpatient care in a hospital or in a health care setting capable of providing acute care comparable to inpatient hospital care.

Due to the use of RDV in both inpatient and outpatient settings that would result following approval of this sNDA, the review team provided additional description that the available data

indicate that most of these events occurred within one-hour postinfusion. The review team also concluded that monitoring patients during infusion and observing patient for at least one hour after infusion for signs and symptoms of hypersensitivity as clinically appropriate is supported by the clinical data.

In Study GS-US-540-9012, slightly higher rates of hypersensitivity or infusion-related reactions occurred in the RDV group compared to the PBO group (5% versus 4%). There were no anaphylactic reactions. Based on these findings, no additional labeling regarding hypersensitivity reactions is warranted at this time beyond the above noted revision. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.3. Cardiac Disorders

Cardiac AEs (all causality) were infrequent in Study GS-US-540-9012, occurring in 2% (7 of 279 subjects) in the RDV group and 3% (9 of 283 subjects) in the PBO group.

Table 25. Treatment-Emergent Cardiac AEs by System Organ Class and Preferred Term, All Causality, Study GS-US-540-9012

SOC Preferred Term	RDV 3 Days N=279 n (%)	PBO 3 Days N=283 n (%)
Cardiac disorders (SOC)	7 (2.5%)	9 (3.2%)
Angina pectoris	1 (0.4%)	1 (0.4%)
Atrial fibrillation	2 (0.7%)	0 (0%)
Cardiac failure congestive	1 (0.4%)	0 (0%)
Acute left ventricular failure	1 (0.4%)	0 (0%)
Acute myocardial infarction	0 (0%)	1 (0.4%)
Bradycardia	0 (0%)	2 (0.7%)
Tachycardia	1 (0.4%)	2 (0.7%)
Palpitations	2 (0.7%)	3 (1.1%)
Mitral valve prolapse	0 (0%)	1 (0.4%)
Total subjects	7 (2.5%)	9 (3.2%)

Source: ADAE dataset, Study GS-US-540-9012
Abbreviations: AE, adverse event; PBO, placebo; RDV, remdesivir; SOC, system organ class

- Grade 3/4 cardiac AEs occurred in 1% (2 of 279 subjects) in the RDV group and 1% (2 of 283 subjects) in the PBO group (see Section 8.4.4).
- There were no Grade 3/4 cardiac ADRs (see Section 8.4.4).
- Cardiac SAEs occurred in 1% (3 of 279 subjects) in the RDV group and 1% (2 of 283 subjects) in the PBO group (see Section 8.4.2).
- No cardiac SAEs were assessed as related to RDV (see Section 8.4.2).
- No cardiac AEs led to discontinuation (see Section 8.4.3).
- Sinus bradycardia occurred in zero of 279 subjects in the RDV group, while two AEs of sinus bradycardia (that were assessed by investigators as part of infusion-related reactions) were reported in the 283 patients who received PBO.

- Cardiac ADRs occurred in 1% (2 of 279 subjects) in the RDV group and 1% (2 of 283 subjects) in the PBO group:
  - RDV: tachycardia (n=1), palpitations (n=1)
  - PBO: tachycardia (n=2)
- No cardiac ADRs led to discontinuation (see Section 8.4.3).

Overall Assessment: The primary review team concludes that the available reported cardiac data do not require specific safety labeling. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.4. Seizure

No seizure events were reported in Study GS-US-540-9012.

Overall Assessment: Although there is no clear indication for an increased risk of seizure events with RDV, seizure was included under Less Common Adverse Reactions in the original product labeling (in hospitalized subjects) due to one drug-related seizure event that led to RDV discontinuation in the adaptive COVID-19 treatment trial 1 (ACTT-1).

In Study GS-US-540-9012, there were no seizure events. Based on these findings, no additional labeling regarding seizure events is warranted at this time. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.5. Rash

Rash events were infrequent in Study GS-US-540-9012, occurring in six subjects (2.2%) in the RDV group and one subject (0.4%) in the PBO group. All rash events were Grade 1 in severity.

- Rash events that were considered related occurred in three subjects (1.1%) in the RDV group.
- No subjects discontinued RDV due to rash.

No Grade 3/4 events, and no events of Stevens Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme were observed in Study GS-US-540-9012.

Overall Assessment: Although no specific safety signal was detected for rash events, rash was included under Less Common Adverse Reactions in the original product labeling (in hospitalized subjects) because some drug-related rash events led to RDV discontinuation.

In Study GS-US-540-9012, the frequency and severity of rash events occurring with RDV was low. Based on these findings, no additional labeling regarding rash events is warranted at this time. Any potential signals of serious rash events associated with RDV use will be closely monitored in the postmarketing setting.

8.5.6. Rhabdomyolysis

There were no cases of rhabdomyolysis in Study GS-US-540-9012.

Overall Assessment: Rhabdomyolysis was not an adverse event of specific concern during the RDV development program. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.7. Pancreatitis

There was one case of pancreatitis in Study GS-US-540-9012, occurring in a PBO recipient.

Overall Assessment: Pancreatitis was not an adverse event of specific concern during the RDV development program. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.8. Pancytopenia

There were no cases of pancytopenia in Study GS-US-540-9012.

Overall Assessment: The primary review team concludes that the available reported data do not require specific safety labeling for pancytopenia. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.9. Hemorrhagic Events

Hemorrhagic events were infrequent in Study GS-US-540-9012, occurring in two subjects in the RDV group (Grade 1 ecchymosis [n=1]; Grade 1 hematochezia [n=1]) and zero subjects in the PBO group. Both events in the RDV group were considered not related to RDV.

Grades 3 to 4 PT/INR elevations were infrequent in Study GS-US-540-9012, occurring in two subjects (0.8%) in the RDV group and five subjects (2.1%) in the PBO group (see Section 8.4.6).

Overall Assessment: The original product labeling (in hospitalized subjects) describes the disproportionate incidence of elevated PT in ACTT-1 and recommends monitoring PT as appropriate.

In Study GS-US-540-9012, the frequency and severity of hemorrhagic events occurring with RDV was low. The primary review team concludes that the available reported data do not require specific safety labeling for hemorrhagic events. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.10. Renal

The renal safety assessment from the original NDA is summarized below:

- In nonclinical safety studies reviewed as part of the original NDA, the kidney was identified as the target organ of toxicity, mainly driven by the excipient sulfobutylether-β-cyclodextrin sodium salt. However, a renal safety signal was not observed in the healthy volunteer studies with RDV.

- SARS-CoV-2 has multi-organ tropism, including the lungs, pharynx, heart, liver, brain, and kidney (Puelles et al. 2020). Renal tropism is a potential explanation of commonly reported clinical signs of kidney injury in patients with COVID-19 (Berlin et al. 2020; Gagliardi et al. 2020; Gandhi et al. 2020; Puelles et al. 2020; Ronco et al. 2020; Shao et al. 2020; Centers for Disease Control and Prevention 2021b). As renal injury and abnormal renal laboratory parameters have been reported in patients with COVID-19, including in patients receiving placebo in clinical trials of RDV, as well as in the EUA cases, and in published literature, discerning the contribution of RDV to renal events in the hospitalized patient population is challenging (Beigel et al. 2020; Berlin et al. 2020; Gagliardi et al. 2020; Gandhi et al. 2020; Gilead Sciences 2020b; Gilead Sciences 2020a; Goldman et al. 2020; Hinton 2020; Puelles et al. 2020; Ronco et al. 2020; Shao et al. 2020; Spinner et al. 2020; Centers for Disease Control and Prevention 2021b; Gilead Sciences 2021b).
- In ACTT-1, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were lower in the RDV group compared to PBO (Beigel et al. 2020; Gilead Sciences 2021b).
- In Study GS-US-540-5773, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were higher in the RDV 10-day group compared to the RDV 5-day group (Goldman et al. 2020; Gilead Sciences 2021b).
- In Study GS-US-540-5774, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were higher in the RDV 10-day group compared to the RDV 5-day group; however, rates of Grade 3/4 renal laboratory abnormalities were higher in the SOC group than in either RDV group (Spinner et al. 2020; Gilead Sciences 2021b).
- Overall, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were lower in Study GS-US-540-5774 in subjects with moderate COVID-19 compared to Study GS-US-540-5773 in subjects with severe COVID-19. Despite the caveats associated with cross-study comparisons, these observations highlight the contribution of disease severity to adverse renal outcomes (Goldman et al. 2020; Spinner et al. 2020; Gilead Sciences 2021b).
- Review of EUA data did not identify any nonconfounded cases of renal injury with sufficient information to assess as related to RDV.
- Based on all available information, the original product labeling described the preclinical renal findings in Section 13 and displayed renal laboratory data (from the RCTs in hospitalized subjects [ACTT-1, GS-US-540-5773, GS-US-540-5774]) in Section 6 of the labeling (Beigel et al. 2020; Gilead Sciences 2020b; Gilead Sciences 2020a; Goldman et al. 2020; Hinton 2020; Spinner et al. 2020; Gilead Sciences 2021b).
- There remains uncertainty about aspects of the safety profile of RDV in the setting of renal impairment. For patients with eGFR >30, the review team concluded that the potential benefit of RDV in this population outweighs the potential risk.
- As a postmarketing requirement, the Applicant is conducting a pharmacokinetic and safety study to further assess potential safety risks in adults with varying degrees of chronic renal impairment (i.e., mild, moderate, and severe) and to inform dosage recommendations for this subpopulation.

In this sNDA in nonhospitalized subjects who are at high risk for progression to severe COVID-19, including hospitalization or death:

- Only one renal AE (Grade 1 pollakiuria in a RDV recipient) was reported; this renal event was assessed as not related to RDV.
- Laboratory data comprise the majority of the renal safety evaluation in Study GS-US-540-9012:
  - Higher rates of Grade 3/4 creatinine clearance decreased (6% versus 2%) and creatinine increased (3% versus 1%) occurred in the RDV group compared to the PBO group (see Section 8.4.6).
  - The narratives for these subjects are summarized in Table 26. Of the 20 subjects with ≥ Grade 3 creatinine clearance (CrCl) decreased (RDV [n=15]; PBO [n=5]), a subset of 11 subjects also had ≥ Grade 3 creatinine increased (RDV [n=8]; PBO [n=3]).
- No Grade 3/4 renal laboratory abnormalities led to discontinuation (see Section 8.4.3).

Table 26. Subjects With Grade 3/4 Creatinine Clearance Decreased or Grade 3/4 Creatinine Increased, Study GS-US-540-9012

Treatment	Age	Race	Gender	BMI (kg/m^2)	ConMeds[1]	Study Day	CrCl (mL/min)	Cr (mg/dL)
RDV x 3 days								
(b) (6)	63	White	F	24.5	Valacyclovir	1 (predose)[2]	62[2] [Grade 2]	0.89[2]
						1 (predose)	62.5 [Grade 2]	0.89
						3	62.9 [Grade 2]	0.89
						7	65.7 [Grade 2]	0.86
						14	57.3 [Grade 3]	0.98
(b) (6) (Comorbidity: HTN)	51	White	F	21.9	Lisinopril	-2[2]	117[2]	0.52[2]
						1 (predose)	135	0.45
						3	91.5 [Grade 3]	0.69 [Grade 3]
						9	105.1 [Grade 2]	0.59 [Grade 2]
						15	109.9 [Grade 2]	0.56
(b) (6) (Comorbidity: overweight)	68	White	M	29.3	N/A	1 (predose)[2]	148.1[2]	0.70[2]
						1 (predose)	159.5	0.65
						3	146.2	0.71
						9	131.6 [Grade 2]	0.79
						16	106.9 [Grade 3]	0.97 [Grade 2]
(b) (6) (Comorbidities: HTN, diabetes)	72	Asian	F	24.7	HCTZ, metformin, ciprofloxacin	-1[2]	67[2] [Grade 2]	0.72[2]
						1 (predose)	67.2 [Grade 2]	0.72
						3	69.1 [Grade 2]	0.69
						7	73.4 [Grade 2]	0.65
						14	59.3 [Grade 3]	0.81
(b) (6) (Comorbidities: HTN, diabetes, overweight)	61	White	M	28.0	Metformin	1 (predose)[2]	61[2] [Grade 2]	1.26[2]
						1 (predose)	64.6 [Grade 2]	1.18
						3	68.6 [Grade 2]	1.12
						9	58.7 [Grade 3]	1.28
						15	64.1 [Grade 2]	1.19
(b) (6) (Comorbidity: HTN)	78	White	M	20.7	Losartan, hydralazine	-1[2]	32.2[2] [Grade 3]	1.70[2]
						1 (predose)	35.6 [Grade 3]	1.54
						3	32.3 [Grade 3]	1.70
						7	28.3 [Grade 4]	1.95 [Grade 1]
						14	37 [Grade 3]	1.49

Treatment	Age	Race	Gender	BMI (kg/m^2)	ConMeds[1]	Study Day	CrCl (mL/min)	Cr (mg/dL)
(b) (6) (Comorbidities: HTN, diabetes, obesity)	51	Other	F	31.5	N/A	-1[2]	159.7[2]	0.58[2]
						1 (predose)	170.6	0.54
						3	145.1 [Grade 2]	0.63
						7	118.8 [Grade 3]	0.78 [Grade 2]
						13	118.3 [Grade 3]	0.85 [Grade 3]
(b) (6) (Comorbidities: HTN, diabetes, obesity)	51	White	F	50.8	Ramipril, metformin	-1[2]	282[2]	0.58[2]
						1 (predose)	256.2	0.57
						3	213.6 [Grade 2]	0.68
						7	222 [Grade 2]	0.66
						14	144 [Grade 3]	1.02 [Grade 3]
(b) (6) (Comorbidities: HTN, diabetes, obesity)	46	White	F	30.5	Enalapril, metformin	-84	114.4[2]	0.60[2]
						1 (predose)	163.6	0.59
						3	161.9	0.59
						7	112.8 [Grade 3]	0.85 [Grade 2]
						14	157.2	0.61
(b) (6) [3] (Comorbidities: HTN, diabetes, obesity)	56	Black	M	30.6	Enalapril, metformin	-85[2]	N/A	0.80[2]
						1 (predose)	219	0.62
						1 (predose)	170[2]	N/A
						3	215.1	0.62
						6	165.1 [Grade 2]	0.81 [Grade 2]
						13	139.3 [Grade 3]	0.96 [Grade 3]
						19	194.8 [Grade 2]	0.69
(b) (6) (Comorbidity: overweight)	58	White	M	27.1	N/A	-1[2]	151.6[2]	0.69[2]
						1 (predose)	142.3	0.73
						5	95.1 [Grade 3]	1.10 [Grade 3]
						8	74.7 [Grade 3]	1.40 [Grade 3]
						15	74.5 [Grade 3]	1.40 [Grade 3]
(b) (6) (Comorbidity: overweight)	19	White	F	27.0	N/A	-1[2]	141.1[2]	0.81[2]
						1 (predose)	137.7	0.83
						3	91.4 [Grade 3]	1.25 [Grade 3]
						8	132.9	0.86
						14	157.1	0.74
(b) (6) (Comorbidities: HTN, diabetes, overweight)	85	White	F	26.4	Amlodipine, losartan	-1[2]	44.9[2] [Grade 3]	1.00[2]
						1 (predose)	61.6 [Grade 2]	0.73
						3	56.2 [Grade 3]	0.80
						6	65.1 [Grade 2]	0.69
						15	67.9 [Grade 2]	0.66

Treatment	Age	Race	Gender	BMI (kg/m^2)	ConMeds[1]	Study Day	CrCl (mL/min)	Cr (mg/dL)
(b) (6) (Comorbidities: HTN, obesity)	68	White	M	33.7	Amlodipine, HCTZ, ibuprofen	-2[2]	158.7[2]	0.60[2]
						1 (predose)	202.6	0.47
						3	158.0 [Grade 2]	0.60
						8	106.3 [Grade 3]	0.87 [Grade 3]
						15	140.0 [Grade 3]	0.67 [Grade 2]
(b) (6) (Comorbidities: HTN, obesity)	63	White	F	30.3	HCTZ	-1[2]	83.1[2] [Grade 2]	0.70[2]
						1 (predose)	83.8 [Grade 2]	0.70
						3	90.5	0.65
						7	55.3 [Grade 3]	1.06 [Grade 3]
						15	105.1	0.58
PBO x 3 days								
(b) (6) (Comorbidities: HIV, HCV)	57	Asian	M	23.7	Tenofovir, FTC, DRV, cobicistat	-33[2]	99[2]	0.88[2]
						1 (predose)	145.7	0.61
						3	127 [Grade 2]	0.70
						7	99.9 [Grade 3]	0.89 [Grade 2]
						14	126.8 [Grade 2]	0.72
(b) (6)	63	White	F	23.9	N/A	-1 (predose)	128.4	0.40
						1 (predose)[2]	99.8[2]	0.51[2]
						3	104.4 [Grade 2]	0.49
						9	118.2	0.43
						15	83.4 [Grade 3]	0.61 [Grade 3]
(b) (6)	32	White	F	23.7	N/A	-1[2]	146.1[2]	0.60[2]
						1 (predose)	160.9	0.55
						3	98.3 [Grade 3]	0.90 [Grade 3]
						7	142.7 [Grade 2]	0.62
						14	151.5	0.61
(b) (6) (Comorbidities: HTN, diabetes, overweight)	68	White	M	27.6	Amlodipine, metformin	-1[2]	61.2[2] [Grade 2]	1.26[2]
						1 (predose)	63.2 [Grade 2]	1.22
						3	62.7 [Grade 2]	1.23
						7	50.3 [Grade 3]	1.53 [Grade 1]
						15	68.8 [Grade 2]	1.12

Treatment	Age	Race	Gender	BMI (kg/m^2)	ConMeds[1]	Study Day	CrCl (mL/min)	Cr (mg/dL)
(b) (6) (Comorbidities: HTN, obesity)	52	White	M	33.7	Lisinopril, ibuprofen	-1[2]	143.2[2]	0.89[2]
						1 (predose)	199.2	0.64
						3	112.8 [Grade 3]	1.13 [Grade 3]
						7	105.4 [Grade 3]	1.21 [Grade 3]
						14	114.8 [Grade 3]	1.11 [Grade 3]

Source: ADLB, ADSL datasets; Study GS-US-540-9012
[1] Concomitant medications associated with renal adverse events are listed above; Comorbidities associated with renal adverse events are listed above
[2] Local laboratory result
[3] Discontinued due to subject decision on Day 1.
Centers for Disease Control and Prevention definitions of overweight and obesity available at https://www.cdc.gov/obesity/adult/defining.html.
Abbreviations: DRV, darunavir; FTC, emtricitabine; HCTZ, hydrochlorothiazide; N/A, not applicable; BMI, body mass index; CrCl, creatinine clearance; HTN, hypertension; Cr, creatinine

The Applicant's assessment of the apparent discrepancy between the hospitalized RCT data and nonhospitalized RCT data for the renal laboratory parameters of CrCl decreased and creatinine increased, respectively, is summarized below:

- The Applicant noted the overall number of subjects with these ≥ Grade 3 renal laboratory abnormalities in Study GS-US-540-9012 is small, and several factors could contribute to this apparent discrepancy.
- The Applicant noted that Study GS-US-540-9012 inclusion criteria resulted in a study population enriched with presence of obesity (i.e., BMI ≥30 kg/m^2):
  - Higher rates of obesity (55%) occurred in Study GS-US-540-9012 compared to the rates of obesity in the RCTs in hospitalized subjects (ACTT-1 [45%]; Study GS-US-540-5773 [41%]; Study GS-US-540-5774 [29%]).
- The Applicant assessed that, while the CG formula is a routine method of evaluating renal function, including in Study GS-US-540-9012, the reliance of the CG formula on weight may have created artifacts within this study population. For obese patients, total body weight overestimates CrCl:
  - Eleven out of 15 subjects in the RDV group and two out of five subjects in the PBO group with treatment-emergent Grade 3 CrCl decreased were overweight or obese.
  - Nine out of 15 subjects in the RDV group and four out of five subjects in the PBO group with treatment-emergent Grade 3 CrCl decreased had "supraphysiologic" CrCl levels by CG formula at baseline, which likely contributed to high grading on the DAIDS grading system when CrCl values decreased and could also have contributed to potential inaccuracies in the degree of change in CrCl from baseline.
- The Applicant cited *The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline* that states that higher eGFR measurements such as these are a source of error in eGFR determination (Kidney Disease: Improving Global Outcomes (KDIGO) 2012).
- The Applicant noted that, of the subjects who did not have a supraphysiologic CrCl by CG formula at baseline (RDV [n=6]; PBO [n=1]), most had baseline CrCl values in the 60s that shifted from Grade 2 to Grade 3 with small absolute change in CrCl.
- To further delineate the degree to which weight contributed to inaccuracies in baseline estimates and degree of variance in CrCl using CG formula, the Applicant calculated the eGFR in these patients using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which does not utilize weight in the calculation (National Institute of Diabetes and Digestive and Kidney Diseases n.d.). The change in CrCl was also compared by CG and change in eGFR by CKD-EPI.
  - Using the CKD-EPI formula resulted in a lower degree of supraphysiologic eGFR values at baseline, less variance of eGFR over the course of the study, and 14 of the 20 subjects no longer had treatment-emergent ≥ Grade 3 CrCl decreased.
  - When using the CKD-EPI equation, a lower proportion of subjects receiving RDV (10 out of these 15 RDV recipients) had any treatment-emergent grade change from baseline eGFR, as compared to four out of these five PBO recipients.
  - The Applicant assessed these findings using the CKD-EPI equation highlight the contribution of weight to the discrepancies noted using the CG formula.

- The Applicant assessed that the use of the CG formula in this population enriched for obesity, coupled with the DAIDS grading system, contributed to artifactually high-grade renal laboratory abnormalities that were not clinically meaningful.
- The majority of ≥ Grade 3 CrCl decreased occurred during the Day 7 to 15 timeframe (i.e., after the study dosing period):
  - Of the 15 RDV subjects with ≥ Grade 3 CrCl decreased, 11 of these laboratory abnormalities occurred after the study dosing period.
  - Of the five PBO subjects with ≥ Grade 3 CrCl decreased, three of these laboratory abnormalities occurred after the study dosing period.
- Of the 11 subjects with ≥ Grade 3 creatinine increased (RDV [n=8]; PBO [n=3]), nine subjects (RDV [n=7]; PBO [n=2]) had absolute changes <0.5 mg/dL. The Applicant postulated a rise in serum creatinine of <0.5 mg/dL could reflect daily changes in protein intake or hydration in this nonconfined, nonhospitalized patient population (Nair et al. 2014).
  - Of the eight RDV subjects with ≥ Grade 3 creatinine increased, six of these laboratory abnormalities occurred after the study dosing period.
  - Of the three PBO subjects with ≥ Grade 3 creatinine increased, one of these laboratory abnormalities occurred after the study dosing period.
- In addition to the above considerations, the Applicant also suggested that minor differences in comorbidities (such as diabetes and hypertension) and concomitant medications that predispose for nephrotoxicity could also contribute to the observed discrepancy in renal laboratory abnormalities in these subjects:
  - 15 out of 15 subjects in the RDV group and three out of five subjects in the PBO group had comorbidities and/or concomitant medications that predispose for nephrotoxicity.

Reviewer Comments/Overall Assessment: FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function–Study Design, Data Analysis, and Impact on Dosing *(September 2020) notes the following:*

Estimated CrCl in mL/min Calculated Using the Cockcroft-Gault Equation

In overweight or obese individuals, use of alternative body weight metrics such as ideal body weight or adjusted body weight when calculating CrCl is likely to provide a more accurate estimate of renal function than total body weight.

The clinical narratives and renal laboratory data for these subjects with Grade 3/4 renal laboratory parameters were reviewed and I agree with the Applicant's assessment that several factors could contribute to this apparent discrepancy (Cockcroft and Gault 1976; Pai 2010; Jesudason and Clifton 2012; Brown et al. 2013). None of these Grade 3/4 renal laboratory parameters appeared to be clinically meaningful and none resulted in treatment discontinuation. PK data were collected in five of 15 RDV recipients with Grade 3/4 renal laboratory parameters; overlapping exposures were observed in RDV recipients with versus without Grade 3/4 renal laboratory parameters (see Section 4.5.3).

Acknowledging the caveats associated with cross-study comparisons, although the above Grade 3/4 renal laboratory parameters were numerically higher with RDV versus PBO in the

nonhospitalized trial, the rates of these Grade 3/4 renal laboratory parameters were lower compared to hospitalized trials.

Based on all available information, no additional labeling is warranted aside from displaying Study GS-US-540-9012 renal laboratory data in Section 6. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.11. Safety Profile by Outpatient Location

Given the IV administration and a 3-day treatment duration, it is possible the safety profile of RDV could be adversely impacted by the level of monitoring in the outpatient setting. This section contains a brief summary of our findings, organized by the location where IV RDV was administered.

Of the 279 subjects treated with RDV, 227 subjects (81%) received at least one dose of RDV at an outpatient facility, 44 subjects (16%) received at least one dose of RDV in a home health care setting, and eight subjects (3%) received at least one dose of RDV at an SNF. These numbers are used in the below analyses.

Reviewer Comment: Of the 235 subjects who received the initial dose of RDV at an outpatient facility (Table 7), the location subsequently changed for eight subjects (seven subjects received the other two doses of RDV at home and one subject received one dose of RDV at home).

The following table (Table 27) provides a safety overview for subjects who received study drug at an outpatient facility compared to those who received study drug in a home health care setting.

Given the small number of subjects who received study drug at an SNF (RDV [n=8]; PBO [n=7]), safety analyses by SNF residence were not feasible.

Table 27. Safety Overview for Outpatient Facility Vs. Home Health Care Setting, Study GS-US-540-9012

	Outpatient Facility		Home Health	
Subjects Experiencing Event	**RDV 3 Days N=227 n (%)**	**PBO 3 Days N=228 n (%)**	**RDV 3 Days N=44 n (%)**	**PBO 3 Days N=49 n (%)**
Any AE	93 (41%)	104 (46%)	22 (50%)	24 (49%)
Any Grade 3 or 4 AE	7 (3%)	17 (8%)	3 (7%)	3 (6%)
SAE	4 (2%)	16 (7%)	1 (2%)	3 (6%)
D/c of study drug due to AE	1 (0.4%)	4 (2%)	1 (2%)	1 (2%)
Graded laboratory abnormalities	170 (76%)	177 (79%)	32 (74%)	38 (79%)
Grade 3 or 4 laboratory abnormalities	22 (10%)	18 (8%)	5 (12%)	5 (10%)

Source: ADAE dataset, Study GS-US-540-9012
Abbreviations: D/c, discontinuation; PBO, placebo; RDV, remdesivir; AE, adverse event; SAE, serious adverse event

Because RDV can be given in a variety of settings, including outpatient facility, home health care or SNFs, the review team included the following statement in Section 6 of the product labeling to provide additional context regarding safety outcomes.

"The safety in subjects who received RDV in the home health setting was overall comparable to subjects who received RDV at an outpatient facility, but this conclusion is based on limited data."

Additionally, the postinfusion monitoring and recommendations for product labeling were reviewed in more detail and summarized below.

Postinfusion Monitoring in the Home Health Setting

Monitoring for hypersensitivity and infusion-related reactions varied for subjects who received IV RDV via home health services. Of the 44 subjects who received IV RDV in home health setting, 35 subjects were at sites that utilized their own home health service for RDV infusion, wherein the monitoring protocol was determined by the site investigator. Nine subjects were at sites that utilized the Applicant-sponsored home-health vendor for at-home infusion, wherein monitoring guidance was provided to the site by the Applicant. In-person postinfusion monitoring by nursing staff was not recommended for either scenario given the increased risk of SARS-CoV-2 transmission in the home environment during a time of the pandemic when vaccination was either not yet available or just becoming available to health care workers.

- For the non-Applicant-sponsored home-health vendors, the monitoring protocol was determined by the site investigator. While direct guidance was not provided by the Applicant in such instances, the Applicant noted that the study protocol contained the following information to assist investigators in their decision making:
  - Section 5.3.2 Infusion-related Reactions: "Infusion-related reactions have been observed during and following administration of RDV. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a severe infusion-related reaction occur, immediately discontinue administration of RDV and initiate appropriate treatment. Please refer to Section 7.6."
  - Section 6.8 Criteria for Discontinuation of Study Treatment: States that an infusion-related systemic reaction ≥ Grade 2 or infusion-related localized reaction ≥ Grade 3 warranted study treatment discontinuation.
  - Section 7.6 Toxicity Management: "Remdesivir infusions will be administered to participants at the site under close supervision or in the participant's home by a home health service provider. Health care professionals administering RDV infusions will have the appropriate medication available for immediate use in case of hypersensitivity or infusion-related reactions. The participant should be treated according to the SOC for management of hypersensitivity reaction or infusion-related reactions. Postinfusion monitoring should be done according to site or home health protocol. All information related to home administration of RDV will be provided to the investigator by the home health provider, wherever applicable, in a timely manner."
- For the Applicant-sponsored home-health vendor (UBC), the following monitoring guidance was provided by the Applicant:
  - Orders included monitoring every 30 minutes for 2 hours after each infusion and that nursing staff have over-the-counter diphenhydramine available in the event of hypersensitivity.
  - UBC's *Request for Home Visit Services/Physician Order Form*, also states: "Follow up with the study participant every 30 minutes for 2 hours after each infusion on Days 1, 2,

and 3. Report to the site if the subject has a reaction, and follow any special instructions listed in the *Request for Home Visit Services/Physician Order Form*."

Postinfusion monitoring was not performed in-person due to heightened risk of transmission of SARS-CoV-2 to nursing staff in the patient's home environment. Instead, monitoring was performed by phone and no vital signs or other in-person monitoring was required unless medically necessary.

Overall, no subjects required diphenhydramine for treatment of hypersensitivity event.

Please also refer to Section 8.5.2 for further details regarding hypersensitivity reactions. Based on the totality of data from hospitalized and nonhospitalized settings, the majority of hypersensitivity reactions occurred within the first hour (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000OtherR.pdf). Therefore, the review team concluded that monitoring patients during infusion and observing patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate is supported by the clinical data.

Reviewer Comment: Postinfusion monitoring was not performed in-person for any of the 44 subjects who received RDV at home. Monitoring procedures for most subjects (35 out of 44) who received RDV at home were investigator-determined.

Overall Assessment: The original product labeling (in hospitalized subjects) includes a Warnings and Precautions section that clearly describes the hypersensitivity reactions, including infusion-related and anaphylactic reactions, that have been observed with RDV administration and outlines risk mitigation strategies for health care providers to consider.

The safety in subjects who received RDV in the home health setting was overall comparable to subjects who received RDV at an outpatient facility, but this assessment is based on limited data.

The limitations of the currently available Phase 3 data in nonhospitalized patients preclude a comprehensive assessment of safety in subjects who received RDV in a skilled nursing facility.

We will continue to monitor closely in the postmarketing setting for any potential serious safety signals associated with RDV use in the outpatient setting.

8.6. Safety Analyses by Demographic Subgroups

Consistent with our approach for the overall safety review, the impact of age, sex, and race on the frequencies of adverse events were assessed for Study GS-US-540-9012. While subjects aged ≥65 years had higher rates of serious or severe AEs compared to younger subjects, these findings were also observed in the placebo group and reflect the epidemiology of COVID-19 and the disproportionately higher rates of adverse outcomes among older subjects. Otherwise, we did not find any demographic subgroups at substantially higher risk for serious or severe AEs. This section contains a brief summary of our findings, organized by demographic variable. The discussion is limited to Study GS-US-540-9012 subjects treated with RDV.

Age

Subjects <65 years of age (n=239) were compared to subjects ≥65 years old (n=40). The older cohort comprised 14% of the RDV group. All-cause AEs of any severity occurred in 40% and 55% respectively; Grade 3/4 AEs occurred in 3% and 10% respectively; SAEs occurred in 1%

and 5% respectively; graded laboratory abnormalities occurred in 73% and 87% respectively; Grade 3/4 laboratory abnormalities occurred in 8% and 23% respectively.

Reviewer Comment: Subjects aged ≥65 years had higher rates of SAEs, Grade 3/4 AEs, and overall AEs compared to younger subjects. Similar findings were also observed in the placebo group in Study GS-US-540-9012. While the low proportion of subjects aged ≥65 could contribute to the imbalances observed, these findings overall reflect the epidemiology of COVID-19 where elderly subjects are at higher risk for severe disease and adverse outcomes (Berlin et al. 2020; Gandhi et al. 2020; Puelles et al. 2020; Centers for Disease Control and Prevention 2021a; Centers for Disease Control and Prevention 2021b; Centers for Disease Control and Prevention 2022; World Health Organization 2022).

Gender

Women comprised 47% of the RDV group (131/279). All-cause AEs of any severity occurred in 47% of women and 38% of men; Grade 3/4 AEs occurred in 3% of women and 4% of men; SAEs occurred in 2% of women and 2% of men; graded laboratory abnormalities occurred in 68% of women and 81% of men; Grade 3/4 laboratory abnormalities occurred in 11% of women and 10% of men.

Reviewer Comment: No overall safety differences were observed between male and female subjects.

Race

Differences between racial groups were more difficult to assess due to the predominance of white subjects in Study GS-US-540-9012. The RDV group comprised 82% white subjects, 7% black subjects, 2% Asian subjects, and 9% other race.

All-cause AEs of any severity occurred in 36% of white subjects, 60% of black subjects, 83% of Asian subjects, and 72% of other race. Grade 3/4 AEs occurred in 3% of white subjects, 5% of black subjects, 0% of Asian subjects, and 4% of ‘other race’. SAEs occurred in 1% of white subjects, 5% of black subjects, 0% of Asian subjects, and 8% of ‘other race’. Graded laboratory abnormalities occurred in 76% of white subjects, 70% of black subjects, 50% of Asian subjects, and 79% of ‘other race’. Grade 3/4 laboratory abnormalities occurred in 10% of white subjects, 10% of black subjects, 17% of Asian subjects, and 13% of ‘other race’.

Reviewer Comment: No clear safety differences were apparent based on race, but the lower enrolment percentages of some racial subgroups preclude definitive conclusions.

Overall Demographic Safety Analysis Conclusion: Adverse events occurred more frequently in subjects aged ≥65 years (regardless of RDV or PBO) and are consistent with the epidemiology of COVID-19 where elderly subjects are at higher risk for severe disease and adverse outcomes (Berlin et al. 2020; Gandhi et al. 2020; Puelles et al. 2020; Centers for Disease Control and Prevention 2021a; Centers for Disease Control and Prevention 2021b; Centers for Disease Control and Prevention 2022; World Health Organization 2022). Safety analyses by sex and race showed that adverse events occurred with similar frequency and severity in these demographic subgroups.

8.7. Specific Safety Studies/Clinical Trials

No additional trials have been conducted to evaluate specific safety concerns.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The relatively short duration of RDV treatment (3 days) and follow-up (28 days) in Study GS-US-540-9012 limits the assessment for oncologic events. There were no treatment-emergent oncologic events in Study GS-US-540-9012.

Reviewer Comment: Based on the available data from the Phase 3 trials (from the original NDA and this sNDA), there is no clinical evidence of carcinogenicity for RDV.

8.8.2. Human Reproduction and Pregnancy

Pregnant and lactating women were excluded from participation in Study GS-US-540-9012 by the Applicant.

A search of the Applicant's global safety database identified a total of 256 pregnancy cases involving RDV exposure cumulative to November 1, 2021. The Applicant defined valid cases as those that have all of the elements for the purpose of expedited reporting (patient, drug, event, and reporter). All other cases are considered invalid. Of the 256 pregnancy cases, there were 21 invalid cases (of which 18 cases reported patients who were not receiving any Applicant-made product at time of pregnancy; two cases [2021-0525166, 2021-0530158] reported no adverse event; and one case [2020-0467476] reported a 57-year-old female who was not pregnant at time of RDV administration). The 235 valid pregnancy cases are discussed below.

The 235 pregnancy cases were reported from the compassionate use program (CUP) (IN-US-540-5755 [n=137]), spontaneous reporting (n=37), literature spontaneous reporting (n=32), clinical literature (n=12), expanded access program (EAP) (Study GS-US-540-5821, [n=12]), market research (n=3), and digital media case (n=2).

Of the 235 pregnancy cases, 231 cases reported events relating to RDV exposure during pregnancy which included maternal exposure during pregnancy (n=226), exposure during pregnancy (n=4), and pregnancy (n=1).

Of the 235 pregnancy cases, 86 reported live birth with no congenital anomaly and nine reported adverse pregnancy outcomes (live birth with congenital anomaly [n=4]; still birth with congenital anomaly [n=1]; still birth [n=2]; abortion spontaneous [n=1], abortion induced [n=1]). The birth outcomes of the remaining cases are unknown.

There were five cases of congenital anomalies (four from live births and one from a still birth) which were identified in patients who received RDV for COVID-19. In four cases, RDV exposure was not in the first trimester. In the fifth case, the precise timing of earliest RDV exposure was unknown since the date of the last menstrual period was not provided but could be deduced to be after the first trimester based on the gestational age at birth and RDV administration dates. These five cases are summarized below:

- Pulmonary artery stenosis congenital (mother case 2020-0470037/ baby case 2020-0472508).
- Ventricular septal defect, atrial septal defect, patent ductus arteriosus, premature baby, respiratory distress, and pneumonia (mother case 2020-0461422/ baby case 2020-0489750).
- 3-week male neonate who was treated with RDV for 5 days and experienced anomalous pulmonary venous connection which was assessed by the health care provider (HCP) to have occurred much earlier in gestation (baby case 2020-0473345 was identified by Medical Dictionary for Regulatory Activities SOC of Congenital, familial and genetic disorders, no mother case was available).
- Microcephaly, hyperbilirubinemia and small for gestational age attributed to intrauterine growth restriction by the HCP (mother case 2020-0485674/baby case 2020-0485676; CUP). Hypoxic-ischemic insult, which may have occurred in this case as the mother required high flow oxygen during RDV course in the 3rd trimester, can result in decreased brain size. The 21-year-old mother also developed gestational hypertension a month prior to delivery and 1 month after RDV administration, which subsequently prompted an induction of labor.
- 22-year-old primigravida mother (mother case 2020-0489078/baby case 2020-0489915; literature) with history of tuberous sclerosis complex, placenta previa, who received RDV during the 2nd trimester (unknown administration dates and duration) in critical condition (intubated). The mother delivered a preterm infant at 25 weeks and 5 days by urgent Cesarean-section on the ICU bed due to worsening maternal status. The infant experienced Grade 2 intraventricular hemorrhage, patent ductus arteriosus and had findings suggestive of possible tuberous sclerosis (family history in the mother).

The two cases of still birth are summarized below:

- Case 2020-0474294: 33-year-old female who experienced fetal death at 29 weeks and 1-day gestation. Patient was hospitalized for COVID-19 and had progressive clinical deterioration requiring IMV, ECMO and continuous renal replacement therapy. While on ECMO, the patient experienced intrauterine fetal demise (IUFD). Placental pathologist reported the most likely cause of this IUFD was a serious maternal COVID-19 superimposed on chronic maternal vascular malperfusion characterized by small for gestational age, atriovenous malformations, and remote placental infarctions.
- Case 2020-0486085: 31-year-old female at 22 weeks gestation who was hospitalized for worsening respiratory status from COVID-19. Through the patient's worsening clinical course, the patient required intubation and ICU admission and received four doses of RDV. Approximately 5 days after the last dose of RDV, patient experienced IUFD while in critical condition (requiring intubation, paralytic use and vasopressor therapy). Patient's condition continued to decline after the IUFD; patient required ECMO and eventually died due to COVID-19.

Cases of spontaneous abortion (n=1) and induced abortion (n=1) are summarized below:

- Case 2020-0459959: 32-year-old female with history of recreational intravenous drug use (IVDU) who had a spontaneous abortion at 17-week gestation in the setting of methicillin-sensitive *Staphylococcus aureus* endocarditis. HCP assessed that concurrent methicillin-sensitive *Staphylococcus aureus* endocarditis, bacteremia, and IVDU in the setting of severe COVID-19 provided possible alternative explanations for spontaneous abortion.

- Case 2020-0464814: 29-year-old female with history of IVDU and systemic lupus erythematosus underwent an induced abortion. Investigator reported the patient had planned to terminate the pregnancy when the patient learned of a positive human chorionic gonadotropin level 3 days prior to hospitalization, when the patient went to the emergency room but was discharged. Subsequently, the patient experienced worsening COVID-19, was hospitalized and underwent induction of abortion during this hospitalization.

Six pregnancy cases reported fatal events relating to severe COVID-19 (2020-0464418, 2020-0468489, 2020-0469007), cardio-respiratory arrest (2020-0487477), COVID-19 progression (2021-0542060), and event of death (2020-0502917):

- Case 2020-0464418: 28-year-old female who received 10 days of RDV and was reported to have died from COVID-19 1 day later.
- Case 2020-0468489: 33-year-old female with history of hepatitis B and mitral valve stenosis, presented with critical COVID-19 requiring intubation and ECMO. Patient had a massive pulmonary embolism and with medical team's decision, natural death was allowed.
- Case 2020-0469007: 31-year-old female hospitalized for declining respiratory function and later died after a worsening course with cause of death of severe COVID-19 pneumonia.
- Case 2020-0487477: 29-year-old female, with history of morbid obesity, who was hospitalized at 20 weeks gestation. Patient had a worsening clinical course, complicated by methicillin-resistant *Staphylococcus epidermidis* bacteremia and had a cardiopulmonary arrest 1 month after receiving the last RDV dose.
- Literature spontaneous case 2021-0542060 listed RDV in the medications received by a pregnant individual who died to COVID-19.
- Case 2020-0502917: 44-year-old female who suffered a worsening course requiring intubation and vasopressors and died with unknown cause of death. A healthy infant at 36 weeks and 4 days was born and survived and reported as "doing well."

Postpartum

A search of the Applicant's global safety database identified a total of four postpartum cases involving RDV exposure cumulative to November 1, 2021:

- Case 2020-0468810 (CUP) reported serious events of respiratory failure and postpartum hemorrhage and nonserious events of hypoxia, urinary tract infection, and maternal exposure during pregnancy.
- Spontaneous case 2021-0543591 reported nonserious event of breast milk discoloration.
- Case 2020-0467636 (EAP) reported serious events of pneumothorax and pericardial effusion, nonserious events of pleural effusion, uterine disorder, hepatomegaly, and vascular pseudoaneurysm.
- Literature spontaneous case 2021-0531987 reported serious event of dyspnea.

Lactation

A search of the Applicant's global safety database identified a total of 12 lactation cases involving RDV exposure cumulative to November 1, 2021. These 12 cases reported PTs of exposure via breast milk (n=11) and breast milk discoloration (n=1, 2021-0543591); no additional adverse events were reported from these cases.

Overall Assessment: The reported events occurred in patients who are at risk for adverse pregnancy outcomes due to the sequelae of COVID-19 (Zambrano et al. 2020). There is insufficient evidence to suggest a causal relationship between RDV and adverse pregnancy or infant outcomes based on the limited data currently available.

As a postmarketing commitment, a study to evaluate the pharmacokinetics and safety of RDV in pregnant individuals with COVID-19 is ongoing (Mirochnick. M et al. 2020). Additionally, as part of their pharmacovigilance plan, the Applicant is collecting data on pregnancy exposures and outcomes as reported to their global safety database. The Applicant is also collaborating in the COVID-19 International Drug Pregnancy Registry (COVID-PR) (ClinicalTrials.gov 2021).

8.8.3. Pediatrics and Assessment of Effects on Growth

In the original NDA, the Applicant included an initial indication for RDV for (b) (4) through extrapolation of efficacy from adults receiving the same dose of RDV as proposed for adolescent patients. The Agency agreed with this proposal because adult and pediatric populations with moderate to severe COVID-19 generally display similar symptoms, and virologic response to an antiviral drug such as RDV is expected to be similar in adults and pediatric patients (Castagnoli et al. 2020; Chiotos et al. 2020; Shekerdemian et al. 2020; Delahoy et al. 2021; Leidman et al. 2021). Furthermore, the Agency concluded that it was appropriate to include adolescents (≥12 years old and ≥40 kg) based on the historical concordance of adult and adolescent dosing regimens observed for other drugs (Momper et al. 2013).

Additionally, the physiologically based PK model and the population PK model supported use of the adult dose above this weight cutoff. The Agency assessed that, using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of RDV and metabolites in adolescents ≥12 years old and ≥40 kg as observed in healthy adults. Additional supportive data were provided from the RDV Phase 3 clinical trials in which the safety in adult subjects weighing 40 to 50 kg (i.e., encompassing weight ranges that are observed in adolescents) was similar to adult subjects weighing >50 kg. There was also supportive data from 39 pediatric patients ≥12 years of age and ≥40 kg who received RDV via expanded access; however, the available clinical data from these patients was limited. Confirmatory data will be provided in this age and weight range (i.e., 12 years of age and older and weighing at least 40 kg) in the Pediatric Research Equity Act PMR (September 2005).

In conformance with current regulatory requirements, the Applicant submitted an initial Pediatric Study Plan (iPSP) for RDV on April 9, 2020. The document was reviewed and found to be generally satisfactory by both the Division of Antivirals as well as the Pediatric Review Committee (PeRC). The Applicant incorporated the Agency's recommendations, and the revised PSP was approved by the Division of Antivirals and the PeRC. The Division of Antivirals issued a notice of Agreed PSP on July 9, 2020. The Agreed iPSP included the Applicant's agreement to

ensure adolescents weighing ≥40 kg are included in the dedicated pediatric trial irrespective of whether adolescents are included in the initial indication. The Applicant agreed with the Agency's assessment that PK data generated in adolescents: (1) will help confirm that use of the adult dose in the adolescent population is appropriate and; (2) will help inform dosing for the younger/lower weight populations. The pediatric study reflects the Pediatric Research Equity Act PMR that was issued.

In brief, the pediatric development plan includes the following study to evaluate the safety and efficacy of RDV in children ages 0 to <18 years of age:

- Study GS-US-540-5823 is an open-label, single-arm study to investigate the safety, tolerability, efficacy, and PK of RDV in pediatric subjects birth to <18 years of age who are hospitalized with laboratory proven SARS-CoV-2 infection. The study will allow for enrollment of adolescents <18 years of age. Full-term neonates 0 to <14 days of age and preterm neonates and infants 0 to <56 days of age will be enrolled in a staggered fashion, following confirmation of PK and short-term safety data in neonates 14 days to <28 days of age (at least n=4).

Table 28. Study GS-US-540-5823

Cohort	N	Description	Dosing
1	12	≥12 years to <18 years and weight ≥40 kg	200 mg IV on Day 1 followed by 100 mg IV QD for up to 10 days
2	12	≥28 days to <18 years and weight ≥20 kg to <40 kg	5 mg/kg IV on Day 1 followed by 2.5 mg/kg IV QD for up to 10 days
3	12	≥28 days to <18 years and weight ≥12 kg to <20 kg	
4	12	≥28 days to <18 years and weight ≥3 kg to <12 kg	
5	4	≥14 days to <28 days of age, gestational age >37 weeks and weight at Screening ≥2.5 kg	
6	*	0 days to <14 days of age, gestational age >37 weeks and birth weight ≥2.5 kg	Dose-TBD; duration is for up to 10 days
7	*	0 days to <56 days of age, gestational age ≤37 weeks and birth weight ≥1.5 kg	Dose-TBD; duration is for up to 10 days
8[1]	*	<12 years and weight ≥40 kg	200 mg IV on Day 1 followed by 100 mg IV QD for up to 10 days

Source: https://www.clinicaltrials.gov/ct2/show/NCT04431453
* No minimum number
[1] Exploratory Cohort 8 was added in the September 22, 2020, protocol amendment
Abbreviations: IV, intravenous; QD, once daily; TBD, to be determined

(b) (4)

The Division agreed with the Applicant's proposal

(b) (4)

The Applicant intends

(b) (4)

(b) (4)

The Applicant requested a deferral of required pediatric assessments in pediatric patients birth to <12 years of age, until data from Study GS-US-540-5823 (including the preliminary PK data) are available and have been reviewed by the Agency. The Division agreed with this proposal. The deferral request was presented to the PeRC, and the PeRC agreed with the Applicant's proposal and the Division of Antivirals' recommendations.

For this sNDA in nonhospitalized patients, in conformance with current regulatory requirements, the Applicant submitted an initial Pediatric Study Plan (iPSP) for RDV on September 24, 2021. The document was reviewed and found to be generally satisfactory by both the review division as well as the Pediatric Review Committee (PeRC). The Applicant incorporated the Agency's recommendations, and the revised PSP was approved by the Division of Antivirals and the PeRC. The Division of Antivirals issued a notice of Agreed PSP on October 26, 2021.

The Applicant intends (b) (4)

The Applicant has requested a deferral of required pediatric assessments in pediatric patients birth to <12 years of age, until data from Study GS-US-540-5823 (including the preliminary PK data) are available and have been reviewed by the Agency. The Division is in agreement with this proposal. The deferral request was presented to the PeRC, and the PeRC agreed with the Applicant's proposal and the Division of Antivirals' recommendations.

GS-US-540-9012

Among eight adolescents (RDV [n=3], PBO [n=5]), only one AE (mild fatigue in one PBO recipient) occurred.

Reviewer Comment: The limitations of the currently available Phase 3 data in nonhospitalized patients preclude a comprehensive assessment of safety in pediatric subjects.

Postmarketing Data/Expanded Access Data/EUA Data

A search of the Applicant's global safety database identified a total of 211 pediatric cases from postmarketing, CUP, and EAP involving RDV exposure cumulative to November 1, 2021. Of the 211 cases, there were 188 valid cases (postmarketing [spontaneous, literature, or solicited] n=91, CUP n=95, EAP n=2) and 23 invalid cases. The majority of the cases (n=179, 85%) were received from the United States (n=130), Spain (n=18), United Kingdom (n=16), and Japan (n=15). The cases were reported in 91 male (43%), 81 female (38%), and 39 gender not reported (18%) patients. Age categories included adolescent (n=77), child (n=69), infant (n=27), neonate (n=22), fetus (n=9), toddler (n=6), and unknown age (n=1).

The 211 cases reported 406 events (serious [n=199]; nonserious [n=207]) and these are briefly summarized below:

- Of the 406 total events, 163 (40%) and 102 (25%) events were reported in the adolescent and child groups, respectively.
- In adolescents, the most common events (33 of 163, 20%) were from the Investigations SOC and mostly related to hepatic abnormalities (i.e., ALT increased, AST increased, liver function test increased, transaminases increased).
- The child group reported 34 of 102 (33%) events and toddler group reported five of six (83%) events from the SOC of injury, poisoning and procedural complications, mostly due to the event of off-label use.
- In neonates, the most common events (17 of 53, 32%) were from the SOC of Injury, poisoning and procedural complications due to events of fetal exposure during pregnancy and off-label use.
- In the fetus group, the most common events (10 of 25, 40%) were from the SOC of Injury, poisoning and procedural complications mostly due to events of fetal exposure during pregnancy and fetal exposure timing unspecified.

Twenty pediatric cases reported fatal events; these were assessed by HCPs as related to severe COVID-19 or its complications:

- Case 2020-0465468: 4-month-old with history of pulmonary hypertension, atrial septal defect, and patent ductus arteriosus received RDV for 10 days who, approximately 9 days after last RDV dose, experienced a bradycardic arrest with prolonged resuscitation and died.
- Case 2020-0484373: 17-year-old male with history of cardiac arrest, tetralogy of Fallot repair, epilepsy, tracheostomy dependent, restrictive lung disease, hypoxic ischemic encephalopathy who developed refractory respiratory failure, shock and arrhythmia which resulted in fatal cardiac arrest.
- Case 2020-0491427: 4-month-old female with history of serious cardiac condition (not further specified), who received RDV (unknown dose and duration) and died from an unknown cause.
- Case 2020-0468016: 17-year-old male with history of morbid obesity, prediabetes, who had a worsening clinical course developing multisystem inflammatory syndrome in children (MIS-C), acute respiratory distress syndrome (ARDS) (requiring intubation), cardiogenic shock (requiring vasopressors), acute renal failure (requiring dialysis), who developed hepatic failure in the setting of multi-organ failure. Narrative noted that some level of organ dysfunction had occurred prior to RDV dosing.
- Case 2020-0466131: 5-year-old female with SAR-CoV-2 meningoencephalitis. Patient received RDV midway through a month-long hospitalization. Clinical course included multiple lumbar punctures, a suboccipital craniectomy and C1 laminectomy. Patient had severe brain edema with herniation and herniated through the surgical defect on hospital day 32.
- Case 2020-0463913: 6-year-old male who, during bone marrow engraftment, developed COVID-19. Midway through the long hospitalization, patient experienced sepsis and was

treated for 10 days with RDV. A few days later, patient had worsening of respiratory status and required intubation and initiation of multiple vasopressors to treat sepsis. In the setting of ongoing hypotension, renal failure occurred. Patient died due to COVID-19.

- Case 2020-0459161: 11-year-old female with history of interstitial lung disease. Hospitalized with COVID-19 and had progressive clinical decline. Developed multiorgan failure, enterococcal sepsis, bacteremia, pneumothorax, pneumomediastinum, hypoxemia and renal toxicity. Cause of death of multi-organ failure in the context of COVID-19 and nosocomial sepsis.
- Case 2020-0459841: 6-month-old female with history of trachea-oesophageal fistula, tracheostomy, tetralogy of Fallot and tracheobronchomalacia was hospitalized for COVID-19 and treated with RDV. Subsequently died 4 months later from cardiorespiratory failure and chronic lung disease.
- Case 2020-0462831: 14-year-old male with history of seizure disorder was hospitalized for COVID-19 and died after a prolonged hospitalization. Last RDV dose was 3 weeks prior to death.
- Case 2020-0465437: 12-year-old male with history of TAPVR, recurrent SVT was hospitalized for conversion of SVT and was noted to be COVID-19 positive. Patient decompensated acutely developing respiratory distress requiring BiPAP as well as cardiogenic shock requiring milrinone and epinephrine. Patient died due to COVID-19 shortly thereafter. Received one dose of RDV.
- Case 2020-0467612 describes a 12-year-old male with history of Charcot-Marie-Tooth disease, sleep apnea, depression who was hospitalized for COVID-19. Clinical course noted worsening of pneumonia developing cardiovascular collapse requiring aggressive fluids, vasopressor therapy, and ECMO. Patient received RDV for 2 days and was discontinued due to progressive multiorgan failure. After family meeting, aggressive measures were stopped, and patient became asystolic and died.
- Case 2020-0484178: 15-year-old female with history of asthma, celiac disease, epilepsy, G-tube dependence who developed hypoxia from COVID-19 and was hospitalized. Patient developed progressive renal dysfunction along with COVID-19 progression. RDV was stopped at this time, however the renal decline continued. With ongoing clinical deterioration, a family decision was made to stop aggressive measures; patient became asystolic and died.
- Case 2020-0489464: 16-year-old female with history of chronic kidney disease, neurogenic bladder, spina bifida, hydrocephalus, ventricular shunt hospitalized for COVID-19 had progressive hypoxic respiratory failure and then developed septic shock requiring vasopressor therapy. Approximately 12 days after the last dose of RDV, patient had a hypotensive bradycardic arrest and died from hypoxemic respiratory failure and septic shock.
- Case 2020-0490618: 15-year-old female hospitalized for COVID-19 and received RDV. Patient experienced facial flushing on only 1 day of RDV that did not recur subsequently; 5 days after last RDV dose, patient died due to COVID-19.

- Case 2021-0511545: 11-year-old female rapidly progressive interstitial lung disease, juvenile dermatomyositis, was hospitalized for complications of immunosuppressive therapy and was treated for *Pneumocystis jirovecii*. On hospital day 20, patient was COVID-19 positive on BAL and a number of therapies were initiated including RDV. Patient developed septic shock from Enterococcus faecium and subsequently died from multiorgan failure.
- Case 2021-0522632: 7-year-old female with history of microcephaly and hypothyroidism who developed ARDS, multisystem inflammatory syndrome in children (MIS-C), myocarditis, and bradycardia attributed to potentially both RDV and myocarditis. Had ongoing clinical decline requiring ECMO and died of multi-organ failure.
- Case 2021-0522633: 4-year-old female was hospitalized for COVID-19. Despite treatment with RDV, patient had continued clinical decline, developing ARDS, hemorrhagic infarction of the lungs with subsequent abscess formation of both lungs. Also required ECMO throughout hospitalization. Patient eventually died due to COVID-19.
- Case 2021-0542988: 3-month-old female was hospitalized for high fever and rash and noted to have low oxygen saturations of 80%. Patient was found to be COVID-19 positive and admitted to the PICU. Despite aggressive efforts and three doses of RDV, the patient experienced cardiorespiratory arrest and died.
- Case 2021-0545116: 6-day-old female (with a COVID-19 positive mother) was SARS-CoV-2 infected. The preterm neonate experienced respiratory distress syndrome and was treated with dexamethasone. With continued decline, RDV was given. Patient developed ST elevation as well as bradycardia in the setting of worsening hypoxic respiratory failure. Despite aggressive ventilatory support and medical management, the patient continued to decline and died from respiratory failure secondary to COVID-19.
- Case 2021-0553186: 15-year-old male with history of obesity was hospitalized for acute respiratory failure due to COVID-19, requiring high flow nasal cannula at 30 LPM. However, patient acutely developed severe shortness of breath and hypoxemia, oxygen desaturation, and then cardiac arrest. After 90 minutes of cardiopulmonary resuscitation/advanced cardiovascular life support, return of spontaneous circulation was not achieved and the patient died. The causes of death were cardiac arrest and pulmonary embolus.

Overall assessment of pediatric postmarketing data/expanded access data/EUA data: The reported events occurred in patients who are at risk for adverse outcomes due to the sequelae of COVID-19 (Castagnoli et al. 2020; Shekerdemian et al. 2020; Delahoy et al. 2021; Leidman et al. 2021). There is insufficient evidence to suggest a causal relationship between RDV and adverse pediatric outcomes based on the limited data currently available.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The potential for drug abuse, withdrawal, or rebound with RDV was not evaluated but is not anticipated.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Emergency Use Authorization

The EUA outlines mandatory reporting of all medication errors and adverse events (death, serious adverse events) considered to be potentially related to RDV. Based on the review of EUA data (hospitalized subjects), no additional labeling is warranted at this time. Please refer to the OSE review by Kate McCartan, Kimberley Swank, Rachna Kapoor and Ida-Lina Diak for details (Reference ID in DARRTS: 4917887). Routine pharmacovigilance will be in place to detect postmarketing signals.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 3 trial population. The eligibility criteria for this trial in nonhospitalized subjects with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, may mitigate potential safety concerns that may be observed with wider usage in the postmarket setting. Emergence of new events can be managed by routine pharmacovigilance activities.

8.10. Additional Safety Issues From Other Disciplines

All additional safety issues from other disciplines are included in this review.

8.11. Integrated Assessment of Safety

In nonhospitalized adults and pediatric patients 12 years of age and older and weighing at least 40 kg with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, the overall safety profile for the 3-day course of IV RDV is consistent with the known safety profile of RDV.

Higher rates of AEs, Grade 3/4 AEs, SAEs, and discontinuations due to AEs occurred in the PB) group compared to the RDV group.

No SAEs or discontinuations due to AEs were assessed by investigators as related to study drug.

Only one subject in the RDV group experienced a Grade 3/4 ADR; this was a laboratory event of ALT increased and AST increased.

Nausea was the only clinical ADR that occurred with ≥5% greater frequency. Nausea was also the only ADR with a ≥2% risk difference between RDV and PBO (7% versus 4%). Other ADRs occurred at similar or lower rates compared to PBO.

The notable laboratory abnormalities were the higher rates of Grade 3/4 creatinine clearance decreased (6% versus 2%) and creatinine increased (3% versus 1%) in the RDV group compared to the PBO group.

- These findings describe a total of 20 subjects (15 subjects in the RDV group and five subjects in the PBO group) with ≥ Grade 3 CrCl decreased, of whom a subset of 11 subjects (eight subjects in the RDV group and three subjects in the PBO group) also had ≥ Grade 3 creatinine increased.
- These findings will be displayed in product labeling. Of note, the approved label already outlines that monitoring of renal function is recommended while receiving RDV.
- It should be noted that analyses of the clinical narratives and renal laboratory data for these subjects suggested several factors could contribute to this apparent discrepancy.
- Use of the CG formula in overweight or obese individuals can be problematic. If total body weight is used when calculating creatinine clearance, as occurred in this trial, it results in a less accurate estimate of renal function in overweight or obese individuals compared to using other body weight metrics (such as ideal body weight or adjusted body weight) to calculate creatinine clearance (Cockcroft and Gault 1976; Kidney Disease: Improving Global Outcomes (KDIGO) 2012; Nair et al. 2014; September 2020; Shao et al. 2020; National Institute of Diabetes and Digestive and Kidney Diseases n.d.).
- Use of the CG formula in this population enriched for obesity, coupled with the DAIDS grading system, could have contributed to artifactually high-grade renal laboratory abnormalities that were not clinically meaningful.
    - Nine out of 15 subjects in the RDV group and four out of five subjects in the PBO group with treatment-emergent Grade 3 CrCl decreased had “supraphysiologic” CrCl levels by CG formula at baseline, which could have contributed to high grading on the DAIDS grading system when CrCl values decreased and could also have contributed to potential inaccuracies in the degree of change in CrCl from baseline.
    - Using the CKD-EPI formula (which does not utilize weight in the calculation) resulted in a lower degree of supraphysiologic eGFR values at baseline, less variance of eGFR over the course of the study, and 14 of the 20 subjects no longer had treatment-emergent ≥ Grade 3 CrCl decreased.
- Of the 11 subjects with ≥ Grade 3 creatinine increased (RDV [n=8]; PBO [n=3]), nine subjects (RDV [n=7]; PBO [n=2]) had absolute changes <0.5 mg/dL.
    - Of the eight RDV subjects with ≥ Grade 3 creatinine increased, six of these laboratory abnormalities occurred after the study dosing period.
    - Of the three PBO subjects with ≥ Grade 3 creatinine increased, one of these laboratory abnormalities occurred after the study dosing period.
- None of these Grade 3/4 renal laboratory parameters appeared to be clinically meaningful and none resulted in treatment discontinuation.

Hypersensitivity reactions and hepatotoxicity, the major safety issues identified in the original NDA review (in hospitalized subjects), were infrequent in this sNDA (in nonhospitalized subjects).

- The approved labeling (in hospitalized subjects) includes a Warnings and Precautions section that clearly describes the hypersensitivity reactions, including infusion-related and anaphylactic reactions, that have been observed for RDV and outlines risk mitigation strategies for health care providers to consider.
- During the original NDA review, a suggested timeframe for postinfusion monitoring was not described because it was encompassed by the level of monitoring commensurate with ongoing, inpatient care in a hospital or in a health care setting capable of providing acute care comparable to inpatient hospital care.
- Due to the use of RDV in both inpatient and outpatient settings that would result following approval of this sNDA, the review team provided additional description that the available data indicate that most of these events occurred within one-hour postinfusion. The review team also concluded that monitoring patients during infusion and observing patient for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate is supported by the clinical data.

There is interest in the potential home use of parenteral COVID-19 treatments. The safety in subjects who received RDV in the home health setting was overall comparable to subjects who received RDV at an outpatient facility, but this assessment is based on limited data.

No notable differences appeared following EUA and postmarketing safety analyses. No additional labeling of EUA and postmarketing data are warranted at this time. This section provides concise and issue-based integrated conclusions about the important safety issues and their relevance to the benefit-risk assessment and regulatory decision.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting will not be convened for this application.

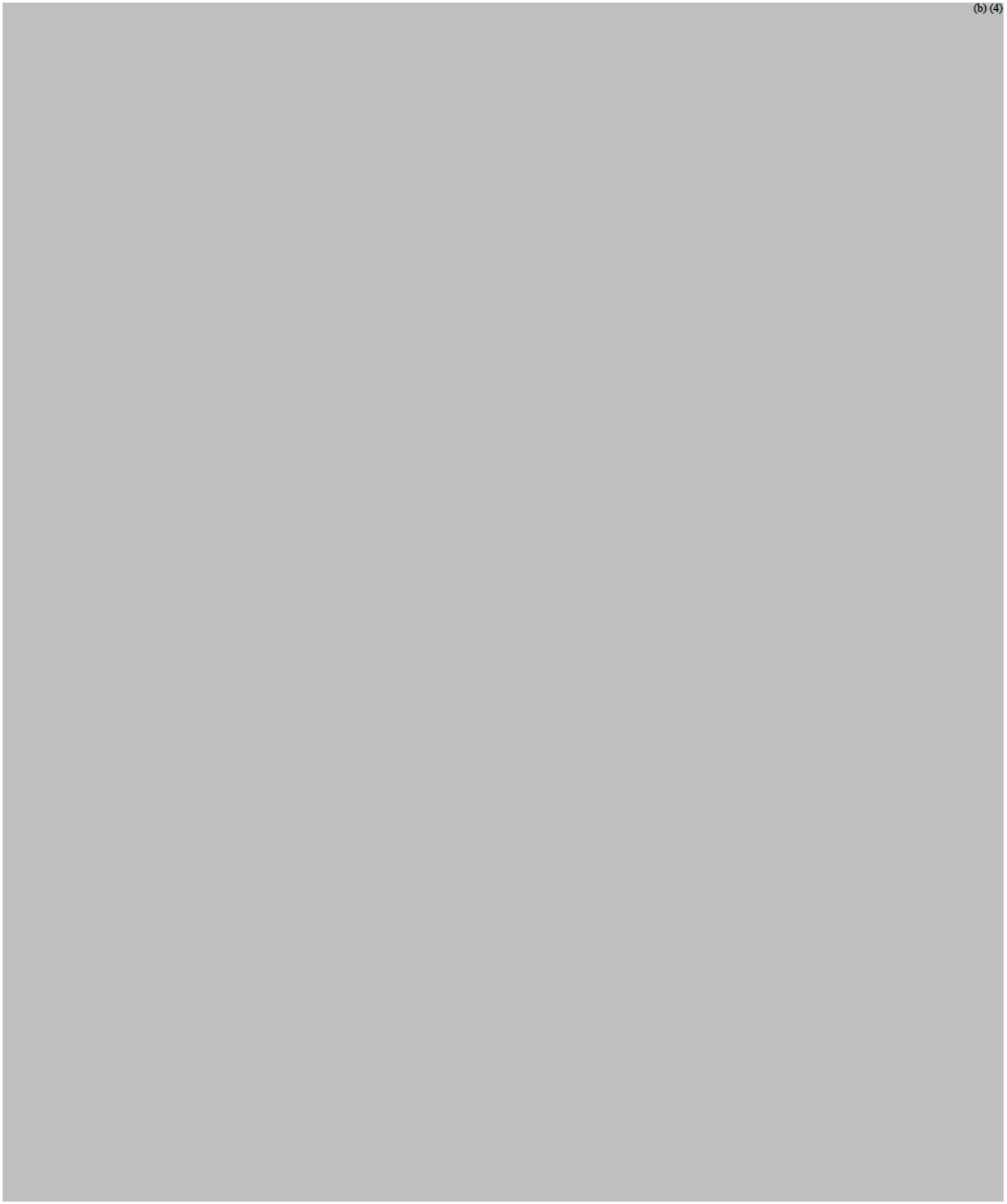
10. Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed labeling. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted.

(b) (4)

(b) (4)



(b) (4)

[redacted]

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the package insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

11. Risk Evaluation and Mitigation Strategies

No issues were identified to necessitate risk evaluation and mitigation strategies.

12. Postmarketing Requirements and Commitments

Postmarketing requirements (PMRs) and postmarketing commitments (PMCs) were still under discussion at the time this review was completed. This section includes PMRs and PMCs that will be proposed by the review team.

- The following PREA PMR will be issued: Conduct a study to evaluate the safety, tolerability, and pharmacokinetics of remdesivir in non-hospitalized pediatric subjects from birth to less than 12 years of age with coronavirus disease 2019 (COVID-19). A dedicated outpatient pediatric study is not required if pharmacokinetics and safety can be obtained from the ongoing trial in hospitalized pediatric population.
  - Rationale: Safety and pharmacokinetic (PK) data are needed in pediatric patients. The trial will collect safety and PK data across the range of pediatric ages and weight bands. (b) (4) .
- The following PMR will be issued: Evaluate the impact of the nsp12 A376V substitution on remdesivir susceptibility of virus or replicon in cell culture or in a biochemical assay of RdRp activity if virus or replicon are unable to be recovered.
  - Rationale: Treatment-emergent substitutions are potentially associated with reduced susceptibility to remdesivir and should be evaluated for their impact on remdesivir antiviral activity in cell culture.
- The following PMR will be issued: Evaluate by NGS sequence analysis the viral genes nsp8, nsp10, nsp12, nsp13, and nsp14, at baseline and Day 7 time points for subjects in Study GS-US-540-9012 who met the following criteria: Exhibited any postbaseline increase in viral RNA and had viral RNA levels at Day 7 that were greater than the Day 7 75th percentile value (5.0 $\log_{10}$ copies/mL). Submit phenotypic analysis for treatment-emergent amino acid substitutions in nsp8, nsp10, nsp12, nsp13, and nsp14.
  - Rationale: Analysis of viral RNA data identified 16 subjects in the RDV treatment arm in Study GS-US-540-9012 who exhibited apparent viral RNA rebound and had high viral RNA levels at Day 7 potentially indicative of treatment-emergent resistance; however, Day 7 sequencing data were not reported for subjects in the RDV arm, and sequencing was only attempted for subjects who had evaluable viral RNA at Day 14. Based on the viral RNA kinetics observed in the trial, this approach is inadequate to detect potential treatment-emergent resistant variants that may have been present at earlier time points when viral RNA rebound peaked at a high level on Day 7 in some subjects. Additional

sequence analyses should be carried out at baseline and at the Day 7 time point for the subjects who met the following criteria: Exhibited any postbaseline increase in viral RNA and had viral RNA levels at Day 7 (actual study days 5 to 9) that were greater than the Day 7 75th percentile viral RNA value (5.0 $\log_{10}$ copies/mL).

- The following PMC will be issued: Submit viral sequencing data for baseline respiratory samples and postbaseline samples collected at Day 2, Day 3, Day 7, or Day 14, for remdesivir-treated subjects and evaluated placebo subjects in Study GS-US-540-9012 with viral RNA shedding above the limit of detection for the sequencing assay including submission of associated fastq files for successfully sequenced samples. Submit phenotypic analysis for clinical isolates with treatment-emergent amino acid substitutions in accordance with the virology analysis plan for Study GS-US-540-9012.
  - Rationale: The current data are inadequate to evaluate the risk of treatment-emergent resistance. Complete datasets, including raw NGS sequence data, are needed for adequate independent analysis. Identified treatment-emergent substitutions may be associated with reduced susceptibility to remdesivir and should be evaluated for their impact on remdesivir antiviral activity in cell culture.

13. Appendices

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13.2. Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The financial disclosures described below do not affect approvability of RDV.

Covered Clinical Study (Name and/or Number): Study GS-US-540-9012

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 311 Overall: 60 Principal Investigators, 251 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Dr. (b) (6) is a sub-investigator on Study GS-US-540-9012. Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 2 Dr. (b) (6) and Dr. (b) (6) are principal investigators on Study GS-US-540-9012.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant adequately examined financial disclosure information from all clinical investigators for the covered clinical trial, as recommended in the Guidance for Industry: Financial Disclosure by Clinical Investigators. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Those investigators who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3) are noted in the above template. The Form FDA 3455 for each investigator was provided.

Overall, the number of investigators with a financial interest is low. Due to the multicenter nature of these trials, the potential bias by any one investigator is minimized.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

13.3. Expanded Access

No nonhospitalized subjects received RDV for treatment of COVID-19 under expanded access.

13.4. Review Team

See next page for reviewer signatures.

Table 29. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division
Clinical	Kirk Chan-Tack, MD	OND/OID/DAV
Reviewer	**Signature:** Kirk M. Chan-tack -S Digitally signed by Kirk M. Chan-tack -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300392632, cn=Kirk M. Chan-tack -S Date: 2022.01.19 20:38:08 -05'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Cross-Disciplinary	Kimberly Struble, PharmD	OND/OID/DAV
Cross-Disciplinary Team Lead	**Signature:** Kimberly A. Struble -S Digitally signed by Kimberly A. Struble -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300077275, cn=Kimberly A. Struble -S Date: 2022.01.19 13:43:02 -05'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Clinical Virology	William Ince, PhD	OND/OID/DAV
Reviewer	**Signature:** William L. Ince -S Digitally signed by William L. Ince -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000523497, cn=William L. Ince -S Date: 2022.01.20 08:35:04 -05'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Clinical Virology	Julian J. O'Rear, PhD	OND/OID/DAV
Team Leader	**Signature:** Julian J. O'rear -S Digitally signed by Julian J. O'rear -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150659, cn=Julian J. O'rear -S Date: 2022.01.20 09:28:41 -05'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Statistical	Daniel Rubin, PhD	OTS/OB/DBIV
Reviewer	**Signature:** Daniel Rubin -S Digitally signed by Daniel Rubin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Daniel Rubin -S, 0.9.2342.19200300.100.1.1=2000365304 Date: 2022.01.19 15:33:49 -05'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Statistical	Thamban Valappil, PhD	OTS/OB/DBIV
Team Leader	**Signature:** Thamban I. Valappil -S Digitally signed by Thamban I. Valappil -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151694, cn=Thamban I. Valappil -S Date: 2022.01.19 18:13:24 -05'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Statistical	Dionne Price, PhD	OTS/OB/DBIV
Deputy Director	**Signature:** Dionne L. Price -S Digitally signed by Dionne L. Price -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300164533, cn=Dionne L. Price -S Date: 2022.01.20 07:37:04 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division
Clinical Pharmacology	Mario Sampson, PharmD	OTS/OCP/DIDP
Reviewer	**Signature:** Mario Sampson -S Digitally signed by Mario Sampson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mario Sampson -S, 0.9.2342.19200300.100.1.1=2001365806 Date: 2022.01.19 16:18:13 -06'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Clinical Pharmacology	Vikram Arya, PhD, FCP	OTS/OCP/DIDP
Associate Director for Therapeutic Review	**Signature:** Vikram Arya -S Digitally signed by Vikram Arya -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vikram Arya -S, 0.9.2342.19200300.100.1.1=1300221914 Date: 2022.01.20 08:19:25 -05'00'	
Discipline and Title or Role	**Reviewer Name**	**Office/Division**
Clinical	Yodit Belew, MD	OND/OID/DAV
Signatory Authority	**Signature:**	

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/

SAEBYEOL JANG
01/20/2022 11:29:54 AM

YODIT BELEW
01/20/2022 11:37:17 AM