CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214787Orig1s010

Trade Name:	Veklury
Generic or Proper Name:	remdesivir
Sponsor:	Gilead Sciences, Inc.
Approval Date:	January 21, 2022
Indication:	For the use as a 3-day dosing regimen for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s010

APPROVAL LETTER

NDA 214787/S-10

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: Madelyn Low, MBS
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Low:

Please refer to your supplemental new drug application (sNDA) dated and received October 21, 2021 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Veklury (remdesivir) injection, 5 mg/ml; Veklury (remdesivir) for injection, 100 mg/vial.

This Prior Approval sNDA provides for the use of Veklury (remdesivir) as a 3-day dosing regimen for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study for ages birth to less than 12 years or weighing < 40 kg in an outpatient setting for this application because this product is ready for approval for use in adults and pediatric patients 12 years of age and older, and the pediatric study in children less than 12 years of age has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

4220-1 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.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Final Protocol Submission:	Submitted
Study Completion:	02/2022
Final Report Submission:	09/2022

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 147753, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that you have fulfilled the pediatric study requirement for ages 12 to less than 18 years for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Veklury was approved on October 22, 2020, we have become aware of a SARS-CoV-2 substitution that was identified as treatment-emergent in Study GS-US-540-9012. We have also identified subjects in Study GS-US-540-9012 who exhibited apparent viral rebound, a signal of potential treatment-emergent resistance. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of treatment-emergent resistance.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4220-2 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.

The timetable you submitted on December 27, 2021 states that you will conduct this study according to the following schedule:

Study Completion: 05/2022
Final Report Submission: 06/2022

4220-3 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 post-baseline 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.

The timetable you submitted on January 11, 2022 states that you will conduct this study according to the following schedule:

Study Completion: 08/2022
Final Report Submission: 09/2022

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit the protocol(s) to your IND 147753, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4220-4 Submit viral sequencing data for baseline respiratory samples and post-baseline 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.

The timetable you submitted on January 11, 2022, states that you will conduct this study according to the following schedule:

Study Completion:	08/2022
Final Report Submission:	09/2022

Submit clinical protocols to your IND 147753 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Saebyeol Jang, PhD, RAC, Regulatory Project Manager, at (240) 402-9953 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antivirals
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

YODIT BELEW
01/21/2022 12:37:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s010

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VEKLURY safely and effectively. See full prescribing information for VEKLURY.

VEKLURY® (remdesivir) for injection, for intravenous use
VEKLURY® (remdesivir) injection, for intravenous use
Initial U.S. Approval: 2020

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	01/2022
Dosage and Administration	01/2022
Dosage and Administration Overview (2.1)	01/2022
Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg (2.3)	01/2022
Dosage Preparation and Administration (2.5)	01/2022
Warnings and Precautions, Hypersensitivity Including Infusion-related and Anaphylactic Reactions (5.1)	01/2022

----------INDICATIONS AND USAGE----------

VEKLURY is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. (1)

----------DOSAGE AND ADMINISTRATION----------

- Testing: In all patients, before starting VEKLURY and during treatment as clinically appropriate, perform renal and hepatic laboratory testing. Assess prothrombin time before starting VEKLURY and monitor as clinically appropriate. (2.2)
- Recommended dosage in adults and pediatric patients 12 years of age and older and weighing at least 40 kg: a single loading dose of VEKLURY 200 mg on Day 1 followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2 via intravenous infusion. The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made. (2.3)
- For hospitalized patients requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. (2.3)
- For hospitalized patients not requiring invasive mechanical ventilation and/or ECMO, the recommended treatment duration 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. (2.3)
- For non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, the recommended total treatment duration is 3 days (2.3).
- Administer VEKLURY via intravenous (IV) infusion over 30 to 120 minutes. (2.5)
- Renal impairment: VEKLURY is not recommended in patients with eGFR less than 30 mL/min. (2.4)
- Dose preparation and administration: Refer to the full prescribing information for further details for both formulations. (2.5)
- Storage of prepared dosages: VEKLURY contains no preservative. (2.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

- For injection: 100 mg of remdesivir as a lyophilized powder, in a single-dose vial. (3)
- Injection: 100 mg/20 mL (5 mg/mL) remdesivir, in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity including infusion-related and anaphylactic reactions: Hypersensitivity reactions have been observed during and following administration of VEKLURY. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent signs and symptoms of hypersensitivity. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment. (5.1)
- Increased risk of transaminase elevations: Transaminase elevations have been observed in healthy volunteers and have also been reported in patients with COVID-19 who received VEKLURY. Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate. Consider discontinuing VEKLURY if ALT levels increase to greater than 10 times the upper limit of normal. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation. (5.2)
- Risk of reduced antiviral activity when coadministered with chloroquine phosphate or hydroxychloroquine sulfate: Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY. (5.3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence greater than or equal to 5%, all grades) observed with treatment with VEKLURY are nausea, ALT increased, and AST increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VEKLURY is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are *[see Clinical Studies (14)]*:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

- VEKLURY may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion or hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary *[see Warnings and Precautions (5.1)]*.
- Administer VEKLURY for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) by intravenous infusion only. Do not administer by any other route.
- There are TWO different formulations of VEKLURY:
  - VEKLURY for injection (supplied as 100 mg lyophilized powder in vial) must be reconstituted with Sterile Water for Injection prior to diluting in a 100 mL or 250 mL 0.9% sodium chloride infusion bag.
  - VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial) must be diluted in a 250 mL 0.9% sodium chloride infusion bag.
- There are differences in the way the two formulations are prepared. Carefully follow the product-specific preparation instructions below *[see Dosage and Administration (2.5)].*

2.2 Testing Before Starting and During Treatment with VEKLURY

Determine eGFR in all patients before starting VEKLURY and monitor while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.4) and Use in Specific Populations (8.4, 8.6)].*

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.7)].*

Determine prothrombin time in all patients before starting VEKLURY and monitor while receiving VEKLURY as clinically appropriate *[see Adverse Reactions (6.1)].*

2.3 Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

The recommended dosage for adults and pediatric patients 12 years of age and older and weighing at least 40 kg is a single loading dose of VEKLURY 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2 via intravenous infusion.

Hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made.

- The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
- The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or 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.

Non-hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.

- The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

VEKLURY must be diluted prior to intravenous infusion. Refer to Dosage and Administration (2.5) for detailed preparation and administration instructions.

2.4 Renal Impairment

VEKLURY is not recommended in patients with eGFR less than 30 mL per minute *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].*

2.5 Dosage Preparation and Administration

There are differences in the way the two formulations are prepared. Carefully follow the product-specific preparation instructions below.

VEKLURY for Injection (Supplied as 100 mg Lyophilized Powder in Vial)

Reconstitution Instructions

Remove the required number of single-dose vial(s) from storage. For each vial:

- Aseptically reconstitute VEKLURY lyophilized powder by adding 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized powder.

- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear, colorless to yellow solution, free of visible particles, should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved. Discard the vial if the contents are not completely dissolved.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Use reconstituted product immediately to prepare the diluted drug product *[see Dosage and Administration (2.5)].*

Dilution Instructions

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer intravenous medication immediately after preparation when possible.

- Reconstituted VEKLURY for injection, containing 100 mg/20 mL remdesivir solution, must be further diluted in either a 100 mL or 250 mL 0.9% sodium chloride infusion bag. Refer to Table 1 for instructions.

Table 1 Recommended Dilution Instructions—Reconstituted VEKLURY for Injection Lyophilized Powder

VEKLURY dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted VEKLURY for injection
Loading dose 200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
	100 mL	40 mL	40 mL (2 × 20 mL)
Maintenance dose 100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag following instructions in Table 1, using an appropriately sized syringe and needle.
- Withdraw the required volume of reconstituted VEKLURY for injection from the VEKLURY vial following instructions in Table 1, using an appropriately sized syringe. Discard any unused portion remaining in the reconstituted vial.

- Transfer the required volume of reconstituted VEKLURY for injection to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Administration Instructions

Do not administer the prepared diluted solution simultaneously with any other medication. The compatibility of VEKLURY injection with intravenous solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer VEKLURY via intravenous infusion over 30 to 120 minutes.

Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate *[see Warnings and Precautions (5.1)]*.

Administer the diluted solution with the infusion rate described in Table 2.

Table 2 Recommended Rate of Infusion—Diluted VEKLURY for Injection Lyophilized Powder in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

VEKLURY Injection (Supplied as 100 mg/20 mL [5 mg/mL] Solution in Vial)

Dilution Instructions

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer intravenous medication immediately after preparation when possible.

- Remove the required number of single-dose vial(s) from storage. Each vial contains 100 mg/20 mL of remdesivir. For each vial:

- Equilibrate to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- VEKLURY injection must be diluted in an infusion bag containing 250 mL of 0.9% sodium chloride only. Refer to Table 3 for instructions.

Table 3 Recommended Dilution Instructions—VEKLURY Injection (Supplied as Solution in Vial)

VEKLURY dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of VEKLURY injection
Loading dose 200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
Maintenance dose 100 mg (1 vial)		20 mL	20 mL

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag following instructions in Table 3, using an appropriately sized syringe and needle.
- Withdraw the required volume of VEKLURY injection from the VEKLURY vial following instructions in Table 3, using an appropriately sized syringe.
  - Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
  - Inject the air into the VEKLURY injection vial above the level of the solution.
  - Invert the vial and withdraw the required volume of VEKLURY injection solution into the syringe. The last 5 mL of solution requires more force to withdraw.
- Transfer the required volume of VEKLURY injection to the infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Administration Instructions

Do not administer the prepared diluted solution simultaneously with any other medication. The compatibility of VEKLURY injection with intravenous solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer VEKLURY via intravenous infusion over 30 to 120 minutes.

Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate *[see Warnings and Precautions (5.1)]*.

Administer the diluted solution with the infusion rate described in Table 4.

Table 4 Recommended Rate of Infusion—Diluted VEKLURY Injection Solution in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min

2.6 Storage of Prepared Dosages

VEKLURY for Injection (Supplied as Lyophilized Powder in Vial)

After reconstitution, use vials immediately to prepare diluted solution. The diluted VEKLURY solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

VEKLURY Injection (Supplied as Solution in Vial)

Store VEKLURY injection after dilution in the infusion bags up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

IMPORTANT:

This product contains no preservative. Any unused portion of a single-dose VEKLURY vial should be discarded after a diluted solution is prepared.

3 DOSAGE FORMS AND STRENGTHS

- VEKLURY for injection, 100 mg, available as a sterile, preservative-free white to off-white to yellow lyophilized powder in single-dose vial for reconstitution.
- VEKLURY injection, 100 mg/20 mL (5 mg/mL), available as a clear, colorless to yellow solution, free of visible particles in single-dose vial.

4 CONTRAINDICATIONS

VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product *[see Warnings and Precautions (5.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Including Infusion-related and Anaphylactic Reactions

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of VEKLURY; most occurred within one hour. 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 during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. 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)]*.

5.2 Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of VEKLURY followed by 100 mg doses for up to 10 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of VEKLURY. Transaminase elevations have also been reported in patients with COVID-19 who received VEKLURY *[see Adverse Reactions (6.1)]*. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus VEKLURY in clinical trials of VEKLURY, discerning the contribution of VEKLURY to transaminase elevations in patients with COVID-19 can be challenging.

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.1) and Use in Specific Populations (8.7)]*.

- Consider discontinuing VEKLURY if ALT levels increase to greater than 10 times the upper limit of normal.
- Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.

5.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine Phosphate or Hydroxychloroquine Sulfate

Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY *[see Drug Interactions (7) and Microbiology (12.4)].*

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hypersensitivity Including Infusion-related and Anaphylactic Reactions *[see Warnings and Precautions (5.1)]*
- Increased Risk of Transaminase Elevations *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of VEKLURY is based on data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19, one Phase 3 study in 279 non-hospitalized adult and pediatric subjects (12 years of age and older weighing at least 40 kg) with mild-to-moderate COVID-19, four Phase 1 studies in 131 healthy adults, and from patients with COVID-19 who received VEKLURY under the Emergency Use Authorization or in a compassionate use program.

Clinical Trials Experience in Subjects with COVID-19

NIAID ACTT-1 was a randomized, double-blind, placebo-controlled clinical trial in hospitalized subjects with mild, moderate, and severe COVID-19 treated with VEKLURY (n=532) or placebo (n=516) for up to 10 days. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days *[see Clinical Studies (14.1)]*. The collection of adverse event data in this trial was limited to severe (Grade 3) or potentially life-threatening (Grade 4) adverse events, serious adverse events, adverse events leading to study drug discontinuation, and moderate (Grade 2) severity or higher hypersensitivity reactions. Rates of adverse reactions (≥ Grade 3), serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 5.

Table 5 Summary of Adverse Reaction Rates in Hospitalized Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1

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

a. Seizure (n=1), infusion-related reaction (n=1).
b. Seizure (n=1), infusion-related reaction (n=1), transaminases increased (n=3), ALT increased and AST increased (n=1), GFR decreased (n=2), acute kidney injury (n=3).

Study GS-US-540-5773 was a randomized, open-label clinical trial in hospitalized subjects with severe COVID-19 treated with VEKLURY 200 mg on Day 1 and 100 mg once daily for 5 (n=200) or 10 days (n=197). Adverse reactions were reported in 33 (17%) subjects in the 5-day group and 40 (20%) subjects in the 10-day group *[see Clinical Studies (14.2)]*. The most common adverse reactions occurring in at least 5% of subjects in either the VEKLURY 5-day or 10-day group, respectively, were nausea (5% vs 3%), AST increased (3% vs 6%), and ALT increased (2% vs 7%). Rates of any adverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 6.

Table 6 Summary of Adverse Reaction Rates in Hospitalized Subjects with Severe COVID-19 in Study 5773

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

a. Transaminases increased (n=5), hepatic enzyme increased (n=1), hypertransaminasaemia (n=1).
b. Transaminases increased (n=4), hepatic enzyme increased (n=2), LFT increased (n=2), hypertransaminasaemia (n=1), ALT increased (n=1), ALT increased and AST increased (n=2), injection site erythema (n=1), rash (n=1).

Study GS-US-540-5774 was a randomized, open-label clinical trial in hospitalized subjects with moderate COVID-19 treated with VEKLURY 200 mg on Day 1 and 100 mg daily for 5 (n=191) or 10 days (n=193), or standard of care (SOC) only (n=200) *[see Clinical Studies (14.3)]*. Adverse reactions were reported in 36 (19%) subjects in the 5-day group and 25 (13%) subjects in the 10-day group. The most common adverse reaction occurring in at least 5% of subjects in the VEKLURY groups was nausea (7% in the 5-day group, 4% in the 10-day group). Rates of any adverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 7.

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

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

a. Attribution of events to study drug was not performed for the SOC group.
b. Heart rate decreased.

c. ALT increased (n=2), ALT increased and AST increased (n=1), hypertransaminasaemia (n=1), blood alkaline phosphatase increased (n=1), rash (n=2), heart rate decreased (n=1).

Study GS-US-540-9012 was a randomized, double-blind, placebo-controlled clinical trial in subjects who were non-hospitalized, were symptomatic for COVID-19 for ≤7 days, had confirmed SARS-CoV-2 infection, and had at least one risk factor for progression to hospitalization treated with VEKLURY (n=279; 276 adults and 3 pediatric subjects 12 years of age and older weighing at least 40 kg) or placebo (n=283; 278 adults and 5 pediatric subjects 12 years of age and older weighing at least 40 kg) for 3 days. Of the 279 subjects treated with VEKLURY, 227 subjects received at least one dose of VEKLURY at an outpatient facility, 44 subjects received at least one dose of VEKLURY in a home healthcare setting, and 8 subjects received at least one dose of VEKLURY at a skilled nursing facility. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days *[see Clinical Studies (14.4)]*. Adverse reactions (all grades) were reported in 34 (12%) subjects in the VEKLURY group and 25 (9%) subjects in the placebo group. The most common adverse reaction occurring in at least 5% of subjects in the VEKLURY group was nausea (6%). There were no serious adverse reactions or adverse reactions leading to treatment discontinuation in either treatment group. Safety in subjects who received VEKLURY in a home healthcare setting was comparable to that observed in the overall GS-US-540-9012 study population, but these findings are based on limited data.

Less Common Adverse Reactions

Clinically significant adverse reactions that were reported in <2% of subjects exposed to VEKLURY in clinical trials are listed below:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)].*
- Generalized seizure
- Rash

Emergency Use Authorization Experience in Subjects with COVID-19

The following adverse reactions have been identified during use of VEKLURY under Emergency Use Authorization:

- General disorders and administration site conditions: Administration site extravasation
- Skin and subcutaneous tissue disorders: Rash
- Immune system disorders: Anaphylaxis, angioedema, infusion-related reactions, hypersensitivity
- Investigations: Transaminase elevations

Laboratory Abnormalities

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

The frequencies of laboratory abnormalities (Grades 3-4) occurring in at least 3% of subjects with COVID-19 receiving VEKLURY in Trials NIAID ACTT-1, 5773, and 5774 are presented in Table 8, Table 9, and Table 10, respectively.

Table 8 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1

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

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

Table 9 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Subjects with Severe COVID-19 in Trial 5773

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

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

Table 10 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Subjects with Moderate COVID-19 in Trial 5774

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

SOC=Standard of care.

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

The frequencies of laboratory abnormalities (Grades 3-4) occurring in at least 2% of subjects with COVID-19 receiving VEKLURY in Trial GS-US-540-9012 are presented in Table 11.

Table 11 Laboratory Abnormalities (Grades 3-4) Reported in ≥2% of Non-Hospitalized Subjects in Trial 9012

Laboratory Parameter Abnormality[a]	VEKLURY 3 Days N=279	Placebo N=283
Creatinine clearance decreased[b]	6%	2%
Creatinine increased	3%	1%
Glucose increased	6%	6%
Lymphocytes decreased	2%	1%
Prothrombin time increased	1%	2%

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

7 DRUG INTERACTIONS

Due to potential antagonism based on data from cell culture experiments, concomitant use of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended *[see Warnings and Precautions (5.3) and Microbiology (12.4)].*

Drug-drug interaction trials of VEKLURY and other concomitant medications have not been conducted in humans. Remdesivir and its metabolites are in vitro substrates and/or inhibitors of certain drug metabolizing enzymes and transporters. The clinical relevance of these in vitro assessments has not been established *[see Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to VEKLURY during pregnancy. Pregnant and recently pregnant individuals can go to https://covid-pr.pregistry.com to enroll or call 1-800-616-3791 to obtain information about the registry.

Risk Summary

Available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) *(see Data).* There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk
COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Animal Data

Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at nontoxic doses in pregnant animals. During organogenesis, exposures to the predominant circulating metabolite (GS-441524) were 4 times higher (rats and rabbits) than the exposure in humans at the RHD. In a pre/postnatal development study, exposures to the predominant circulating metabolite of remdesivir (GS-441524) were similar to the human exposures at the RHD.

8.2 Lactation

Risk Summary

There are no available data on the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and metabolites have been detected in the nursing pups of mothers given remdesivir, likely due to the presence of remdesivir in milk *(see Data).* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VEKLURY and any potential adverse effects on the breastfed child from VEKLURY or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data

Animal Data

Remdesivir and its metabolites were detected in the plasma of nursing rat pups, likely due to the presence of remdesivir and/or its metabolites in milk, following daily intravenous administration of remdesivir to pregnant rats from Gestation Day 6 to Lactation Day 20. Exposures in nursing pups were approximately 1% that of maternal exposure on Lactation Day 10.

8.4 Pediatric Use

The safety and effectiveness of VEKLURY for the treatment of COVID-19 have been established in pediatric patients 12 years and older and weighing at least 40 kg, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Use in this age group is based on extrapolation of pediatric efficacy from adequate and well-controlled studies in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Clinical trials of VEKLURY in hospitalized subjects included 30 adult subjects weighing 40 to 50 kg. The safety in this weight group was comparable to adult subjects weighing greater than 50 kg. Thirty-nine pediatric patients 12 years and older and weighing at least 40 kg received VEKLURY in a compassionate use program in hospitalized subjects; the available clinical data from these patients are limited.

All pediatric patients 12 years of age and older and weighing at least 40 kg must have eGFR determined before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.2, 2.4)].*

The safety and effectiveness of VEKLURY have not been established in pediatric patients younger than 12 years of age or weighing less than 40 kg.

8.5 Geriatric Use

Of the 1,062 hospitalized subjects with SARS-CoV-2 infection randomized in ACTT-1, 36% were 65 years or older. Of the 397 hospitalized subjects with SARS-CoV-2 infection randomized in Study GS-US-540-5773, 42% were 65 years or older. Of the 584 hospitalized subjects with SARS-CoV-2 infection randomized in Study GS-US-540-5774, 27% were 65 years or older. Of the 562 non-hospitalized subjects with SARS-CoV-2 infection randomized in Study GS-US-540-9012, 17% were 65 years or older. Reported clinical experience has not identified differences in responses between the elderly and younger patients *[see Clinical Studies (14)]*. No dosage adjustment is required in patients over the age of 65 years. In general, appropriate caution should be exercised in the administration of VEKLURY and monitoring of elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The pharmacokinetics of VEKLURY have not been evaluated in patients with renal impairment. Patients with eGFR greater than or equal to 30 mL per minute have received VEKLURY for treatment of COVID-19 with no dose adjustment of VEKLURY *[see Clinical Studies (14)].*

All patients must have an eGFR determined before starting VEKLURY and while receiving VEKLURY as clinically appropriate. Because the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with betadex sulfobutyl ether sodium (such as VEKLURY) is not recommended in patients with eGFR less than 30 mL per minute *[see Dosage and Administration (2.2, 2.4)].*

8.7 Hepatic Impairment

The pharmacokinetics of VEKLURY have not been evaluated in patients with hepatic impairment.

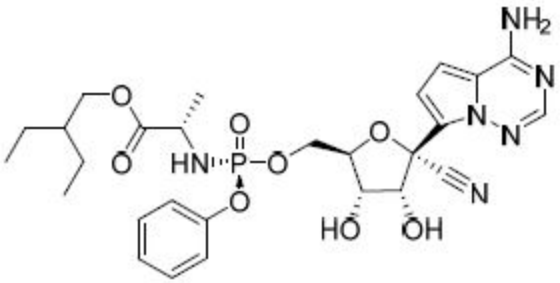
Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)].*

10 OVERDOSAGE

There is no human experience of acute overdosage with VEKLURY. Treatment of overdose with VEKLURY should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with VEKLURY.

11 DESCRIPTION

VEKLURY contains remdesivir, a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor. The chemical name for remdesivir is 2-ethylbutyl *N*-{(*S*)-[2-*C*-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-*O*-yl]phenoxyphosphoryl}-L-alaninate. It has a molecular formula of $C_{27}H_{35}N_6O_8P$ and a molecular weight of 602.6 g/mol. Remdesivir has the following structural formula:



VEKLURY for injection contains 100 mg of remdesivir as a sterile, preservative-free lyophilized white to off-white to yellow powder in a single-dose clear glass vial. It requires reconstitution and then further dilution prior to administration by intravenous infusion *[see Dosage and Administration (2.4)]*. The inactive ingredients are 3 g betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

VEKLURY injection contains 100 mg/20 mL (5 mg/mL) of remdesivir as a sterile, preservative-free, clear, colorless to yellow solution in a single-dose clear glass vial. It requires dilution prior to administration by intravenous infusion *[see Dosage and Administration (2.5)]*. The inactive ingredients are 6 g betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Remdesivir is an antiviral drug with activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

Remdesivir and metabolites exposure-response relationships and the time course of pharmacodynamics response are unknown.

12.3. Pharmacokinetics

The pharmacokinetic (PK) properties of remdesivir and metabolites are provided in Table 12. The multiple dose PK parameters of remdesivir and metabolites in healthy adults are provided in Table 13.

Table 12 Pharmacokinetic Properties of Remdesivir and Metabolites (GS-441524 and GS-704277)

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

ND=not detected

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.

b. Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.

c. Median (Study GS-US-399-4231).

d. Mean (Study GS-US-399-4231).

Table 13 Multiple Dose PK Parameters[a] of Remdesivir and Metabolites (GS-441524 and GS-704277) Following IV Administration of VEKLURY 100 mg to Healthy Adults

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

CV=Coefficient of Variation; ND=Not detectable (at 24 hours post-dose)

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505).

Specific Populations

Pharmacokinetic differences based on sex, race, age, renal function, and hepatic function on the exposures of remdesivir have not been evaluated.

Pediatric Patients

The pharmacokinetics of VEKLURY in pediatric patients have not been evaluated.

Using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of remdesivir and metabolites in patients 12 years of age and older and weighing at least 40 kg as observed in healthy adults *[see Use in Specific Populations (8.4)].*

Drug Interaction Studies

Clinical drug-drug interaction studies have not been performed with VEKLURY.

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

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

12.4 Microbiology

Mechanism of Action

Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to a nucleoside monophosphate intermediate by carboxyesterase 1 and/or cathepsin A, depending upon the cell type. The nucleoside monophosphate is subsequently phosphorylated by cellular kinases to form the pharmacologically active nucleoside triphosphate metabolite (GS-443902). Remdesivir triphosphate (RDV-TP) acts as an analog of adenosine triphosphate (ATP) and competes with high selectivity (3.65-fold) over the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination (position i+3) during replication of the viral RNA. In a biochemical assay assessing RDV-TP incorporation by the MERS-CoV RdRp complex, RDV-TP inhibited RNA synthesis with an IC_{50} value of 0.032 µM. RDV-TP can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur at higher nucleotide concentrations. When remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase.

Antiviral Activity

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell lines Calu-3 and A549-hACE2 with EC_{50} values of 280 nM after 72 hours of treatment and 115 nM after 48 hours of treatment, respectively.

Remdesivir EC_{50} values for SARS-CoV-2 in A549-hACE2 cells were not different when combined with chloroquine phosphate or hydroxychloroquine sulfate at concentrations up to 2.5 µM. In a separate study, the antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate or hydroxychloroquine sulfate reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2, and normal human bronchial epithelial cells.

Based on cell culture susceptibility testing by plaque assay and/or N protein ELISA assay, remdesivir retained similar antiviral activity (≤1.5-fold change) against clinical isolates of SARS-CoV-2 variants containing the P323L substitution in the viral polymerase including the Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Epsilon (B.1.429) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates.

SARS-CoV-2 RNA shedding results from GS-US-540-5776 (ACTT-1) indicate that remdesivir does not significantly reduce the amount of detectable SARS-CoV-2 RNA in oropharyngeal or nasopharyngeal swabs or plasma samples in hospitalized patients compared to placebo, and SARS-CoV-2 RNA shedding results from GS-US-540-9012 indicate that remdesivir does not significantly

reduce the amount of detectable SARS-CoV-2 RNA in nasopharyngeal swabs in non-hospitalized patients compared to placebo.

Resistance

SARS-CoV-2 isolates with reduced susceptibility to remdesivir have been selected in cell culture. In a selection with GS-441524, the parent nucleoside of remdesivir, virus pools emerged expressing amino acid substitutions at V166A, N198S, S759A, V792I, C799F, and C799R in the viral RNA-dependent RNA polymerase (nsp12). When these substitutions were individually introduced into a wild-type recombinant virus by site-directed mutagenesis, 1.7- to 3.5-fold reductions in susceptibility to remdesivir were observed. In a cell culture resistance selection experiment with remdesivir, nsp12 amino acid substitution E802D emerged, resulting in a 2.5-fold reduction in susceptibility to remdesivir. In another selection with remdesivir using a SARS-CoV-2 isolate containing the P323L substitution in the viral polymerase, a single amino acid substitution at V166L emerged. Recombinant SARS-CoV-2 with substitutions at P323L alone or P323L+V166L in combination exhibited 1.3- and 1.5-fold reductions in remdesivir susceptibility, respectively.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified two substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduction in susceptibility to remdesivir in cell culture and attenuated SARS-CoV pathogenesis in a mouse model. When individually introduced into a SARS-CoV-2 recombinant virus, the corresponding substitutions at F480L and V557L each conferred 2-fold reduced susceptibility to remdesivir.

SARS-CoV-2 nsp12 E802D substitution has emerged in one individual treated with remdesivir. The E802D substitution resulted in a 2.5-fold increase in the remdesivir EC_{50} value.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Given the short-term administration of VEKLURY for the treatment of COVID-19, long-term animal studies to evaluate the carcinogenic potential of remdesivir were not conducted.

Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and in vivo rat micronucleus assays.

Impairment of Fertility

Nonclinical toxicity studies in rats demonstrated no adverse effect on male fertility at exposures of the predominant circulating metabolite (GS-441524) approximately 2 times the exposure in humans at the RHD.

Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered by daily intravenous administration at a

systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD.

13.2 Animal Toxicology and/or Pharmacology

Intravenous administration (slow bolus) of remdesivir to male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts.

Intravenous administration (slow bolus) of remdesivir to rats at dosage levels of ≥3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction.

Kidney-related effects in rats and monkeys were observed at exposures of the predominant circulating metabolite (GS-441524) that are lower than the exposure in humans at the RHD.

14 CLINICAL STUDIES

14.1 NIAID ACTT-1 Study in Hospitalized Subjects with Mild/Moderate and Severe COVID-19

A randomized, double-blind, placebo-controlled clinical trial (ACTT-1, NCT04280705) of hospitalized adult subjects with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19 compared treatment with VEKLURY for 10 days (n=541) with placebo (n=521). Mild/moderate disease was defined as SpO_2 >94% and respiratory rate <24 breaths/minute without supplemental oxygen; severe disease was defined as an SpO_2 ≤94% on room air, a respiratory rate ≥24 breaths/minute, an oxygen requirement, or a requirement for mechanical ventilation. Subjects had to have at least one of the following to be enrolled in the trial: radiographic infiltrates by imaging, SpO_2 ≤94% on room air, a requirement for supplemental oxygen, or a requirement for mechanical ventilation. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days, for 10 days of treatment via intravenous infusion. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

At baseline, mean age was 59 years (with 36% of subjects aged 65 or older); 64% of subjects were male, 53% were White, 21% were Black, and 13% were Asian; 24% were Hispanic or Latino; 105 subjects had mild/moderate disease (10% in both treatment groups); 957 subjects had severe disease (90% in both treatment groups). Subjects in this trial were unvaccinated. A total of 285 subjects (27%) (n=131 received VEKLURY) were on invasive mechanical ventilation or ECMO. The most common comorbidities were hypertension (51%), obesity (45%), and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

The primary clinical endpoint was time to recovery within 29 days after randomization. Recovery was defined as discharged from the hospital without limitations on activities, discharged from the hospital with limitations on activities and/or requiring home oxygen, or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the VEKLURY group compared to 15 days in the placebo group (recovery rate ratio 1.29 [95% CI 1.12 to 1.49], p<0.001). Among subjects with mild/moderate disease at enrollment

(n=105), the median time to recovery was 5 days in both the VEKLURY and placebo groups (recovery rate ratio 1.22 [95% CI 0.82 to 1.81]). Among subjects with severe disease at enrollment (n=957), the median time to recovery was 11 days in the VEKLURY group compared to 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52]).

A key secondary endpoint was clinical status on Day 15 assessed on an 8-point ordinal scale consisting of the following categories:

1. not hospitalized, no limitations on activities;
2. not hospitalized, limitation on activities and/or requiring home oxygen;
3. hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
4. hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
5. hospitalized, requiring supplemental oxygen;
6. hospitalized, on noninvasive ventilation or high-flow oxygen devices;
7. hospitalized, on invasive mechanical ventilation or ECMO; and
8. death.

Overall, the odds of improvement in the ordinal scale were higher in the VEKLURY group at Day 15 when compared to the placebo group (odds ratio 1.54 [95% CI 1.25 to 1.91]).

Overall, 29-day mortality was 11% for the VEKLURY group vs 15% for the placebo group (hazard ratio 0.73 [95% CI 0.52 to 1.03]).

14.2 Study GS-US-540-5773 in Hospitalized Subjects with Severe COVID-19

A randomized, open-label multi-center clinical trial (Study 5773, NCT04292899) in adult subjects with confirmed SARS-CoV-2 infection, an SpO_2 of ≤94% on room air, and radiological evidence of pneumonia compared 200 subjects who received VEKLURY for 5 days with 197 subjects who received VEKLURY for 10 days. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects on mechanical ventilation at screening were excluded. All subjects received 200 mg of VEKLURY on Day 1 and 100 mg once daily on subsequent days via intravenous infusion, plus standard of care.

At baseline, the median age of subjects was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian; 22% were Hispanic or Latino. More subjects in the 10-day group than the 5-day group required invasive mechanical ventilation or ECMO (5% vs 2%), or high-flow oxygen support (30% vs 25%), at baseline. Subjects in this trial were unvaccinated. Median duration of symptoms and hospitalization prior to first dose of VEKLURY were similar across treatment groups.

The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale consisting of the following categories:

1. death;
2. hospitalized, receiving invasive mechanical ventilation or ECMO;
3. hospitalized, receiving noninvasive ventilation or high-flow oxygen devices;
4. hospitalized, requiring low-flow supplemental oxygen;

5. hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to COVID-19);
6. hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration); and
7. not hospitalized.

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

14.3 Study GS-US-540-5774 in Hospitalized Subjects with Moderate COVID-19

A randomized, open-label multi-center clinical trial (Study 5774, NCT04292730) of hospitalized adult subjects with confirmed SARS-CoV-2 infection, SpO_2 >94% and radiological evidence of pneumonia compared treatment with VEKLURY for 5 days (n=191) and treatment with VEKLURY for 10 days (n=193) with standard of care (n=200). Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days via intravenous infusion.

At baseline, the median age of subjects was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian; 18% were Hispanic or Latino. Subjects in this trial were unvaccinated. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalization prior to first dose of VEKLURY were similar across treatment groups.

The primary endpoint was clinical status on Day 11 assessed on a 7-point ordinal scale consisting of the following categories:

1. death;
2. hospitalized, receiving invasive mechanical ventilation or ECMO;
3. hospitalized, receiving noninvasive ventilation or high-flow oxygen devices;
4. hospitalized, requiring low-flow supplemental oxygen;
5. hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to COVID-19);
6. hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration); and
7. not hospitalized.

Overall, the odds of improvement in the ordinal scale were higher in the 5-day VEKLURY group at Day 11 when compared to those receiving only standard of care (odds ratio 1.65 [95% CI 1.09 to 2.48], p=0.017). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only standard of care were not statistically significant (odds ratio 1.31 [95% CI 0.88 to 1.95]). All-cause mortality at Day 28 was ≤2% in all treatment groups.

14.4 Study GS-US-540-9012 in Non-Hospitalized Subjects with Mild-to-Moderate COVID-19 and at High Risk for Progression to Severe Disease

A randomized, double-blind, placebo-controlled, clinical trial (Study 9012, NCT04501952) evaluated VEKLURY 200 mg once daily for 1 day followed by VEKLURY 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 554 adult and 8 pediatric subjects (12 years of age and older and weighing at least 40 kg) who were non-hospitalized, had mild-to-moderate COVID-19, were symptomatic for COVID-19 for ≤7 days, had confirmed SARS-CoV-2 infection, and had at least one risk factor for progression to hospitalization. Risk factors for progression to hospitalization included age ≥60 years, obesity (BMI ≥30), chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, and sickle cell disease. Subjects who received, required, or were expected to require supplemental oxygen were excluded from the trial. Subjects were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (<60 vs ≥60 years), and region (US vs ex-US) to receive VEKLURY (n=279) or placebo (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of subjects aged 60 or older); 52% were male, 80% were White, 8% were Black, and 2% were Asian; 44% were Hispanic or Latino; median body mass index was 30.7 kg/m^2. Subjects in this trial were unvaccinated. VEKLURY or placebo was first administered to subjects in outpatient facilities (84%), home healthcare settings (13%), or skilled nursing facilities (3%). The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3, 6) days; median viral load was 6.3 log_{10} copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the VEKLURY and placebo treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause mortality through Day 28. Events occurred in 2 (0.7%) subjects treated with VEKLURY compared to 15 (5.3%) subjects concurrently randomized to placebo (hazard ratio 0.134 [95% CI 0.031 to 0.586]; p=0.0076). No deaths were observed through Day 28.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VEKLURY for injection: 100 mg (NDC 61958-2901-2), is supplied as a single-dose vial containing a sterile, preservative-free white to off-white to yellow lyophilized powder. It requires reconstitution and further dilution prior to administration by intravenous infusion *[see Dosage and Administration (2.4)]*. Discard unused portion. The container closure is not made with natural rubber latex.

VEKLURY injection: 100 mg/20 mL (5 mg/mL) (NDC 61958-2902-2), is supplied as a single-dose vial containing a sterile, preservative-free, clear, colorless to yellow aqueous-based solution. It requires dilution prior to administration by intravenous infusion *[see Dosage and Administration (2.4)].* Discard unused portion. The container closure is not made with natural rubber latex.

Storage and Handling

Do not reuse or save reconstituted or diluted VEKLURY for future use. These products contain no preservative; therefore, partially used vials should be discarded *[see Dosage and Administration (2.5)]*.

VEKLURY for Injection

Store VEKLURY for injection, 100 mg vials below 30°C (below 86°F) until required for use.

After reconstitution, use vials immediately to prepare diluted solution. Dilute the reconstituted solution in 0.9% sodium chloride injection, USP within the same day as administration. The diluted VEKLURY solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

VEKLURY Injection

Store VEKLURY injection vials at refrigerated temperature (2°C to 8°C [36°F to 46°F]) until required for use.

Dilute within the same day as administration. Prior to dilution, equilibrate VEKLURY injection to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution. Store VEKLURY injection after dilution in the infusion bags for no more than 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have been seen in patients receiving VEKLURY during and after infusion. Advise patients to inform their healthcare provider if they experience any of the following: changes in heart rate; fever; shortness of breath, wheezing; swelling of the lips, face, or throat; rash; nausea; sweating; or shivering *[see Warnings and Precautions (5.1)].*

Increased Risk of Transaminase Elevations

Inform patients that VEKLURY may increase the risk of hepatic laboratory abnormalities. Advise patients to alert their healthcare provider immediately if they experience any symptoms of liver inflammation *[see Warnings and Precaution (5.2)].*

Drug Interactions

Inform patients that VEKLURY may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal

products, including chloroquine phosphate or hydroxychloroquine sulfate *[see Warnings and Precautions (5.3), Drug Interactions (7), and Microbiology (12.4)].*

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to VEKLURY during pregnancy *[see Use in Specific Populations (8.1)].*

Pregnancy

Inform patients to notify their healthcare provider immediately in the event of a pregnancy *[see Use in Specific Populations (8.1)].*

Lactation

Inform mothers that it is not known whether VEKLURY can pass into their breast milk *[see Use in Specific Populations (8.2)]*.

PATIENT INFORMATION

VEKLURY® (VEK-lur-ee)
(remdesivir)
for injection

VEKLURY® (VEK-lur-ee)
(remdesivir)
injection

What is VEKLURY?

VEKLURY is a prescription medicine used for the treatment of coronavirus disease 2019 (COVID-19) in adults and children 12 years of age and older and weighing at least 88 pounds (40 kg) who are:

- Hospitalized, **or**
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

It is not known if VEKLURY is safe and effective in children under 12 years of age or weighing less than 88 pounds (40 kg).

Do not take VEKLURY if you are allergic to remdesivir or any of the ingredients in VEKLURY. See the end of this leaflet for a complete list of ingredients in VEKLURY.

Before receiving VEKLURY, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. It is not known if VEKLURY can harm your unborn baby. **Tell your healthcare provider right away if you are or if you become pregnant.**
  Pregnancy Registry: There is a pregnancy registry for individuals who receive VEKLURY during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. It is not known if VEKLURY can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VEKLURY may interact with other medicines.

Especially tell your healthcare provider if you are taking the medicines chloroquine phosphate or hydroxychloroquine sulfate.

How will I receive VEKLURY?

- **Hospitalized**: VEKLURY is given to you through a vein by intravenous (IV) infusion one time each day for up to 10 days. Your healthcare provider will decide how many doses you need.
- **Not hospitalized:** VEKLURY is given to you through a vein by intravenous (IV) infusion one time each day for 3 days.
- Your healthcare provider will do certain blood tests before starting and during treatment with VEKLURY.

What are the possible side effects of VEKLURY?

VEKLURY may cause serious side effects, including:

- **Allergic reactions.** Allergic reactions can happen during or after infusion with VEKLURY. Your healthcare provider will monitor you for signs and symptoms of allergic reactions during your infusion and for at least 1 hour after your infusion. Tell your healthcare provider right away if you get any of the following signs and symptoms of an allergic reaction:
  - changes in your heart rate
  - fever
  - shortness of breath, wheezing
  - swelling of the lips, face, or throat
  - rash
  - nausea
  - sweating
  - shivering
- **Increase in liver enzymes.** Increases in liver enzymes are common in people who have received VEKLURY and may be a sign of liver injury. Your healthcare provider will do blood tests to check your liver enzymes before and during treatment with VEKLURY as needed. Your healthcare provider may stop treatment with VEKLURY if you develop liver problems.

The most common side effect of VEKLURY is nausea.

These are not all of the possible side effects of VEKLURY.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of VEKLURY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about VEKLURY that is written for healthcare professionals.

What are the ingredients in VEKLURY?
Active ingredient: remdesivir
Inactive ingredients:

VEKLURY for injection: betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

VEKLURY injection: betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

Manufactured and distributed by: Gilead Sciences, Inc., Foster City, CA 94404

214787-GS-003
For more information, call 1-800-445-3235 or go to www.VEKLURY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: January/2022

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/

YODIT BELEW
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s010

OFFICER/EMPLOYEE LIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 25, 2022

TO: Administrative file for NDA 214787, Supplement 10

FROM: Saebyeol Jang, PhD, RAC
Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Infectious Diseases

SUBJECT: Officer/Employee List for NDA 214787, Supplement 10

APPLICATION/DRUG: NDA 214787, Veklury (remdesivir) for injection, 100 mg/vial; Veklury (remdesivir) injection, 5mg/mL, for intravenous use

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Arya, Vikram
Belew, Yodit
Birnkrant, Debra
Chan-Tack, Kirk
Diak, Ida-Lina
Fanari, Melina
Griffiths, LaShawn
Hyon, Kyong
Ince, William
Jang, Saebyeol
Kapoor, Rachna
Kolejian, Sevan
Kronstein, Philip
Lewis, David
McCartan, Kate
Min, Stacey
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Price, Dionne
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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
01/25/2022 04:30:56 PM

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
Received Date(s)	October 21, 2021
PDUFA Goal Date	April 21, 2022
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:

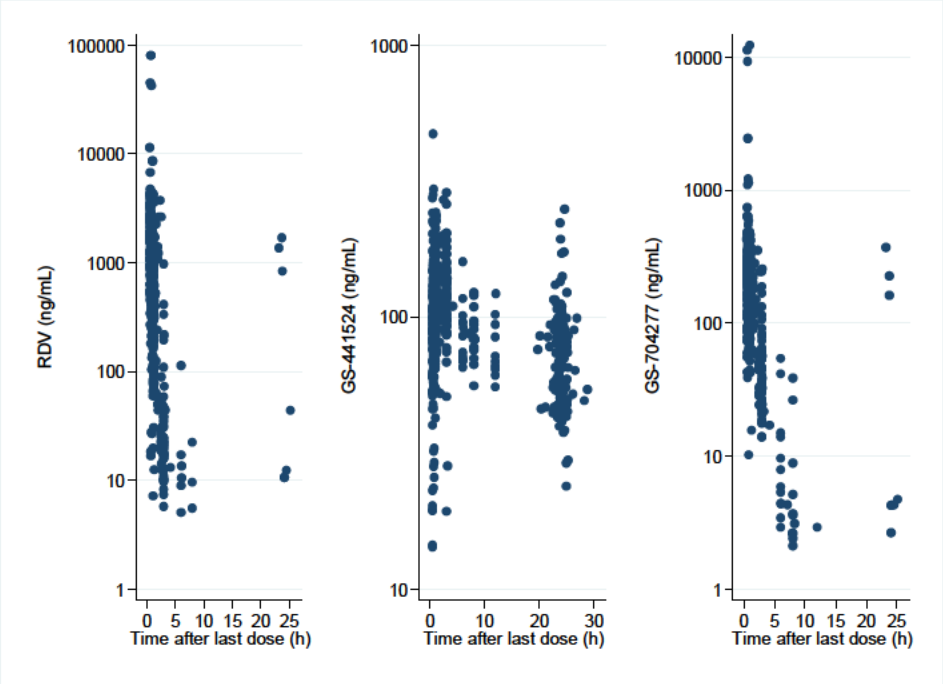
- The Applicant postulated that early antiviral treatment in subjects with early stage COVID-19 not requiring hospitalization or oxygen supplementation may prevent disease progression and may also facilitate shorter courses of treatment.
- The Applicant cited an RCT in nonhospitalized patients with influenza 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

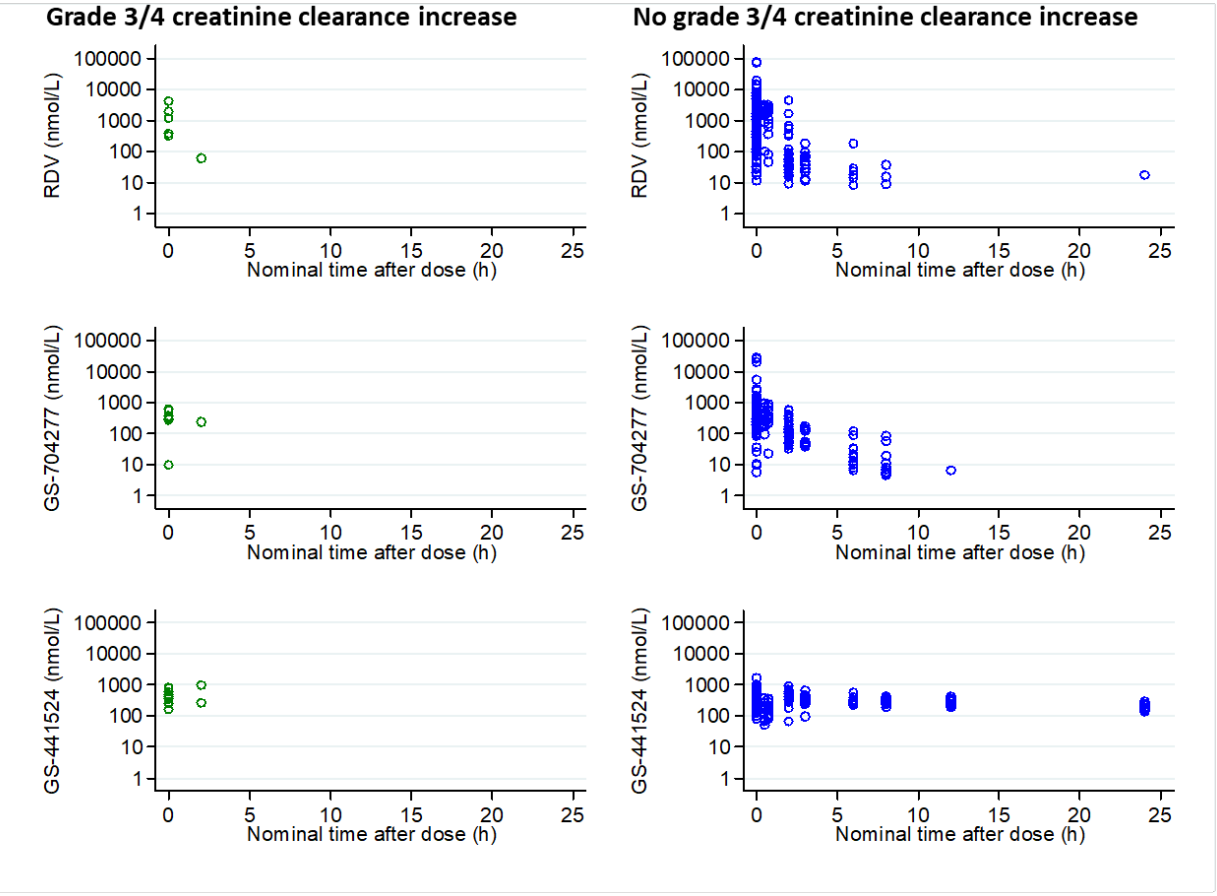
Exposure-Response for Efficacy

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

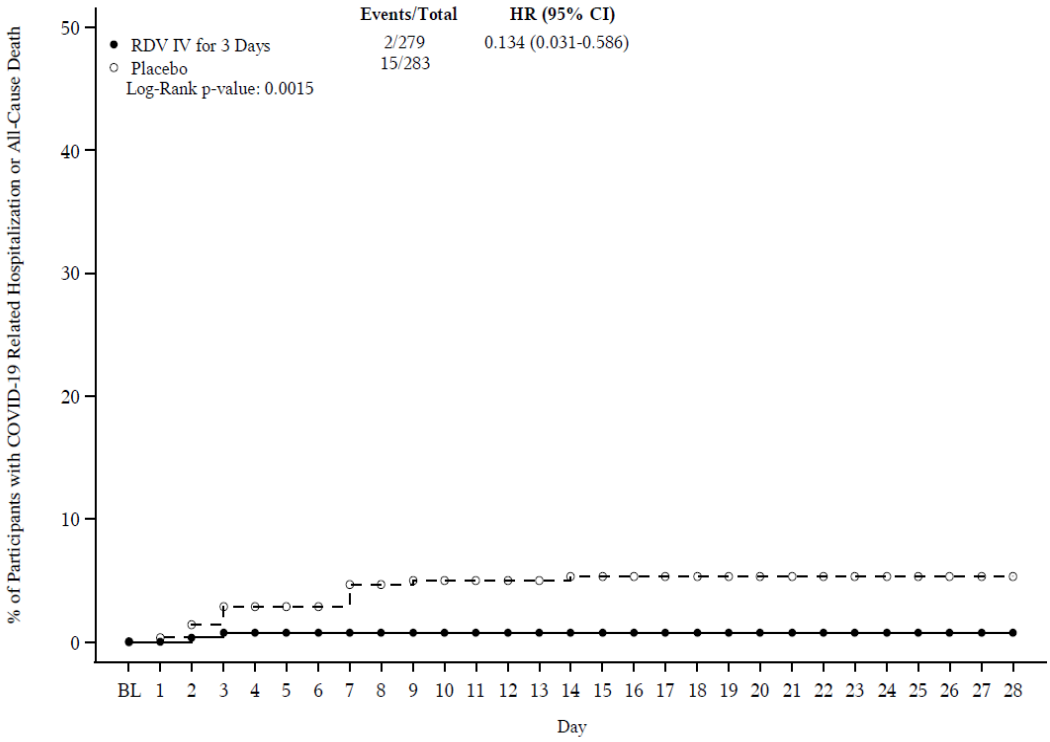
Parameter	RDV IV for 3 Days (N=279)	PBO (N=283)
COVID-19-related hospitalization or all-cause death [n (%)]	2 (0.7)	15 (5.4)
Hazard ratio for RDV vs. placebo	0.13	
95% CI for hazard ratio	0.03 to 0.59	
p-value for hazard ratio	0.008	

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.

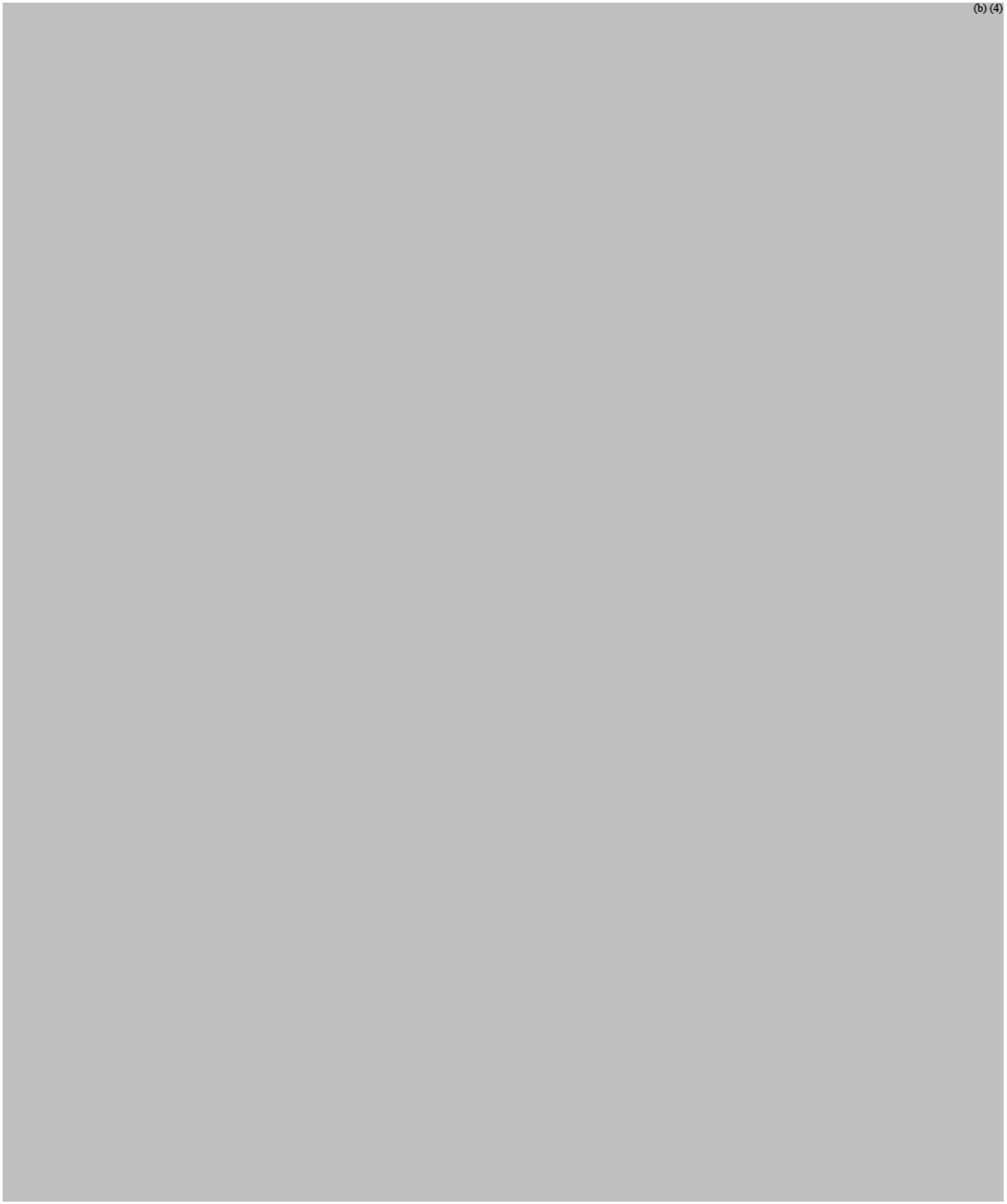
10. Labeling Recommendations

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

13.1. References

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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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s010

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-214787-SUPPL-10
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	10/21/2021	10/21/2021	10/26/2021	04/21/2022	01/06/2022

3. **Provides For:**
   Changes to the United States Prescribing Information (USPI) based on data from Study GS-US-540-9012 titled, "*A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting".*

4. **Review #**: 1

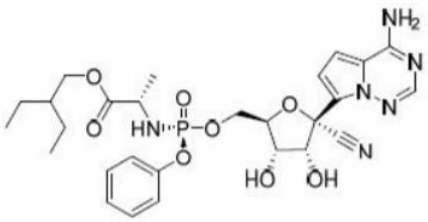
5. **Clinical Review Division**: OID/DAV

6. **Name and Address of Applicant**:
   Gilead Sciences, Inc.
   333 Lakeside Drive
   Foster City, CA
   USA 94404

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
VEKLURY® (remdesivir) for injection, for intravenous use; VEKLURY® (remdesivir) injection, for intravenous use	Lyophilized (for Injection); Solution (Injection)	100 mg (for Injection); 5 mg/mL (Injection)	Intravenous	Rx	No

8. Chemical Name and Structure of Drug Substance:

	**USAN:** Remdesivir **Chemical Name:** 2-ethylbutyl N-{(S)-[2-C-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5 anhydro-d-altrononitril-6-O-yl]phenoxyphosphoryl}-L-alaninate. **Molecular Formula:** $C_{27}H_{35}N_6O_8P$ **MW**: 602.6 g/mol

9. Indication: Treatment of coronavirus disease 2019 (COVID-19)

10. Supporting/Related Documents:
Request for categorical exclusion of environmental assessment was cross referenced to Module 1.12.14; SDN 06, 05/29/2020.

11. Disciplines/Consults: None

12. Executive Summary:
This Prior Approval Efficacy supplement provides for Changes to the United States Prescribing Information (USPI) based on data from Study GS-US-540-9012 titled, "*A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting".*

No updates to the CMC-related Module 3 are provided.

Labeling:
The proposed labeling (Prescribing Information) does not include changes to the CMC-related Sections 3, 11 or 16.

Environmental Analysis
(Cross referenced to Module 1.12.14; SDN 06, 05/29/2020)

6.3. Expected Introduction Concentration (EIC)

The EIC entering the aquatic environment from patient use is calculated without including consideration of metabolism or environmental depletion mechanisms that occur in the waste treatment process. The EIC from patient use is based on the highest annual quantity of the active moiety expected to be produced for use during the next five years; the quantity used in all dosage forms and strengths included in this application; and the quantity used in related applications for remdesivir or its excreted metabolite, GS-441524.

Calculation of the EIC for the aquatic environment assumes all drug products produced in a year are used and enter the publicly owned treatment works (POTWs), even distribution throughout the US per day, and no metabolism or depletion mechanisms. The EIC was calculated using the following formula from the FDA Guidance Document as follows:

EIC-Aquatic (ppb) = A x B x C x D

where

A = (b) (4) kg/year (estimated production of remdesivir over 5 years)
B = 1/1.214 x 10^{11} liters/day per day entering publicly owned treatment works (POTWs)
C = year/365 days
D = 10^{9} µg/kg (conversion factor)

Using this calculation, the EIC from patient use of remdesivir is approximately (b) (4) ppb which meets the categorical exclusion with 21CFR25.31(b) as it is below 1 ppb. To the best of Gilead's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

The applicant has submitted a claim of categorical exclusion including a statement of no extraordinary circumstances. There is no increase in the use of the active moiety. The expected introduction concentration (EIC) for remdesivir is less than 1 part per billion (ppb) level at the point of entry into the aquatic environment. The claim of categorical exclusion as specified in 21CFR 25.31 (b) for NDA 214787-SUPPL-10 is acceptable.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Rishi Thakur, Ph.D., CMC reviewer, Branch II, DPMAI, OLDP, OPQ

16. Secondary Reviewer:
David B. Lewis, Ph.D., Branch Chief, Branch II, DPMAI, OLDP, OPQ

Rishi Thakur

Digitally signed by Rishi Thakur
Date: 1/06/2022 12:03:30PM
GUID: 5407887b000a1c7a2c99827ec2cd922d

David Lewis

Digitally signed by David Lewis
Date: 1/06/2022 01:45:36PM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s010

CLINICAL MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW

NDA: 214787 SE-010 SDN 190 (0105) DATE REVIEWED: 12/14/2021
Virology Reviewer: William L. Ince, Ph.D.

CDER Receipt Date:	Assigned Date:	Review Complete Date	PDUFA Date
10/21/2021	10/22/2021	12/14/2021	4/21/2022

Applicant
Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA phone 650 574 3000 www.gilead.com

Amendments: None

Additional Submissions Reviewed

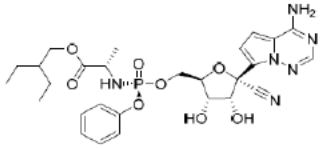
SDN	eCTD (SN)	Received	Assigned	Description	Appendix
190	0105	10/21/2021	10/22/2021	Supplement	*NA*
197	0110	11/2/2021	11/3/2021	Interim virology report	A
211	0117	12/3/2021	12/6/2021	Response to Virology IR - Assays	*NA*
217	0122	12/9/2021	12/10/2021	Response to Virology IR – Activity against variants	D
218	0123	12/10/2021	12/13/2021	Response to Virology/Statistics IR – Sequence data	B/C
224	0127	12/23/2021	12/23/2021	Response to Virology IR – Activity against variants	E
226	0129	12/27/2021	1/7/2022	Revised labeling	*NA*
227	0130	12/27/2021	1/7/2022	Response to PMC/PMR proposal	*NA*
231	0133	1/10/2022	1/10/2022	Revised labeling	*NA*
234	0134	1/11/2022	1/12/2022	Response to PMC/PMR proposal	F
236	0136	1/13/2022	1/13/2022	Response to PMC/PMR proposal	G

NA – Not applicable. Material was reviewed and relevant information was incorporated into the review body.

Product Names: Veklury® (remdesivir, GS-5734)

Chemical Names: 2-Ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate

Structure:



Remdesivir (GS-5734)

Molecular Formula: $C_{27}H_{35}N_6O_8P$
Molecular Weight: 602.6
Drug Category: Antiviral
Indication: (b) (4)
.
Dosage Form/Route of administration: 100 mg powder for aqueous reconstitution/intravenous
Supporting documents: Pre-IND 125566 submissions; IND147753; IND14771

Abbreviations: CDC, US Centers for Disease Control and Prevention; CSR, clinical study report; HA, hemagglutinin; IC, inhibitory concentration; IRD, NIH Influenza Research Database; LOD, limit of detection; LLOQ, lower limit of quantitation; MDCK, Madin-Darby Canine Kidney; NA, neuraminidase; NCBI, National Center for Biotechnology Information; NGS, next generation sequencing; NP, nasopharyngeal; RBC, red blood cell; RDV, remdesivir; RT-PCR, reverse transcription polymerase chain reaction.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: **214787 SE-010 SDN 190 (0105) DATE REVIEWED**: **12/14/2021**
Virology Reviewer: William L. Ince, Ph.D.

SUMMARY

Non-Clinical Virology

Remdesivir 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, Ph.D. [N214787.000]).

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 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 (UTP) that would be complementary to GS-443902 incorporated into the template RNA (Tchesnokov et al., 2020); however, this may also lead to misincorporation of a complementary nucleotide and mutagenesis of the second strand.

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 anti-nucleoprotein 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 Ph.D., Reference ID in DARRTS: 4917124 (N214787.S-009.MI.219)].

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: 0.048-0.077 µM). 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

Clinical Virology

Clinical virology data from trial GS-US-540-9012 submitted to support this supplement include longitudinal quantitative nasopharyngeal viral RNA data and preliminary baseline and post-baseline 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, a total of 431 subjects were included in the Virology Analysis Set (RDV n=217; placebo n=214), which included all subjects who (i) were randomized into the study, (ii) received at least 1 dose of study treatment, and (iii) 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).

Viral RNA shedding

Nasopharyngeal swabs were collected at baseline (Day 1) and Days 2, 3, 7, and 14. Quantitative 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 Full Analysis Set who met the following criteria: A) progressed to COVID-19-related hospitalization or all-cause death by Day 28 (N=17) AND/OR B) had 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 remdesivir arm and 38 in the placebo arm), 80 subjects (46 in the RDV arm and 34 in the placebo 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 3 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 post-baseline nsp12 sequence data were available for 18 subjects in the RDV arm and 14 subjects in the placebo 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, but did not achieve alleviation of symptoms 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 trial 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.

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. Please refer to Dr. Eric Donaldson's Clinical Virology review of the original NDA for full details.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: 214787 SE-010 SDN 190 (0105) DATE REVIEWED: 12/14/2021
Virology Reviewer: William L. Ince, Ph.D.

INTRODUCTION AND BACKGROUND

Remdesivir (VEKLURY®) is a severe acute respiratory virus type 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor indicated for the treatment of adults and pediatric patients 12 years of age and older, weighing at least 40 kg, and hospitalized with coronavirus infectious disease 2019 (COVID-19) (approved 10/22/2021). Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to a nucleoside intermediate by carboxyesterase 1 and/or cathepsin A to form a pharmacologically active nucleoside that is phosphorylated by cellular kinases to form a triphosphate analog of ATP, which functions as an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) to disrupt viral mRNA and progeny genome synthesis. Refer to the original NDA Clinical Virology Review (N214787.000) for information regarding non-clinical virology and pivotal clinical efficacy results for registrational studies.

In this supplemental new drug application (sNDA), the Applicant's proposed indication is (b) (4)). The intended target population for this treatment is non-hospitalized patients with confirmed SARS-CoV-2 infection who are at high risk for COVID-19 disease progression, including hospitalization or death. The Applicant's recommended dosage and duration for the indication is a single loading dose of Veklury® 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of Veklury® 100 mg on Days 2 and 3 via intravenous infusion.

The sNDA is supported by a single trial, GS-US-540-9012 (NCT04501952): *A Phase 3, Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting*. Virology data from trial GS-US-540-9012 submitted with this supplement include:

- Longitudinal quantitative nasopharyngeal viral RNA data
- A summary of preliminary baseline and post-baseline sequence analyses of 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.
- Preliminary non-clinical antiviral activity evaluations of remdesivir against SARS-CoV-2 Omicron variants in cell culture.

There are currently 7 direct-acting antivirals authorized or approved for the treatment of SARS-CoV-2 infection. In addition to IV remdesivir (VEKLURY®), which is currently indicated for the treatment of patients hospitalized with COVID-19 (approved 10/22/2020), there are three IV monoclonal antibody products that are available under Emergency Use Authorization for the treatment of COVID-19: casirivimab + imdevimab (authorized 11/21/2020), and bamlanivimab + etesevimab (authorized 2/9/2021), and sotrovimab (authorized 5/26/2021). The bamlanivimab monotherapy EUA (authorized 11/8/2020) was rescinded on 4/16/2021. These antibody products are currently indicated for treatment for patients at high risk of progression to severe disease or hospitalization. One antibody product to date has been authorized for pre-exposure prophylaxis (PrEP), tixagevimab+cligavimab, for immunocompromised patients or patients for whom vaccination is not recommended (initially authorized 12/8/2021 and re-authorized 12/20/2021). Two oral, direct-acting, small molecule SARS-CoV-2 inhibitors have been granted Emergency Use Authorization: nirmaltrevir+ritonavir (authorized 12/22/2021) and molnupiravir (authorized 12/23/2021). Vaccines that have been authorized or approved for use in the U.S. include the Pfizer-BioNTech COVID-19 vaccine (authorized 12/11/2020), the Moderna COVID-19 vaccine (authorized 12/18/2020), and the Janssen COVID-19 vaccine (authorized 2/17/2021). Immunocompromised individuals exhibit reduced responses to vaccination and experience reduced vaccine effectiveness (Embi et al., 2021), and additional doses are recommended for this population (CDC). In addition to direct-acting antiviral therapy, baricitinib, a Janus kinase (JAK) 1 and 2 inhibitor, has been authorized for use in combination with remdesivir for the treatment of COVID-19 in hospitalized patients (EUA granted 11/19/2020). Other interventions, such as the tailored use of dexamethasone to treat the inflammatory

response, has substantially reduced mortality among subjects hospitalized with COVID-19 (RECOVERY Collaborative Group, 2021).

NONCLINCIAL VIROLOGY

Key nonclinical and clinical virology characteristics, including mechanism of action, antiviral activity, and resistance mechanisms in cell culture have been reviewed and described previously (see Clinical Virology review of the original NDA by E. Donaldson, Ph.D. [N214787.000]).

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 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 (UTP) that would be complementary to GS-443902 incorporated into the template RNA (Tchesnokov et al., 2020); however, this may also lead to misincorporation of a complementary nucleotide and mutagenesis of the second strand.

Additional antiviral activity data for RDV against SARS-CoV-2 Variants of Concern/Interest Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Epsilon (B.1.429) were submitted to NDA 214787 on 9/29/2021 and reviewed [SDN 182; reviewed by E. Donaldson Ph.D., Reference ID in DARRTS: 4917124 (N214787.S-009.MI.219)]. In a plaque reduction assay 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 anti-nucleoprotein 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 [SDN 182; reviewed by E. Donaldson Ph.D., Reference ID in DARRTS: 4917124 (N214787.S-009.MI.219)].

Preliminary cell culture antiviral activity data from evaluations of RDV and GS-441524 against a representative of the Omicron variant, which has rapidly risen in frequency in the U.S. and globally (the Omicron viral isolate used in testing remdesivir and GS-441524 originates from the first patient with Omicron infection identified in Belgium; the identity of the isolate was confirmed by full genome sequencing of the cell culture-propagated virus stock), along with Alpha, Beta, Gamma, and Delta variants, in an authentic virus inhibition assay were submitted to NDA 214787 during the S-010 review cycle (Appendix E). The preliminary data indicate that RDV and GS-441524 retain activity against each of these variants (EC_{50} value range: 0.048-0.077 µM). While a wild type control virus was not included in the reported results, EC_{50} values against Omicron were within 2-fold of variants previously evaluated and shown to be susceptible relative to wild type (WA1), and these data are also consistent with posted pre-print data showing similar activity against Omicron and wild type and other variants evaluated (Vangeel et al., 2021 [pre-print]). 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. Some Omicron variants also contain an F694Y substitution in nsp12; however, this substitution is likely a sequencing artifact introduced by a sequencing primer. Together, these data indicate that RDV does not have significantly reduced activity against the evaluated variants in cell culture, including Omicron variants. However, complete study reports and additional data are needed to confirm the antiviral activity of RDV against Omicron variants. Data from initial evaluations are expected January 14, 2022. (b) (4) (Appendix E).

CLINICAL VIROLOGY REVIEW OF EFFICACY
CLINICAL TRIAL PROTOCOL

Title: GS-US-540-9012 (NCT04501952): A Phase 3, Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting.

Study GS-US-540-9012 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of RDV therapy for outpatients with early-stage COVID-19 who were at risk of disease progression. Subjects with at least 1 of the following preexisting risk factors for progression to hospitalization were enrolled: chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (body mass index [BMI] ≥ 30 kg/m2), immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease. Participants aged ≥ 60 years were enrolled regardless of the presence of other preexisting risk factors for progression.

Primary endpoints:

- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28
- Proportion of subjects with treatment-emergent AEs

Secondary virologic endpoints:

- Time-weighted average change in SARS-CoV-2 viral load [sic] from baseline to Day 7

Exploratory virologic endpoints:

- Time-weighted average change in SARS-CoV-2 viral load [sic] from baseline to Day 14
- Time to first negative SARS-CoV-2 RT-PCR
- Proportion of subjects with negative SARS-CoV-2 PCR at each study visit
- Emergence of viral resistance to RDV

Inclusion criteria relevant to Virology:

1. High risk defined as:
   - Age ≥ 18 years (at all sites) or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted) and with at least 1 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)
     - Immunocompromised state; having a solid organ transplant, blood, or bone marrow transplant; immune deficiencies; HIV with a low CD4 [sic] 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

2. SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [e.g., RT-PCR] or antigen testing) ≤ 4 days prior to screening
3. 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)
4. Not currently receiving, requiring, or expected to require supplemental oxygen
5. Not currently requiring hospitalization (hospitalization defined as ≥ 24 hours of acute care).

Exclusion criteria relevant to Virology:

1. Participation in any other clinical trial of an experimental treatment and prevention for COVID-19
2. Prior hospitalization for COVID-19 (hospitalization defined as ≥ 24 hours of acute care)
3. 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
4. Requiring oxygen supplementation
5. ALT or AST ≥ 5 × upper limit of normal (ULN) at screening or within 90 days of screening
6. Currently breastfeeding (nursing)
7. Known hypersensitivity to the study drug, the metabolites, or formulation excipient
8. Use or planned use of exclusionary medications (refer to Section 5.4 of protocol)

Design:

A total of 584 subjects were randomized in a 1:1 ratio to receive RDV intravenous (IV) for 3 days or placebo. A total of 562 subjects were included in the Full Analysis Set. The dosing of RDV in this study was 200 mg on Day 1 and 100 mg on each of Days 2 and 3. In addition to the primary clinical endpoint, other criteria for efficacy evaluation included hospitalizations, medically attended visits (MAVs), and deaths up to Day 28 to assess disease progression. COVID-19 symptoms recorded by participants on the COVID-19-adapted InFLUenza Patient-Reported Outcome (FLU-PRO) Plus questionnaire daily on Days 1 through 14 were used to assess the impact of RDV on symptom alleviation.

Virologic Assessments

Viral RNA shedding

Nasopharyngeal swabs were collected at baseline (Day 1) and Days 2, 3, 7, and 14. Quantitative RT-PCR was carried out on viral RNA extracted from nasopharyngeal swabs using three sets of primers and probes for the quantification of SARS-CoV-2 (N1), the qualitative detection (N2), and the control human RNase P gene (RP), respectively [(b) (4))]. The assay uses the same primer/probe sets as the Emergency Use Authorized CDC 2019-nCoV assay. The absolute quantification is based on the SARS-CoV2 N1 amplicon using a standard curve. The LLOQ is reported as 2,228 copies/mL and the LOD is reported as 1,493 copies/mL.

Sequence analysis

The SARS-CoV-2 Whole Genome Sequencing Assay using ARTIC Primers at (b) (4)) using the ARTIC protocol (Itokawa et al., 2020) and the Illumina-MiSeq or NextSeq deep sequencing platforms. The applicant states that genotypic analysis was attempted on all samples from participants with SARS-CoV-2 RNA titers above the lower limit of quantification of the RT-qPCR viral load assay (2,228 copies/mL); however, the applicant only evaluated a subset of subjects meeting clinical criteria of progression to hospitalization or death or who had evaluable viral RNA at Day 14 based on the amount of RNA required to yield evaluable sequencing results.

Phenotypic analysis

Phenotypic assessments are planned for respiratory samples from trial GS-US-540-9012, as stated by the applicant (Appendix B) but no data have been submitted to date. The SARS-CoV-2 ViroSpot Reduction Assay will be used to evaluate the susceptibility of subject isolates to RDV. The assay is performed at (b) (4)

(b) (4)). The ViroSpot platform determines the EC_{50} and EC_{90} values of the inhibitor against subject virus isolates (passage 1 of virus stock generated from clinical samples) in Vero E6 cell lines in 96-well plates in the presence of serially diluted compound; however, the protocol does not indicate that cells are pre-incubated with RDV to allow time for formation of the active triphosphate prior to infection. After incubation, viral replication is measured by immunostaining with antibodies specific for the viral nucleocapsid protein in infected, fixed cells. The applicant notes that the variation on the EC_{50} value determination of remdesivir against the clinical isolates is expected to be larger than the observed 2-fold variation during validation, which used a well-characterized SARS-CoV-2 lab strain. For these new studies at least a 4-fold difference in EC_{50} value can be expected [2-fold (variation of EC_{50} value determined for the reference) × 2-fold (variation of EC_{50} value of clinical isolate)].

> **FDA reviewer note:** For FDA review of phenotypic data, fold-changes for isolates will also be evaluated relative to the median EC_{50} value for isolates collected from study participants. This method better captures EC_{50} value outliers relative to the EC_{50} values of virus from the study population.

RESULTS

Baseline Virologic Characteristics

Subjects were enrolled between September of 2020 and April of 2021. Of the 562 subjects included in the Full Analysis Set, 531 were enrolled in the US and 31 were enrolled at European sites (Spain, n=17; Denmark, n=10; UK, n=4). A total of 431 were included in the Virology Analysis Set (RDV n=217; placebo n=214), which included all subjects who (i) were randomized into the study, (ii) received at least 1 dose of study treatment, and (iii) were positive SARS-CoV-2 viral RNA at baseline based on the central lab assay (result of “No SARS-CoV-2 detected” was considered negative, results of “Inconclusive,” “<2228copies/mL SARS-CoV-2 detected” and numerical results were considered positive).

Median duration of symptoms prior to first dose of study treatment was identical in the 2 groups (5 days), and median duration from SARS-CoV-2 nucleic acid/antigen confirmation to first dose of study drug was similar (2 days in the RDV group and 3 days in the placebo group) (Table 1). There was no significant difference in median baseline viral RNA shedding levels between the RDV and placebo (6.22 vs 6.26 log_{10} copies/mL) (Table 1).

Table 1: Selected baseline characteristics (Safety Analysis Set)

Characteristic	RDV	Placebo	Total
Duration of symptoms prior to first dose of study drug (days)			
N	279	283	562
Mean (SD)	5 (1.9)	5 (1.9)	5 (1.9)
Median	5	5	5
Q1, Q3	3, 6	4, 6	3, 6
Min, max	0, 18	0, 13	0, 18
Duration from SARS-CoV-2 nucleic acid/antigen confirmation to first dose of study drug (days)			
N	279	283	562
Mean (SD)	2 (1.5)	3 (1.5)	3 (1.5)
Median	2	3	2
Q1, Q3	1, 3	1, 4	1, 4
Min, max	0, 6	0, 7	0, 7
SARS-CoV-2 viral RNA - nasopharyngeal (log_{10} copies/mL)			
N	240	238	478
Mean (SD)	5.95 (1.962)	5.92 (1.987)	5.94 (1.973)
Median	6.22	6.26	6.26
Q1, Q3	4.25, 7.50	4.08, 7.56	4.14, 7.55
Min, max	2.87, 10.56	2.87, 9.99	2.87, 10.56
SARS-CoV-2 viral RNA – nasopharyngeal categories (log10 copies/mL)			

< 6.26 (median)	121 (50.4%)	118 (49.6%)	239 (50.0%)
≥ 6.26 (median)	119 (49.6%)	120 (50.4%)	239 (50.0%)

Source: Applicant analysis, GS-US-540-9012 CSR Table 9.

Virologic response

Viral RNA levels in nasopharyngeal swabs as determined by quantitative RT-PCR were evaluated in the Virology Analysis Set for differences between RDV and placebo groups. There was no significant difference in viral RNA shedding as determined by the pre-defined secondary endpoint of Time-Weighted Average change from baseline to Day 7 ($DAVG_7$) in nasopharyngeal SARS-CoV-2 RNA (median -1.15 vs -1.11 log_{10} copies/mL in the RDV and placebo groups, respectively) (Table 2). Baseline viral RNA levels were similar between RDV and placebo groups in the Virology Analysis Set (median 6.61 vs 6.44 log_{10} copies/mL, in the RDV and placebo groups, respectively), and while decreases from baseline were numerically greater in the RDV arm compared to placebo at Days 2 and 3 (Day 3 median change from baseline: -1.02 vs -0.96 log_{10} copies/mL, respectively), these differences were not statistically significant and not likely to be clinically significant (Table 3 and Figure 1). Furthermore, there were numerically fewer subjects who were negative by RT-PCR at Days 2 and 3 in the RDV arm compared to placebo, although these differences were also not statistically significant (Table 4). In addition, there was no significant difference in Kaplan-Meyer estimates of the time to viral RNA negativity between treatment groups; the median time to virus negativity was >14 (Figure 2). These results were confirmed by independent analysis of the data (not shown).

Table 2: Time-Weighted Average Change from baseline to Day 7 ($DAVG_7$) in nasopharyngeal SARS-CoV-2 viral [RNA] (Virology Analysis Set)

	RDV	Placebo
Time-weighted average change from baseline to Day 7 (log_{10} copies/mL)		
N	211	208
Mean (SD)	−1.24 (1.123)	−1.14 (1.099)
Median	−1.15	−1.11
Q1, Q3	−2.01, −0.54	−1.82, −0.41
Min, max	−4.60, 1.96	−3.56, 2.81
LS mean (SE)	−1.22 (0.06)	−1.16 (0.06)
95% CI	(−1.35, −1.10)	(−1.28, −1.03)
Difference by Day 7 (log_{10} copies/mL)		
LS mean (SE)	0.07 (0.09)	
95% CI	(−0.10, 0.24)	
P value	0.4318	

Source: Applicant analysis, GS-US-540-9012 CSR Table 18.

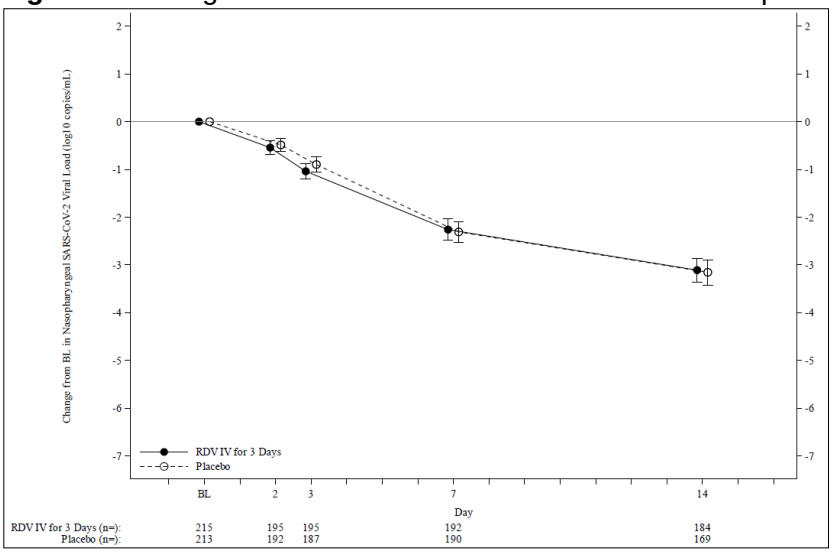
Table 3: Change from Baseline in viral RNA at each time point (Log_{10} copies/mL) (Virology Analysis Set)

	RDV		Placebo	
	Viral RNA	Change from baseline	Viral RNA	Change from baseline
Baseline				
N	215		213	
Mean (SD)	6.31 (1.751)		6.28 (1.786)	
95% CI	(6.08, 6.55)		(6.04, 6.52)	
Median	**6.61**		**6.44**	
Q1, Q3	5.07, 7.65		4.77, 7.61	
Min, Max	3.05, 10.56		3.05, 9.99	
At Day 2				
N	195	195	193	192
Mean (SD)	5.75 (1.674)	-0.54 (1.004)	5.73 (1.707)	-0.49 (0.957)
95% CI	(5.52, 5.99)	(-0.69, -0.40)	(5.49, 5.97)	(-0.62, -0.35)
Median	**5.91**	**-0.46**	**5.96**	**-0.41**
Q1, Q3	4.46, 7.06	-1.07, 0.00	4.37, 6.97	-1.15, 0.07

Min, Max	2.87, 9.14	-3.72, 2.56	2.87, 8.98	-3.22, 4.05
At Day 3				
N	197	195	188	187
Mean (SD)	5.33 (1.464)	-1.04 (1.109)	5.48 (1.673)	-0.90 (1.099)
95% CI	(5.13, 5.54)	(-1.20, -0.88)	(5.24, 5.72)	(-1.06, -0.74)
Median	**5.31**	**-1.02**	**5.62**	**-0.96**
Q1, Q3	4.17, 6.40	-1.82, -0.24	4.04, 6.87	-1.63, -0.17
Min, Max	2.87, 9.00	-4.14, 3.19	2.87, 9.15	-3.33, 2.88
At Day 7				
N	194	192	191	190
Mean (SD)	4.11 (1.355)	-2.26 (1.561)	4.06 (1.186)	-2.31 (1.487)
95% CI	(3.92, 4.30)	(-2.48, -2.04)	(3.89, 4.23)	(-2.52, -2.10)
Median	**3.66**	**-2.37**	**3.71**	**-2.40**
Q1, Q3	3.05, 4.99	-3.40, -1.10	3.05, 5.02	-3.36, -1.26
Min, Max	2.87, 8.55	-5.96, 4.39	2.87, 7.45	-6.01, 4.04
At Day 14				
N	185	184	170	169
Mean (SD)	3.25 (0.669)	-3.11 (1.713)	3.17 (0.600)	-3.15 (1.741)
95% CI	(3.15, 3.34)	(-3.36, -2.86)	(3.08, 3.26)	(-3.42, -2.89)
Median	**3.05**	**-3.35**	**3.05**	**-3.39**
Q1, Q3	2.87, 3.05	-4.32, -2.19	2.87, 3.05	-4.53, -1.75
Min, Max	2.87, 6.99	-7.68, 0.80	2.87, 7.47	-7.12, 0.41

Source: Applicant analysis, GS-US-540-9012 CSR Table 15.9.2.12

Figure 1: Change from Baseline in viral RNA at each time point (Log_{10} copies/mL) (Virology Analysis Set)



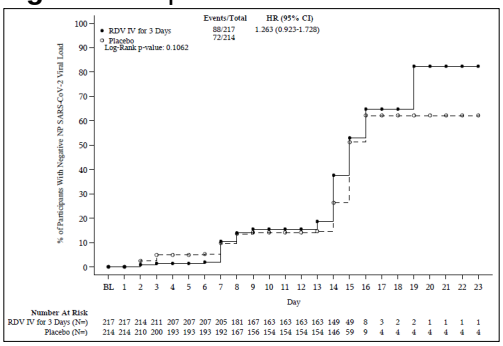
Source: Applicant analysis, GS-US-540-9012 CSR Figure 15.9.5

Table 4: Proportion negative for SARS-CoV-2 RNA by RT-PCR at each Study Day (Virology Analysis Set)

Visit	RDV	Placebo	P- value (Fisher's exact test)
Baseline	0% (0/217)	0% (0/214)	N/A
Day 2	1.0% (2/196)	2.6% (5/193)	0.2815
Day 3	1.0% (2/199)	4.2% (8/191)	0.0575
Day 7	15.4% (31/201)	12.8% 25/195	0.4744
Day 14	44.5% (85/191)	37.6% (67/178)	0.2043

Source: Applicant analysis, GS-US-540-9012 CSR Figure 15.9.2.13.

Figure 2: Kaplan-Meier Estimate of Time to Negative Nasopharyngeal SARS-CoV-2 Viral RNA



Source: Applicant analysis, GS-US-540-9012 CSR Figure 15.9.6

In subset analyses based on baseline viral RNA, higher baseline viral RNA levels (≥6.26 vs, the median baseline RNA level vs <6.26 log_{10} copies/mL) corresponded with longer duration of viral RNA shedding, as determined by the proportion of subjects who were RT-PCR-negative at each time point, consistent with the expectation that higher starting viral RNA levels would take longer to go below the limit of detection (Table 5). Within these subsets, no RDV treatment effect was apparent based on the proportion of subjects who were negative at each time point (Table 5).

Table 5: Proportion RT-PCR-negative at each Study Day by baseline viral RNA level in each treatment group

	Baseline viral RNA log_{10} copies/mL < 6.26		Baseline viral RNA log_{10} copies/mL ≥ 6.26	
Study Day	RDV	Placebo	RDV	Placebo
Baseline	0% (0/97)	0% (0/93)	0% (0/119)	0% (0/121)
Day 2	2.27% (2/88)	5.75% (5/87)	0% (0/107)	0% (0/105)
Day 3	1.18% (1/85)	10.39% (8/77)	0% (0/112)	0% (0/113)
Day 7	27.06% (23/85)	30% (24/80)	5.26% (6/114)*	0% (0/114)*
Day 14	59.52% (50/84)	60% (45/75)	32.71% (35/107)	20.39% (21/103)

Source: FDA Reviewer analysis. ADEFF; Includes PARAM = "Confirmed Negative Nasopharyngeal SARS-CoV-2 PCR", ASTRESC by BCOVNGR.
* P value = 0.0292 Fisher's exact test, RDV vs Placebo

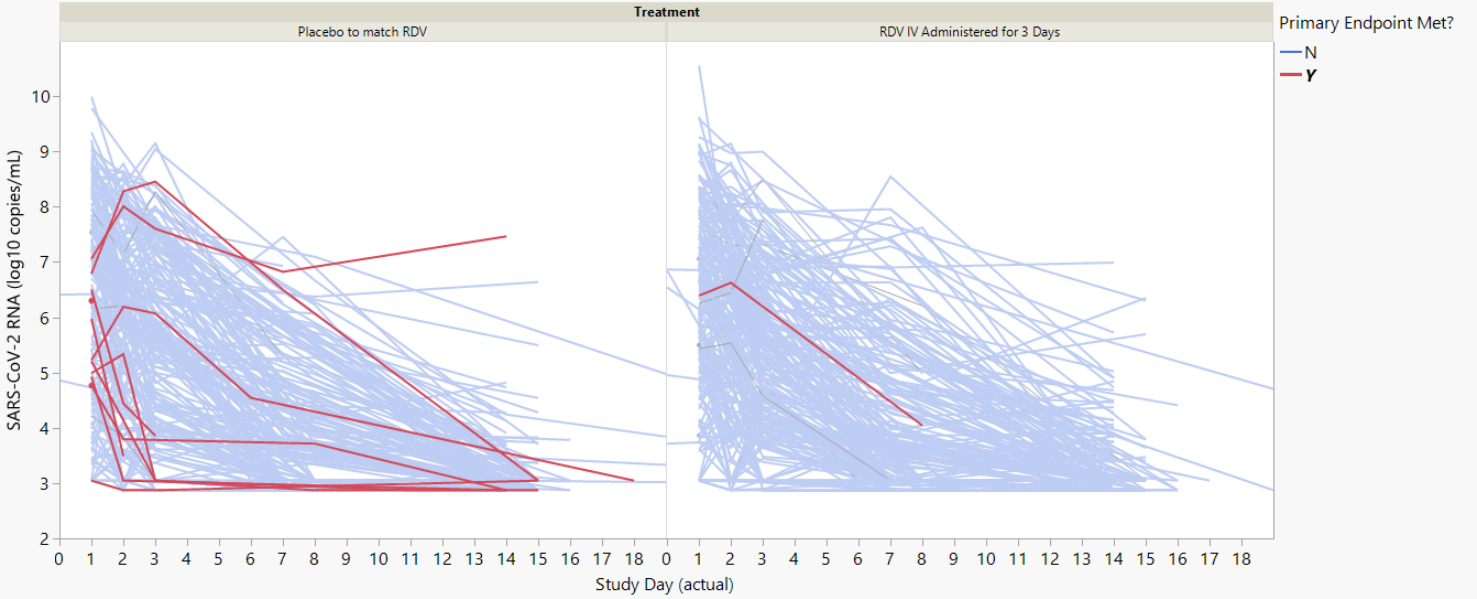
Subjects who met the primary endpoint criteria tended to shed viral RNA for longer than subjects who did not meet the primary endpoint criteria (Table 6 and Figure 3); however, given the small number of subjects meeting the primary endpoint criteria and that viral RNA was assessed only up to Day 14 for most subjects, the results remain difficult to interpret (Table 6 and Figure 3).

Table 6: Proportion RT-PCR-negative in each treatment group by whether or not subjects met the primary endpoint criteria.

	Not meeting primary endpoint criteria		Met primary endpoint criteria	
	RDV	Placebo	RDV	Placebo
Baseline	0% (0/207)	0% (0/197)	0% (0/1)	0% (0/12)
Day 2	1.05% (2/190)	1.67% (3/180)	0% (0/1)	11.11% (1/9)
Day 3	1.04% (2/192)	4.35% (8/184)	0% (0/1)	0% (0/5)
Day 7	15.82% (31/196)	12.63% (24/190)	0% (0/1)	33.33% (1/3)
Day 14	44.97% (85/189)	37.93% (66/174)	NA (0/0)	25% (1/4)

Source: FDA Reviewer analysis. ADEFF. PARAM = "Confirmed Negative Nasopharyngeal SARS-CoV-2 PCR", ASTRESC by EVNTDESC; Excludes EVNTDESC = "Early Terminated Study without COVID-19 Related Hospitalization by Day 28".

Figure 3: Viral RNA levels over time in subjects who did and did not meet the primary endpoint criteria.



Source: FDA Reviewer analyses. ADEFF; PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log_{10} copies/mL)" by EVNTDESC; Excludes EVNTDESC = "Early Terminated Study without COVID-19 Related Hospitalization by Day 28"

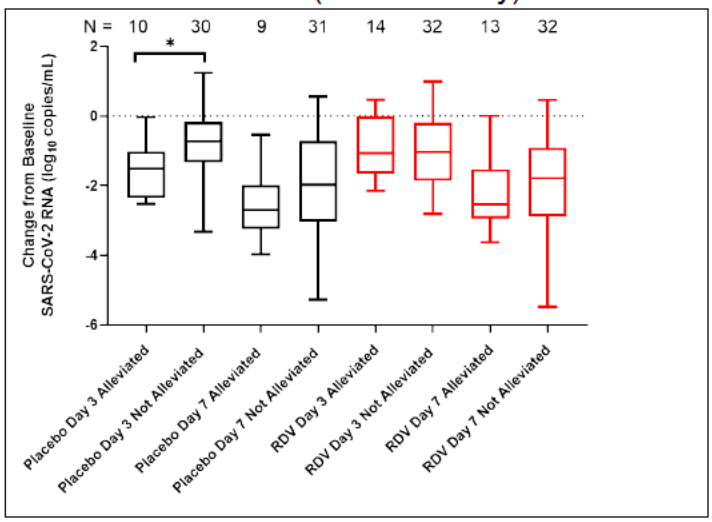
Of the subset of subjects evaluated for alleviation of symptoms, there was no significant difference in the proportion who were negative by RT-PCR at each Study Day within treatment groups based on whether subjects experienced alleviation of symptoms, and there was no significant difference between treatment groups among those who did or did not experience alleviation of symptoms, although there was a trend toward increased rates of negativity at Day 14 in the RDV arm in both subsets (Table 7). Those who experienced alleviation of symptoms tended to experience greater reductions in virus shedding at Days 3 and 7, but there were no significant differences between treatment arms by this measure within subsets who did or did not experience alleviation of symptoms (Figure 4).

Table 7: Proportion RT-PCR-negative in each treatment group by whether or not subjects achieved alleviation of baseline COVID-19 symptoms by Day 14.

	Achieved alleviation of baseline COVID-19 symptoms by Day 14		Not achieved alleviation of baseline COVID-19 symptoms by Day 14	
	RDV	Placebo	RDV	Placebo
Baseline	0% (0/16)	0% (0/10)	0% (0/34)	0% (0/32)
Day 2	0% (0/15)	0% (0/10)	0% (0/33)	0% (0/30)
Day 3	0% (0/14)	0% (0/10)	0% (0/32)	10% (3/30)
Day 7	21.4% (3/14)	22.2% (2/9)	17.6% (6/34)	12.5% (4/32)
Day 14	53.3% (8/15)	30% (3/10)	42.9% (15/35)	33.3% (10/30)

Source: FDA Reviewer analysis. ADEFF; PARAM = "Confirmed Negative Nasopharyngeal SARS-CoV-2 PCR" by PARAM = "Alleviation of Baseline COVID-19 Symptoms". Only a subset of subjects was evaluated for alleviation of symptoms.

Figure 4: Viral RNA change from baseline at Days 3 and 7 in subjects who did (Alleviated) or did not (Not Alleviated) experience alleviation of symptoms by Day 14 grouped by placebo (black) or remdesivir (RDV) treatment. * P = 0.0329 (Mann-Whitney).



Source: FDA Reviewer analyses. ADEFF; PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log10 copies/mL)"; CHG by Visit and "Alleviation of Baseline COVID-19 Symptoms"

Conclusion for viral RNA analyses: Overall, there was no detectable impact of RDV treatment on viral RNA levels in nasopharyngeal swabs as determined by any of the endpoints evaluated. In hospitalized subjects, RDV treatment was associated with reduced viral RNA levels in nasopharyngeal and oropharyngeal samples; however, the associations were inconsistent and respiratory sampling was biased based on who remained hospitalized [NDA 214787 SDN 182, reviewed by E. Donaldson Ph.D., Reference ID in DARRTS: 4917124 (N214787.S-009.MI.219)]. These results are generally consistent with the observations from a study in non-human primates infected with SARS-CoV-2 in which viral RNA levels were reported to be reduced in the lung but not in the upper respiratory tract in RDV-treated animals compared with vehicle-treated animals (Williamson et al., 2020) [previously reviewed in N214787.000 by E. Donaldson Ph.D.]. Overall, viral RNA in nasopharyngeal respiratory samples may not be an appropriate surrogate for assessing antiviral activity of RDV.

Sequence analysis

Preliminary sequence analysis reports were submitted without additional raw sequence data or phenotypic analyses, which precluded an independent and in-depth analysis of the sequence data. The applicant states that (b) (4)).

The applicant had planned to carry out whole viral genome sequence analysis of subjects in the Full Analysis Set who met the following criteria for evaluation:

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=78)

The applicant states that at the time samples were selected for sequencing analysis, the lower limit of detection (sic) for the ARTIC whole genome sequencing (WGS) assay was estimated to be approximately 4.3 log_{10} copies/mL based on the quantitative RT-PCR assay used in the trial. Because this cut-off threshold was

not clearly established, genotypic analysis was attempted on all samples from participants meeting the criteria described above with SARS-CoV-2 RNA titers above the lower limit of quantification of the RT-qPCR viral load assay (2,228 copies/mL). SARS-CoV-2 RNA was amplified from nasopharyngeal swab samples and sequenced using NGS technology to achieve an average depth of approximately 16,000 reads for selected genome regions. The applicant reported all substitutions relative to the wild type reference sequence that were ≥15% of the virus population as determined by deep sequencing.

Interim summary data were submitted to the NDA in two parts. Data listings for the subset of subjects meeting the criteria of COVID-19-related hospitalization or all-cause death by Day 28 (the primary endpoint) were submitted on 11/2/2021 (SDN 197) and included sequence data for nsp8, nsp10, nsp12, nsp13, and nsp14 genome regions (Appendix A). Data listings for subjects who met the criteria of having evaluable RNA at Day 14 were submitted on 12/10/2021 (SDN 218) in response to an information request (Appendix B) and included data for nsp12 only. These data listings were combined for analysis (Appendix C).

Of the subjects meeting the criteria for evaluation and with evaluable samples, summary baseline and/or post baseline nsp12 sequence data were provided for 80 subjects in total (46 in the RDV arm and 34 in the placebo arm), while only 18 and 14 subjects in the RDV and placebo arms, respectively, had both baseline and post-baseline nsp12 sequence data provided (Table 8).

Table 8: Subjects with available sequence data.

	RDV	**Placebo**
Total (Virology Analysis Set)	217	214
Criterion A: Progressed to COVID-19-related hospitalization or all-cause death by Day 28		
Met criterion A	2	15
Any sequence data	1	13
Baseline and postbaseline	0	7
Criterion B: Nasopharyngeal viral RNA above the limit of quantitation of the quantitative RT-PCR assay at Day 14		
Met criterion B	48	23
Any sequence data	45	21
Baseline and postbaseline	18	7
Total [a]		
Met criteria A and/or B	50	38
Any sequence data	46	34
Baseline and postbaseline	18	14

Source: FDA Reviewer analysis. Data submitted in 11/2/2021 (SDN 197) and 12/10/2021 (SDN 218).
a. Total is based in nsp12 sequence data submitted by the sponsor. Of the 17 subjects meeting criteria A (2 in the remdesivir arm and 15 in the placebo arm), 14 also had available nsp8, nsp10, nsp13, and nsp14 sequence data submitted.

Baseline genotype

The baseline variant genotype was determined for 80 subjects (determined from baseline or post-baseline whole viral genome sequence samples) who met the criteria for analysis and for whom sequence data were submitted to the NDA during the review period (Appendix C). The most common variant represented was B.1.2, followed by WHO-designated Alpha and Epsilon variants (Table 9). Other variants were represented by 3 or fewer subjects in this sequence analysis subset. These limited data indicate that currently dominant variants, including Delta, were not significantly represented in the trial, consistent with the emergence of the Delta variant occurring on the tail end of the trial enrollment period (approximately mid-April, 2021; Dougherty et al., 2021).

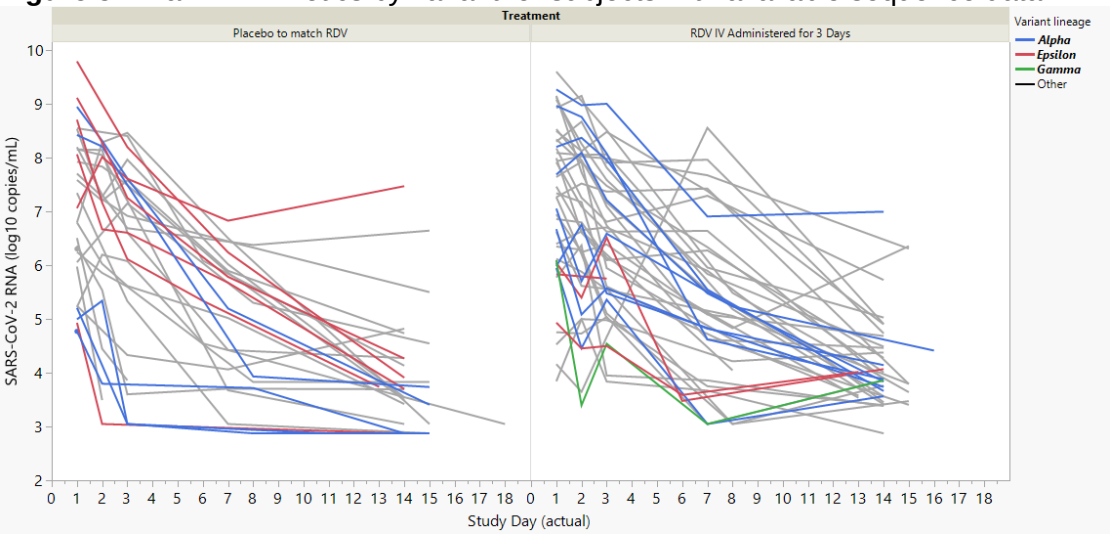
Table 9: SARS-CoV-2 genotype of subjects with available sequence data.

Lineage	WHO variant designation	Placebo	RDV	Total
B.1.2		8	15	23
B.1.1.7 / Q.3	Alpha	6	8	14
B.1.429 / B.1.427	Epsilon	6	3	9
P.1.17	Gamma	0	1	1
B.1.526	Iota	1	0	1
B.1.596		3	0	3
B.1		1	1	2
B.1.1		1	1	2
B.1.1.519		1	1	2
B.1.110.3		1	1	2
B.1.177		1	1	2
B.1.177.1 2		1	1	2
B.1.234		0	2	2
B.1.240		1	1	2
B.1.623		0	2	2
B.1.170		0	1	1
B.1.232		1	0	1
B.1.243		0	1	1
B.1.311		0	1	1
B.1.369		0	1	1
B.1.561		0	1	1
B.1.564		1	0	1
B.1.568		1	0	1
B.1.575.1		0	1	1
B.1.595		0	1	1
C.23		0	1	1

Source: FDA reviewer analysis. Combined interim sequence analyses submitted to NDA 214787 11/2/2021 [SDN 197] and 12/3/2021 [SDN 218] (Appendix C).

There was no clear pattern of viral RNA shedding based on the variant (WHO designated variant vs non-designated variants) among sequenced subjects; as with the overall population, duration of shedding appears to be generally associated with baseline (Day 1) viral RNA levels (Figure 5).

Figure 5: Viral RNA kinetics by variant for subjects with available sequence data.



Source: FDA Reviewer analyses. ADEFF. PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log_{10} copies/mL)". Variant designation based on combined interim sequence analyses submitted to NDA 214787 11/2/2021 [SDN 197] and 12/3/2021 (SDN 218) (Appendix C).

Baseline sequence data were available for 75 subjects. All contained the nsp12 substitution P323L consistent with currently circulating SARS-CoV-2 variants and variants identified in the sequence analysis dataset. Variants carrying the P323L substitution, such as Delta, have been evaluated and not been shown to confer reduced susceptibility to RDV in cell culture. Other baseline nsp12 substitutions identified are listed in Table 10; only nsp12 substitutions S6L, G671V, and V776L were identified in more than one subject and were associated with a single variant each, with the exception of S6L, which was associated with B.1.561 and B.1.623. Of note, most of the placebo subjects evaluated who had baseline polymorphisms detected in nsp12 met the primary endpoint criteria for disease progression; although the samples selected for sequencing were biased based on the criteria. None of the substitutions have otherwise been identified in analyses of potential residues that may affect RDV binding (Mari et al., 2021), although additional empirical data are needed to understand the impact of RdRp variability on RDV antiviral activity. Phenotypic analysis of baseline isolates is planned, according to the applicant. Review of the raw sequence data are also needed to verify these substitutions.

Table 10: Baseline nsp12 polymorphism identified in evaluated subjects in trial GS-US-540-9012

Treatment arm	Baseline polymorphisms (+P323L)	Number of subjects	Variant	Variants in which polymorphism is common [b]
RDV	S6L	3	B.1.561 / B.1.623	
RDV	A529V	1	B.1.2	
RDV	V776L	2	B.1.2	
RDV	P918S	1	B.1.2	
Placebo	A16V	1	B.1.564	
Placebo	**A97V**	1	B.1.2	
Placebo	T141I	1	B.1.2	
Placebo	**P227L**	1	B.1.1.7	
Placebo	**M463I+M633T**	1	B.1.2	
Placebo	**G671V** [a]	2	B.1.429	B.1.617.2 (G671S) / AY.1 - 12
Placebo	**D738Y**	1	B.1.1.7	
Placebo	**A585V** [c]	1	B.1.177.12	

Source: FDA Reviewer analysis. Combined interim sequence analyses submitted to NDA 214787 11/2/2021 [SDN 197] and 12/3/2021 (SDN 218) (Appendix C).
Bold: Baseline polymorphisms identified in subjects who met the primary endpoint.
a. Identified in one subject meeting the primary endpoint criteria and in one subject who did not.
b. https://covdb.stanford.edu/page/mutation-viewer/.
c. Reported in data listings submitted 11/2/2021 only.

The distribution of variants among subjects who progressed to COVID-19-related hospitalization or all-cause death (primary endpoint) was not significantly different than the overall population of subjects evaluated by sequencing (Table 11).

Table 11: Baseline SARS-CoV-2 variant representation among evaluated subjects who progressed to COVID-19-related hospitalization or all-cause death (primary endpoint criteria).

Pango Lineage (WHO nomenclature)	**Number of subjects, n (% of subjects in subset) who progressed to COVID-19-related hospitalization or all-cause death by Day 28**			**Proportion of variant among all evaluated subjects (% of subjects with sequence data)**	**P value (Fisher's exact test)**
	RDV (N = 1)	**PBO (N = 12)**	**Total (N = 13)**		
B.1.1.7 (Alpha)	0	4 (33.3%)	4 (30.8%)	14 (17.5%)	0.2695
B.1.110.3	0	1 (8.3%)	1 (7.7%)	2 (2.5%)	0.3669
B.1.177.12	0	1 (8.3%)	1 (7.7%)	2 (2.5%)	0.3669
B.1.2	0	3 (25%)	3 (23.1%)	23 (28.75%)	>0.9999
B.1.429 (Epsilon)	0	2 (16.7%)	2 (15.4%)	9 (11.25%)	0.6489
B.1.595	1 (100%)	0 (0%)	1 (7.7%)	1 (1.25%)	0.2613
B.1.596	0	1 (8.3%)	1 (7.7%)	3 (3.75%)	0.4583

Source: FDA Reviewer analysis. ADEFF; combined interim sequence analyses submitted to NDA 214787 11/2/2021 [SDN 197] and 12/3/2021 (SDN 218) (Appendix C).

There were 17 subjects who met the primary endpoint criteria (progression to COVID-19-related hospitalization or death by Day 28) in this study and 2 of these subjects were in the RDV-treatment group. The sponsor obtained nsp8, nsp10, nsp12, nsp13, and nsp14 sequencing from 13 of these subjects at baseline met the primary endpoint (Table 8), including only 1 subject in the RDV-treatment group for whom only baseline sequence data were obtained. There were only 7 subjects who met the primary endpoint criteria and who had sequencing data available at both baseline and post-baseline time points and all were in the placebo arm. The baseline genotype of subjects who met the primary endpoint criteria are displayed in Table 10 and include data for nsp8, nsp10, nsp12, nsp13, and nsp14. All subjects in the placebo arm had at least one baseline polymorphism among the regions evaluated. No baseline polymorphisms were identified in the one subject (subject ID: (b) (6)) meeting the primary endpoint in the RDV arm (Table 12).

Table 12: Baseline polymorphisms in the subjects who met the primary endpoint criteria and who had available nsp 8, 10, 12, 13, and 14 sequence data.

Subject ID	Treatment arm	Nsp8	Nsp10	Nsp12 (+P323L)	Nsp13	Nsp14	Lineage
(b) (6)	Placebo	NC	NC	NC	NC	N129D	B.1.2
	Placebo	NC	NC	NC	K460R [a]	NC	B.1.1.7
	Placebo	NC	NC	D738Y	NC	NC	B.1.1.7
	Placebo	NC	NC	M463I, M633T	NC	N129D	B.1.2
	Placebo	NC	NC	NC	NC	NC	B.1.110.3
	Placebo	NC	NC	G671V [b]	D260Y [c]	NC	B.1.429
	Placebo	NC	NC	P227L	NC	NC	B.1.1.7
	Placebo	P133S	NC	A97V	NC	N129D	B.1.2
	Placebo	NC	NC	NC	NC	N129D	B.1.596
	Placebo	Q24R [d],T89T/I	NC	NC	N265S, K460R	NC	B.1.1.7
	Placebo	NC	NC	NC	D260Y	NC	B.1.429
	Placebo	NC	NC	A585V [e]	NC	NC	B.1.177.12
	RDV	NC	NC	NC	NC	NC	B.1.595

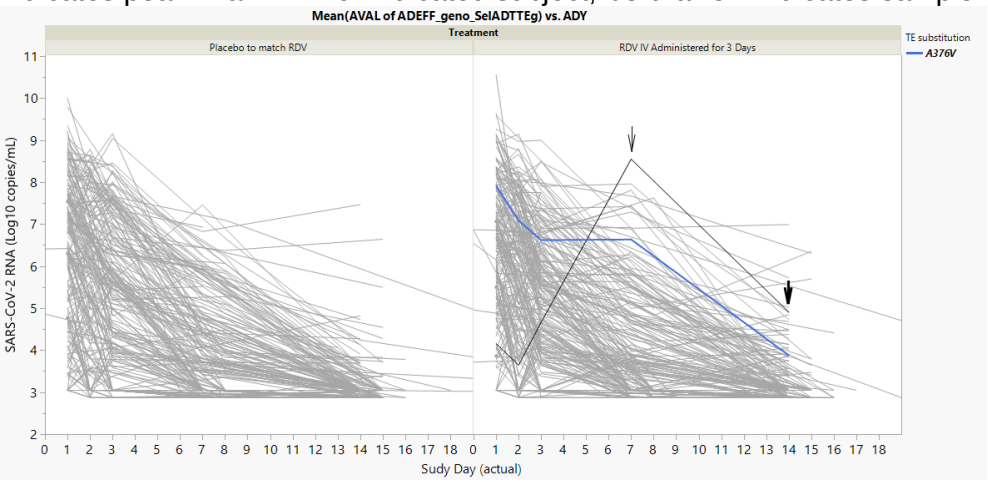
Source: FDA Reviewer analysis. Data derived combined interim sequence analyses submitted to NDA 214787 11/2/2021 [SDN 197] and 12/3/2021 (SDN 218) (Appendix C).
NC: No change reported.
a. Commonly associated with variants Q.3, Q.4
b. Commonly associated with variants B.1.617.2 (G671S) / AY.1 – 12
c. Commonly associated with variants A.28, B.1.427/ B.1.429
d. Commonly associated with variant Q.4
e. Reported in data listings submitted 11/2/2021 only

Treatment-emergent resistance

Baseline and post-baseline nsp12 sequence data were available for 18 subjects in the RDV arm and 14 subjects in the placebo arm overall. For subjects who met the primary endpoint, baseline and post-baseline data were available for 7 subjects in the placebo arm only. Overall, there was one subject (subject ID: (b) (6)) in the RDV arm with a treatment-emergent substitution reported (in ≥15% of sequencing reads): A376V in nsp12 at Day 14; this subject did not meet the primary endpoint criteria, but did not achieve alleviation of symptoms by Day 14. This substitution has not been previously identified or reported. The applicant has not evaluated A376V for its impact on RDV activity in cell culture. Viral RNA kinetics for the subject with the A376V were not clearly distinguished from other subjects with sequence data (Figure 6). One subject (subject ID: (b) (6)) experienced peak viral RNA of 8.5 $\log_{10}$ copies/mL at Day 7 (Figure 6, non-bold arrow); however, sequence analysis reported for nsp12 at Day 14 (Figure 6, bold arrow) did not identify a sequence change relative to baseline. Nsp12 sequence analysis data were not available at Day 7 for subjects in the RDV arm, and any treatment-emergent substitution may have been below the threshold of reporting or detection in

subjects when evaluated at Day 14. Independent analysis of deep sequencing (NGS) data using a lower frequency threshold may identify additional substitutions.

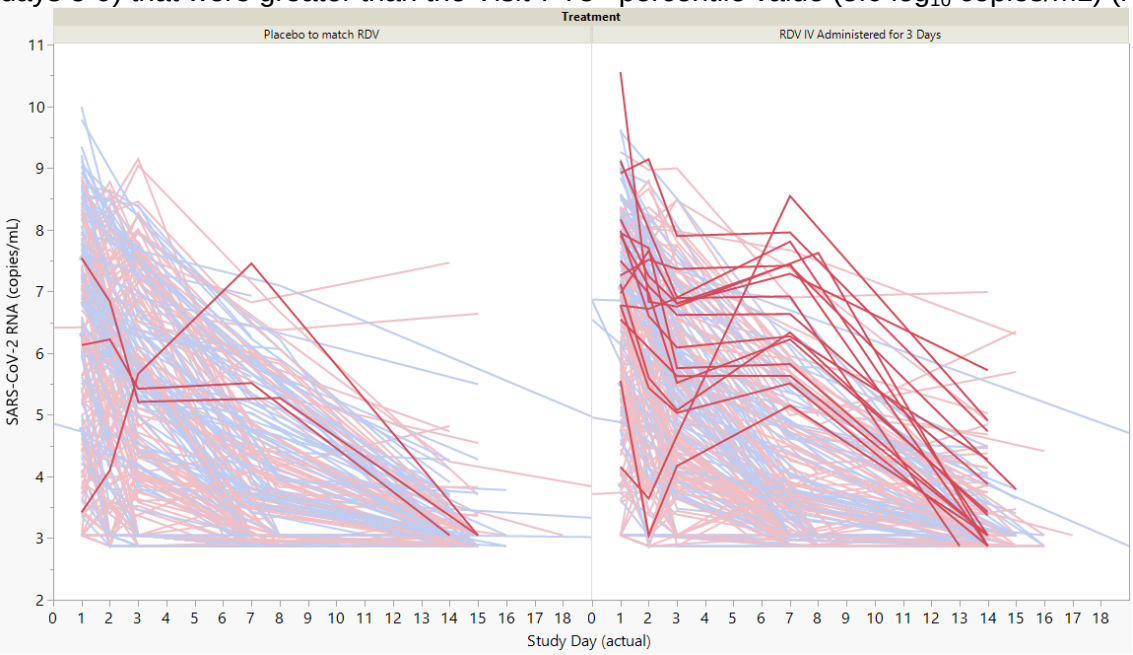
Figure 6: Viral RNA levels over time for subjects with available nsp12 sequence data. Non-bold arrow indicates peak viral RNA for indicated subject; **bold** arrow indicates sample evaluated for nsp12 substitutions.



Source: FDA Reviewer analysis. ADEFF, PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log_{10} copies/mL)". Combined interim sequence analyses submitted to NDA 214787 11/2/2021 [SDN 197] and 12/3/2021 (SDN 218) (Appendix C).
TE, treatment-emergent.

In addition to subject (b) (6), all subjects in the RDV arm who exhibited any increase in viral RNA and had viral RNA levels at Day 7 (actual study days 5-9) that were greater than the Day 7 75th percentile value (5.0 log_{10} copies/mL) were identified for further sequence evaluation at the identified time point (Figure 7; Table 13).

Figure 7: Subjects with viral RNA rebound (any increase) (red) and with RNA levels at Visit 7 (actual study days 5-9) that were greater than the Visit 7 75th percentile value (5.0 log_{10} copies/mL) (red and bold).



Source: FDA Reviewer analysis. ADEFF, PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log_{10} copies/mL)".

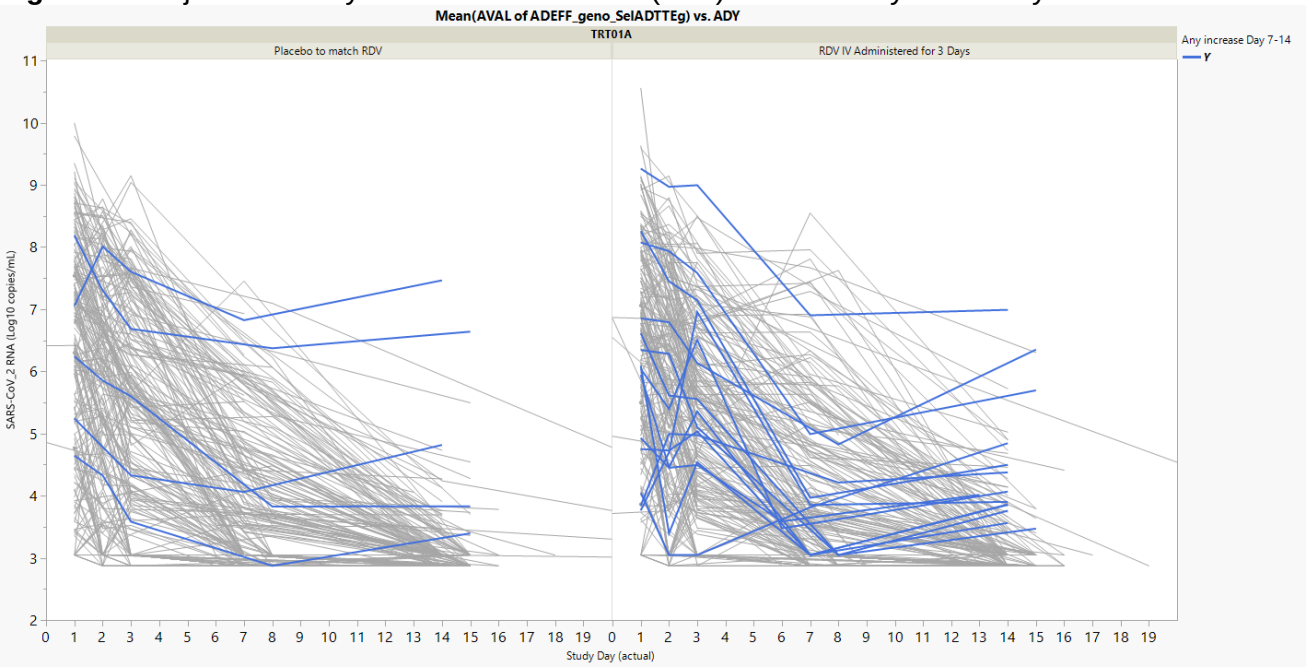
Table 13: RDV-treated subjects and time points identified for further sequence evaluation

Subject ID	Study Day (actual)	SARS-CoV-2 RNA (Log_{10} copies/mL)
(b) (6)	7	5.5
	7	7.4
	7	5.8
	8	7.6
	7	6.2
	7	5.2
	7	6.3
	7	5.6
	7	8.5
	7	6.6
	7	7.3
	7	6.9
	7	7.8
	7	8.0
	7	6.3
	7	7.4

Source: FDA Reviewer analysis. ADEFF, PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log_{10} copies/mL)".

Subjects who exhibited any increase in viral RNA between Day 7 and Day 14 were identified (Figure 8), and sequencing data were available for subset of these subjects during the review cycle; no treatment emergent substitutions were identified among the subjects in this subset with available sequence data (Table 14).

Figure 8: Subjects with any increase in viral RNA (blue) between Day 7 and Day 14.



Source: FDA Reviewer analysis. ADEFF, PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log_{10} copies/mL)".

Table 14: RDV-treated subjects with any increase in viral RNA (blue) between Day 7 and Day 14.

SUBJID	Treatment	SARS-CoV-2 lineage	Day 14 Sequence analysis results	Day 14 SARS-CoV-2 RNA level

				(log_{10} copies/mL)
(b) (6)	RDV	B.1.1	P323L	4.5
	RDV	B.1.1.7	P323L	4.4
	RDV	B.1.1.7	P323L	7.0
	RDV	B.1.170	P323L	3.9
	RDV	B.1.2	Assay Failure	3.6
	RDV	B.1.2	Assay Failure	3.8
	RDV	B.1.369	Assay Failure	3.9
	RDV	B.1.427	Assay Failure	7.5
	RDV	B.1.427	P323L	3.4
	RDV	P.1.17	Assay Failure	6.4
	RDV	Results pending	Results pending	5.7
	RDV	Results pending	Results pending	6.6
	RDV	Results pending	Results pending	3.8
	RDV	Results pending	Results pending	3.5

Source: FDA Reviewer analysis. ADEFF, PARAM: "SARS-CoV-2 Viral Load - Nasopharyngeal (log_{10} copies/mL)".

Conclusion for sequence analysis: The applicant attempted sequencing of viral RNA from baseline and post baseline samples for all subjects who had evaluable viral RNA at Day 14 or who met the primary endpoint definition (progression to COVID-19-related hospitalization or all-cause death), thus the sequence analysis represents a biased assessment of the frequencies of baseline genotypes or treatment-emergent substitutions among trial subjects. For this reason, associations between baseline genotype and virus shedding or other outcomes could not be adequately evaluated. In addition, the data submitted by the applicant are preliminary, and associated raw sequence data need to be submitted and evaluated independently by the Agency. A single treatment-emergent substitution nsp12 A376V was identified that should be evaluated for its impact on RDV susceptibility in cell culture. NGS datasets are needed to confirm the applicant's findings, and additional treatment-emergent substitutions may be identified using a lower frequency threshold. In addition, the sponsor should sequence earlier time points, including those identified above for subjects with apparent rebound and high viral RNA levels at Day 7.

LABELING

Language was added to Section 12.4 if the USPI based on viral RNA shedding data from trial GS-US-540-9012 submitted to NDA 214787 to support S-10. Other updates to Section 12.4 were made based on data supporting the Prior Approval Supplement S-09, submitted 9/21/2021 in an overlapping review cycle [see SDN 182; reviewed by E. Donaldson Ph.D., Reference ID in DARRTS: 4917124 (N214787.S-009.MI.219)].

The following language (red font) was proposed for inclusion in Section 12.4 of labeling under Antiviral Activity based on data submitted to support S-10.

12.4 Microbiology

…

Antiviral Activity

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell lines Calu-3 and A549-hACE2 with EC_{50} values of 280 nM after 72 hours of treatment and 115 nM after 48 hours of treatment, respectively.

Remdesivir EC_{50} values for SARS-CoV-2 in A549-hACE2 cells were not different when combined with chloroquine phosphate or hydroxychloroquine sulfate at concentrations up to 2.5 µM. In a separate study, the antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate or hydroxychloroquine sulfate reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2, and normal human bronchial epithelial cells.

SARS-CoV-2 RNA shedding results from GS-US-540-9012 indicate that remdesivir does not significantly reduce the amount of detectable SARS-CoV-2 RNA in nasopharyngeal swabs in non-hospitalized patients compared to placebo.

…

POST MARKETING REQUIREMENTS (PMR) / COMMITMENTS (PMC)

Number	PMR Description	Timetable
1	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.	Final Protocol Submission: N/A Study Completion: 05/2022 Final Report Submission: 06/2022

Number	PMR Description	Timetable
2	Evaluate by NGS sequence analysis the viral genes nsp8, nsp10, nsp12, nsp13, and nsp14, at baseline and (b) (4) for subjects in trial GS-US-540-9012 who met the following criteria: Exhibited any post-baseline 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.	Final Protocol Submission: MM/YYYY Study Completion: 08/2022 Final Report Submission: 09/2022

Number	PMC Description	Timetable
1	Submit viral sequencing data for baseline respiratory samples and post-baseline 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.	Final Protocol Submission: N/A Study Completion: 08/2022 Final Report Submission: 09/2022

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: **214787 SE-010 SDN 190 (0105) DATE REVIEWED**: **12/14/2021**
Virology Reviewer: William L. Ince, Ph.D.

CONCLUSION:
Virology data submitted to support supplemental NDA S-10 were limited to quantitative, longitudinal viral RNA analyses and summaries of preliminary resistance analyses that were requested during the review cycle. Additional data that were requested from the applicant included baseline serostatus; however, these data were not collected in the trial. There was no association between RDV treatment and viral RNA levels in nasopharyngeal swabs in trial GS-US-540-9012, which may be a result of potentially insufficient exposure of RDV in the upper respiratory tract, or with an overall limited antiviral effect of treatment. The lack of identified treatment-emergent resistance to date is consistent with a lack of potent antiviral activity in sampled compartments; however, additional data, such as raw NGS datasets, are needed to confirm the applicant's findings. Additional treatment-emergent substitutions may be identified in an independent analysis of the NGS datasets using a lower frequency threshold.

William L. Ince, Ph.D.
Clinical Virology Reviewer

CONCURRENCES

Date: _____
HFD-530/Clin Virol TL/J O'Rear

cc:**HFD-530/RPM/Jang**

APPENDIX A: Preliminary data listings submitted 11/2/2021 [SDN 197] as part of an Interim Virology Report.

(b) (4)

[redacted]

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APPENDIX B: Response to IR sent 12/3/2021 and received 12/10/2021 (SDN 218)

Virology Comment (sent 12/3/2021): We note that the preliminary baseline sequence data submitted in the Interim Virology Study Report PC-540-2031, although extremely limited and restricted to subjects who progressed to hospitalization or death, indicate potentially significant baseline SARS-CoV- 2 diversity within the GS-US-540-9012 trial population and/or potential differences in outcome based on the baseline SARS-CoV-2 genotype. Please submit any available baseline and post baseline sequence data that identify the SARS-CoV-2 variant in infected subjects in trial GS-US-540-9012, and include subgroup analysis of the primary endpoint by baseline SARS-CoV-2 lineage. If these data are not immediately available, please provide a timeline for when they will be submitted.

In addition, please submit any baseline SARS-CoV-2 serological data that may have been collected for trial GS-US-540-9012 and include subgroup analysis of the primary endpoint by baseline seropositivity status.

Applicant response (12/10/2021 [SN 0136]:

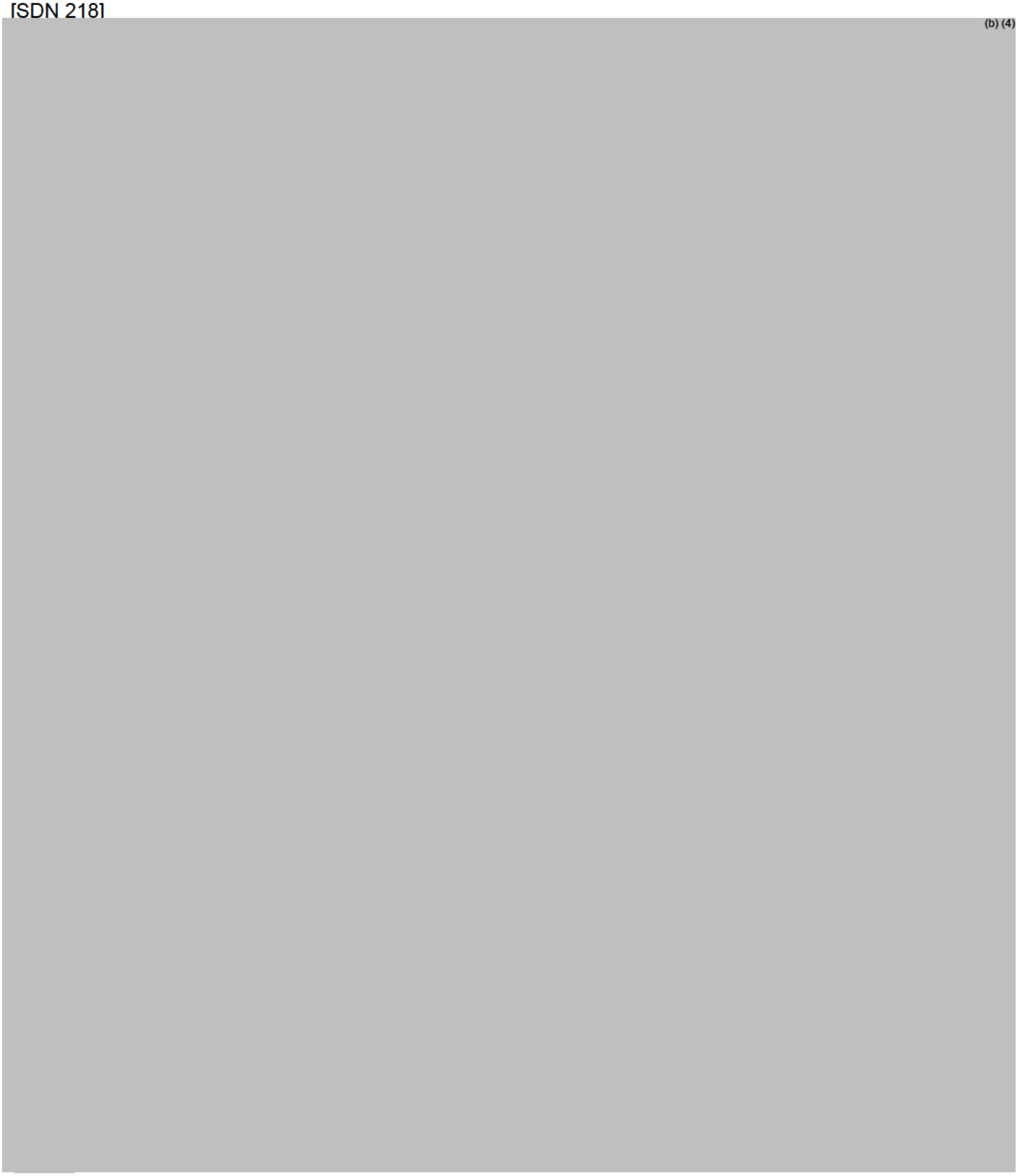
(b) (4)

(b) (4)

FDA reviewer follow-up note: The sponsor submitted additional summary data for sequence analyses. The sponsor has agreed to submit a complete resistance dataset, including raw sequence data as part of a PMC.

APPENDIX C: Combined preliminary nsp12 data listings submitted 11/2/2021 [SDN 197] and 12/10/2021 [SDN 218]

(b) (4)



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APPENDIX D: SDN 217 (SN 0122) received 12/09/2021: Applicant's response to information request regarding the activity of remdesivir against SARS-CoV-2 Variants of Concern/Interest including Omicron sent 12/9/2021.

Agency language is in Arial
Applicant language is in Times New Roman

Agency Information Request sent 12/9/2021 (email):
We note that the susceptibility of an agent against emerging SARS-CoV-2 variants of concern is of importance for product labeling for drugs approved for the treatment of SARS-CoV-2 infection leading to COVID-19 disease. Please provide susceptibility data for remdesivir against the SARS-CoV-2 Omicron (B.1.1.529) variant as soon as possible but no later than COB on January 14, 2022 and provide proposed updates to the remdesivir label at that time.

Applicant's response:

(b) (4)

Activity against Alpha, Beta, Gamma, Delta, and Epsilon variants:
Remdesivir (RDV) is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the CoVs (e.g., SARS CoV 2, SARS CoV, Middle East respiratory syndrome [MERS] CoV), filoviruses (e.g., Ebola virus, Marburg virus), and paramyxoviruses (e.g., respiratory syncytial virus, Nipah virus, Hendra virus).

The activity of remdesivir against SARS-CoV-2 Alpha, Beta, Gamma, Delta, and Epsilon variants has been assessed using two experimental systems. Remdesivir showed antiviral activity in Vero-TMPRSS2 cells using a plaque forming assay against SARS CoV-2 Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Epsilon (B.1.429) variants. Remdesivir also showed antiviral activity in A549-ACE2-TMPRSS2 cells, using an anti-N ELISA, against SARS-CoV-2 Alpha, Beta, Gamma, and Delta variants.

These results indicate potent inhibition of the SARS-CoV-2 variants by remdesivir in two independent experimental systems at a similar level to the previously characterized SARS-CoV-2 WA1 reference.

Table 1 Remdesivir Antiviral Activity Against Clinical Isolates of SARS-CoV-2 Variants

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions	Fold Reduction in Susceptibility
B.1.1.7	UK	Alpha	P323L	no change[a]
B.1.351	South Africa	Beta	P323L	no change[a]
B.1.617.2	India	Delta	P323L, G671S	no change[a]
P.1	Brazil	Gamma	P323L	no change[a]
B.1.429	USA	Epsilon	P323L	no change[a]

a No change: ≤1.5-fold reduction in susceptibility.

(b) (4)

(b) (4)

[redacted]

FDA reviewer follow-up note: The Applicant intends to submit additional data on the antiviral activity of RDV against Omicron variants as they become available. The data provided in response Table 1 were also submitted to NDA 214787 in SDN 182 and reviewed by E. Donaldson, Ph.D.

APPENDIX E: SDN 224 (SN 0127) received 12/23/2021: Applicant's updated response to information request regarding the activity of remdesivir against SARS-CoV-2 Variants of Concern/Interest including Omicron sent 12/21/2021.

Agency language is in Arial
Applicant language is in Times New Roman

Agency Information Request sent 12/21/2021: We refer to our December 8, 2021 information request that you provide susceptibility data for remdesivir against the SARS-CoV-2 Omicron (B.1.1.529) variant as soon as possible but no later than COB on January 14, 2022 and provide proposed updates to the remdesivir label at that time. By COB today (December 21, 2021), please provide a status update on your progress and your anticipated timeframe for submission of the above information.

Applicant's Response:

(b) (4)

[redacted]

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APPENDIX F: SDN 234 (SN 0134) received 1/11/2022: Applicant's response to PMC/PMR proposals sent 1/7/2022.

FDA language is in Arial
Applicant language is in Times New Roman

FDA Proposed PMR 1:

Number	PMR Description	Timetable
1	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.	Final Protocol Submission: N/A Study Completion: 05/2022 Final Report Submission: 06/2022

Applicant's response to proposed PMR 1:
Gilead acknowledges the agreed upon PMR description and timetable.

FDA Proposed PMR 2:

Number	PMR Description	Timetable
2	Evaluate by NGS sequence analysis the viral genes nsp8, nsp10, nsp12, nsp13, and nsp14, at baseline (b) (4) for subjects in trial GS-US-540-9012 who met the following criteria: Exhibited any post-baseline 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.	Final Protocol Submission: MM/YYYY Study Completion: MM/YYYY Final Report Submission: MM/YYYY

Rationale: (b) (4)

(b) (4)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s010

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 1/13/2022

To: Saebyeol Jang
Senior Regulatory Health Project Manager
Division of Antivirals (DAV)

From: Nima Ossareh, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for VEKLURY (remdesivir) for injection, for intravenous use

NDA: 214787 S-10

In response to DAVP's consult request dated October 25, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for VEKLURY (remdesivir) for injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAVP on January 10, 2022, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 13, 2022
To:	Saebyeol Jang Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VEKLURY (remdesivir)
Dosage Form and Route:	for injection, for intravenous use injection, for intravenous use
Application Type/Number:	NDA 214787
Supplement Number:	S-010
Applicant:	Gilead Sciences, Inc

1 INTRODUCTION

On October 21, 2021, Gilead Sciences, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their New Drug Application (NDA) 214787/S-010 for VEKLURY (remdesivir). With this supplement, the Applicant provides data from Study GS-US-540-9012 to support 3-day dosing regimen for VEKLURY (remdesivir) in non-hospitalized patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on October 25, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VEKLURY (remdesivir).

2 MATERIAL REVIEWED

- Draft VEKLURY (remdesivir) PPI received on October 21, 2021, and received by DMPP and OPDP on January 10, 2022.
- Draft VEKLURY (remdesivir) Prescribing Information (PI) received on October 21, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 10, 2022.
- Approved VEKLURY (remdesivir) labeling dated February 22, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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BARBARA A FULLER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Memorandum

Date:	January 10, 2022
Reviewers:	Kate McCartan, MD, Medical Officer Kim Swank, PharmD, Safety Evaluator Division of Pharmacovigilance II
Team Leader:	Rachna Kapoor, Pharm D, MBA Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Veklury (remdesivir)
Subject:	Summary of Adverse Events
Application Type/Number:	NDA 214787/S-10
Applicant:	Gilead Sciences, Inc.
OSE RCM #:	2021-2238

1 INTRODUCTION

The purpose of this Division of Pharmacovigilance II (DPV II) memorandum is to present a high-level overview of cases identified in the FDA Adverse Event Reporting System (FAERS) database, the American College of Medical Toxicology's (ACMT) Toxicology Investigators Consortium (ToxIC) Registry, and the published medical literature with Veklury (remdesivir) for the treatment of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

On November 19, 2021, the Division of Antivirals (DAV) consulted DPV II to provide a safety summary of adverse event reports submitted for remdesivir through December 13, 2021. DAV will use these data to inform any potential changes to the current approved label for remdesivir during their review of the supplemental New Drug Application (sNDA) 214787/S-10.

1.1 BACKGROUND

Remdesivir is a SARS-CoV-2 nucleotide analog ribonucleic acid (RNA) polymerase inhibitor approved for adults and pediatric patients 12 years of age and older and weighing at least 40 kg for the treatment of COVID-19 requiring hospitalization.[1]

On May 1, 2020, FDA issued an Emergency Use Authorization (EUA) to permit the use of remdesivir for the treatment of hospitalized patients with severe COVID-19. On August 28, 2020, FDA reissued the May 1, 2020 letter to expand authorized use of remdesivir by no longer limiting its use to the treatment of patients with severe disease.[2]

On June 15, 2020, the remdesivir Fact Sheet for Healthcare Providers was updated to include additional adverse events under *Hypersensitivity Including Infusion-Related and Anaphylactic Reactions* in the WARNINGS AND PRECAUTIONS section based on postmarketing cases identified by DPV II. These adverse events included tachycardia, bradycardia, dyspnea, wheezing, anaphylaxis, and angioedema.

On October 22, 2020, FDA approved Veklury (remdesivir) 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. At the time of this approval, the EUA letter was reissued to remove uses now approved under the NDA, and to continue authorizing remdesivir for emergency use to treat patients weighting 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.[2]

On October 21, 2021, the Applicant submitted sNDA 214787/S-10 which expands the indication to include the treatment of COVID-19 in non-hospitalized adults and pediatric patients (12 years of age and older weighing at least 40 kg) at high risk for progressing to severe COVID-19, including hospitalization or death, for a duration of 3 days.

1.2 SUMMARY OF REMDESIVIR POSTMARKETING SAFETY SURVEILLANCE

On July 9, 2020, DPV II completed a high-level overview of *all adverse events* in the setting of COVID-19 under the EUA for remdesivir.[3] This memorandum included data from the FAERS

database and medical literature through June 3, 2020. DPV II identified adverse events of interest, which included hypersensitivity reactions, increased transaminases, acute kidney injury (AKI), cardiac arrest, and hypotension. The majority of the adverse events reported were considered potential complications of COVID-19 or currently listed in the remdesivir Fact Sheet for Healthcare Providers.[4] No new safety signals were identified as a result of the safety summary that warranted regulatory action at that time.

On August 28, 2020, DPV II completed a review of *hepatotoxicity* with remdesivir use. This review was in response to a consult from DAV requesting a summary of compelling hepatotoxicity cases with remdesivir use. This memorandum included data from the FAERS database from June 4, 2020 through August 16, 2020. A limited number of compelling hepatotoxicity cases with remdesivir use in patients without significant risk factors for liver injury were identified; however, because many of the cases may have lacked complete details and the contribution of COVID-19 could not be ruled out, our assessment of the potential involvement of remdesivir in causing hepatobiliary adverse events was limited. Based on these findings, DPV II recommended continued routine pharmacovigilance.

On October 15, 2020, DPV II opened four Newly Identified Safety Signals (NISSs) for remdesivir based on postmarketing case reports identified in FAERS, which included *bradycardia* (NISS# 1004228), *acute kidney injury* (NISS# 1004227), *QT prolongation* (NISS# 1004229), and *increased prothrombin time (PT)/international normalization ratio (INR)* (NISS# 1004230). Based on limited information and confounding factors identified in the postmarketing reports, the NISSs were classified as indeterminate signals and closed with active monitoring.

On January 6, 2021, a NISS (NISS# 1004329) for *bradycardia* with remdesivir use was opened in the pre-evaluation phase based on a small number of cases with concerning features (e.g., bradycardia requiring treatment, second or third-degree atrioventricular block, heart rates less than 30 beats per minute). After meetings with a multidisciplinary team to discuss this signal, an information request was sent to the Applicant and the NISS was closed with a plan for active monitoring while FDA awaited the Applicant's response and attempted additional follow up on case reports. On May 12, 2021, FDA received the Applicant's cumulative review of the signal of sinus bradycardia and a NISS was reopened, tracked under Safety Signal ID #1004496, and moved to the evaluation phase.

On October 26, 2021, FDA's multidisciplinary NISS team completed an Integrated Safety Assessment (ISA) evaluating the potential signal of bradycardia in patients receiving remdesivir for the treatment of COVID-19.[5] Bradycardia is a labeled event in the context of infusion-related reactions with remdesivir administration. The ISA focused on bradycardia not associated with an infusion-related reaction and occurring more than two hours after administration of remdesivir. This review encompassed an evaluation of a number of available data streams and multidisciplinary assessments across the Center for Drug Evaluation and Research (CDER) offices. The NISS team evaluated case reports from FAERS, the published medical literature, and the ToxIC registry, as well as nonclinical data, clinical trial data, epidemiology data, and available studies considering potential mechanistic plausibility for remdesivir and bradycardia. Overall, there was insufficient evidence of a causal association between remdesivir and bradycardia and the NISS team recommended continuing routine pharmacovigilance.

1.3 RELEVANT PRODUCT LABELING[1]

The relevant sections from the remdesivir label are detailed below.

> **4 CONTRAINDICATIONS**
> VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any component of the product.
>
> **5 WARNINGS AND PRECAUTIONS**
>
> **5.1 Hypersensitivity Including Infusion-related and Anaphylactic Reactions**
> Hypersensitivity reactions have been observed during and following administration of VEKLURY. Slower infusion rates, with a maximum infusion time up to 120 minutes, can be considered to potentially prevent signs and symptoms of hypersensitivity. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment.
>
> **5.2 Increased risk of Transaminase Elevations**
> Transaminase elevations have been observed in healthy volunteers and have also been reported in patients with COVID-19 who received VEKLURY. Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate. Consider discontinuing VEKLURY if alanine aminotransferase (ALT) levels increase to greater than 10 times the upper limit of normal. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.
>
> **5.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine Phosphate or Hydroxychloroquine Sulfate**
> Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY.
>
> **6. ADVERSE REACTIONS**
> **6.1 Clinical Trials Experience**
> The most common adverse reactions (incidence greater than or equal to 5%, all grades) observed with treatment with VEKLURY are nausea, ALT increased, and AST increased.

2 METHODS AND MATERIALS

2.1 CASE INCLUSION CRITERION

DPV II screened reports retrieved from the search strategies described in **Tables 1 and 2** for cases of adverse events reported with remdesivir use for the treatment of COVID-19. Cases identified in multiple data sources were deduplicated.

2.2 FAERS SEARCH STRATEGY

DPV II searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	Recurring daily searches[†]
Time period of search	December 1, 2019[‡] - December 13, 2021
Search type	DSAD Quick Query FBIS Quick Query/RxLogix PV Signal Quick Query[§]
Product terms	PAM: remdesivir
MedDRA search terms (Version 24.0)	PTs: *Asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, Suspected COVID-19, COVID-19 treatment, COVID-19 prophylaxis, Coronavirus infection, Coronavirus test positive, SARS-CoV-2 test positive, SARS-CoV-2 test false negative, Exposure to SARS-CoV-2, SARS-CoV-2 carrier, Occupational exposure to SARS-CoV-2, SARS-CoV-2 sepsis, SARS-CoV-2 viraemia, SARS-CoV-2 antibody test, Congenital COVID-19, Post-acute COVID-19 syndrome, Vaccine derived SARS-CoV-2 infection, SARS-CoV-2 RNA, SARS-CoV-2 RNA decreased, SARS-CoV-2 RNA fluctuation, SARS-CoV-2 RNA increased*
Other criteria (text string searches)	See **Appendix B**

* See **Appendix A** for a description of the FAERS database.
[†] A separate search strategy was not performed for this Memorandum. DPV II used recurring daily COVID-19 searches, which started on February 11, 2020. The data from this search strategy are through December 14, 2021. Searches recurring daily on Tuesday-Friday with a 1-day prior completion date and on Monday with a 3-day prior completion date.
[‡] The initial search started on February 10, 2020 and included a time period of December 1, 2019 (first COVID-19 cases reported in December 2019) through February 9, 2020. The first case with remdesivir use for the treatment of COVID-19 was retrieved on March 11, 2020 from a foreign reporting source. The first case with remdesivir use under the EUA was retrieved on May 11, 2020.
[§] RxLogix migration occurred on November 9, 2021
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAM= Product Active Moiety, PT=Preferred Term, DSAD= Drug Safety Analytics Dashboard, FBIS= FAERS Business Intelligence Solution,

2.3 LITERATURE CASE SEARCH STRATEGY

DPV II searched the medical literature with the search strategy described in **Table 2**.

Table 2. Literature Case Search Strategy	
Date of search	Recurring daily searches
Database	Embase
Search terms	Drug search for “remdesivir”
Time period of search	January 1, 2020 - December 13, 2021

In addition, we reviewed weekly PubMed and EMBASE Early Alerts for COVID-19 and safety-related articles (March 15, 2020 – December 8, 2021) for cases of adverse events with all COVID-19 treatments, including remdesivir.

2.4 OTHER SAFETY DATA

2.4.1 American College of Medical Toxicology (ACMT) - FDA ACMT COVID-19 Toxicology Investigators Consortium (ToxIC) (FACT) Pharmacovigilance Project Sub-registry

In an effort to identify adverse events occurring with COVID-19 treatments, including remdesivir, FDA contracted with ACMT to establish a multi-center active surveillance network to capture these adverse events. DPV II reviewed all cases reporting adverse events with remdesivir use for the treatment of COVID-19 identified in the ToxIC FACT sub-registry from November 23, 2020 through December 13, 2021. See **Appendix C** for a description of the ACMT ToxIC Registry and FACT Pharmacovigilance Project Sub-registry.

3 RESULTS

3.1 FAERS CASE SELECTION

From December 1, 2019 through December 13, 2021, we identified 5,796 unique cases of adverse events with remdesivir use for the treatment of COVID-19 in FAERS.

3.2 LITERATURE CASE SELECTION

From January 1, 2020 through December 13, 2021, we identified 255 case reports of adverse events with remdesivir use for the treatment of COVID-19 in the medical literature.

3.3 FACT PHARMACOVIGILANCE PROJECT SUB-REGISTRY CASE SELECTION

From November 23, 2020 through December 13, 2021, we identified 386 cases of adverse events with remdesivir use for the treatment of COVID-19 in the ToxIC Registry.

3.4 FINAL CASE SERIES

Table 3 provides the total number of cases identified from FAERS, the medical literature, and the FACT Pharmacovigilance Project Sub-registry that met the selection criteria (see **Section 2**) and describes characteristics of these cases.

Table 3. <u>All</u> Remdesivir Cases Reporting Adverse Events for the Treatment of COVID-19 in the FAERS Database, the Medical Literature, and the FACT Pharmacovigilance Project Sub-registry through December 13, 2021 (n=6,437)	
Source*	
FAERS	5,796 (3,178 EUA)
Literature	255
FACT Pharmacovigilance Project Sub-registry	386 (21 EUA)
Sex	(n=6,325)
Male	3,940
Female	2,383
Transgender	2
Age	(n=6,058)
Range	4 days – 100 years
Median	64
Mean	61
Country	(n=6,436)
US	5,194
Foreign	1,242
Fatal Outcome	1,820

* FAERS - Includes any case identified in either FAERS alone, in both FAERS and the literature, or in both FAERS and FACT Pharmacovigilance Project Sub-registry.
Literature - Includes cases only identified in the literature
FACT Pharmacovigilance Project Sub-registry – Includes cases only identified in the sub-registry.

Labeled Adverse Event of Interest:
Infusion-related reactions (IRRs): 446 cases reported an IRR[a] with use of remdesivir to treat COVID-19. Of these 446 cases reporting an IRR, 174 reported administration site extravasation or infiltration.

Unlabeled Adverse Events of Interest:
Table 4 summarizes the unlabeled adverse events of interest reported in cases with remdesivir use for the treatment of COVID-19.

Table 4. Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events of Interest for the Treatment of COVID-19 (n=2,680)*†	
<u>Hepatobiliary Disorders</u>	(n=115)
Hepatic failure	36
Hyperbilirubinemia/cholestasis	78
Sclerosing cholangitis	1
<u>Blood and Lymphatic System Disorders</u>	(n=259) †
Thrombocytopenia/anemia/leukopenia	194
Hemorrhage (non-neuro)/coagulopathy	78
Thrombocytosis	18
Methemoglobinemia	1
Hemolytic anemia	4

[a] Infusion-related reaction was defined as an adverse event occurring within 2 hours of administration of remdesivir.

Table 4. Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events of Interest for the Treatment of COVID-19 (n=2,680)*†	
Renal and Urinary Disorders	(n=1,059)†
AKI/renal impairment/renal failure	1,050
ATN	19
Bladder calculus	1
Hematuria	9
Renal tubular acidosis	1
Neurologic Disorders	(n=94)†
Ischemic stroke	45
Empty sella syndrome	1
Hemorrhagic stroke/intracranial hemorrhage	12
Dystonia	1
Guillain-Barre syndrome	10
Neuroleptic malignant syndrome/Malignant hyperthermia	4
PRES	4
Tremor	15
Dyskinesia	3
Myasthenia gravis aggravated	3
Skin and Subcutaneous Tissue Disorders	(n=11)
DRESS	2
SJS	1
Livedo Reticularis	2
Bullous dermatitis/blisters/allergic dermatitis	6
Metabolism and Nutrition Disorders	(n=150)†
Hyperkalemia	29
Hypernatremia	18
Hypokalemia	9
Hypophosphatemia	3
Hyperphosphatemia	3
Hypermagnesemia	5
Hyperglycemia	62
Hypoglycemia	14
SIADH	3
Hyponatremia	12
Diabetes insipidus	2
Hypomagnesemia	1
Hypocalcemia	2
Hyperparathyroidism	1
Hyperamylasemia	3
Hypertriglyceridemia	6
Psychiatric Disorders	(n=79)†
Anxiety/agitation	32
Hallucinations/delirium	32
Confusion/mental status changes	20
Suicidal ideation	1

Table 4. Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events of Interest for the Treatment of COVID-19 (n=2,680)*†	
Completed suicide	3
Abnormal dreams	1
Catatonia	1
Psychosis	3
Cardiac Disorders‡	(n=1,114)†
VF/VT/SVT	49
Atrial fibrillation/atrial flutter	82
Tachycardia	52
Cardiac arrest/PEA	239
Hypotension	160
Bradycardia	682
Myocardial infarction	41
QT prolongation§	44
TdP‖	6
Hypertension	24
Arrhythmia	11
AV block (1st and 2nd degree)	19
AV block complete	1
RBBB/LBBB	4
Musculoskeletal and Connective Tissue Disorders	(n=16)
Rhabdomyolysis	16
Investigations	(n=19)†
Increased CPK	11
Increased drug level¶	9
*Decreased drug level***	2
Drug interaction††	4
Gastrointestinal Disorders	(n=71)
Pancreatitis	38
Intestinal/gastric perforation	29
Intestinal ischemia	4
Vascular Disorders	(n=181)†
Pulmonary embolism	83
Deep vein thrombosis	49
Unspecified thrombosis	44
Renal infarction	8
Splenic infarction	4
Ear and Labyrinth Disorders	(n=7)†
Hearing loss/deafness	4
Tinnitus	5

* The table lists AEs reported with remdesivir use; however, causality criteria have not been applied.

†A case may have more than one AE.

‡ Cardiac AEs that were **not** reported in the context of an infusion-related reaction(s)

§ Four patients were on hydroxychloroquine, two patients were on both hydroxychloroquine and azithromycin, one patient was on both hydroxychloroquine and lopinavir/ritonavir, one patient was on chloroquine, five patients were on azithromycin, three patients were on dexmedetomidine, one patient was on diltiazem, two patients were on amiodarone, one patient was on donepezil, one patient was on

Table 4. Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events of Interest for the Treatment of COVID-19 (n=2,680)*†

methadone, one patient was on azithromycin and quetiapine, one patient was on levofloxacin, one patient was on quetiapine, and twenty patients were not on any reported QT prolonging drugs.
|| One patient was on hydroxychloroquine and azithromycin, one patient was on hydroxychloroquine and lopinavir/ritonavir, one patient was on ondansetron, one patient was on fluoxetine and tramadol, one patient was on amiodarone and one patient was not on any QT prolonging medications.
¶ Six cases reported increased tacrolimus levels, one case of increased cyclosporine levels, one case of increased isavuconazole levels and one case reported increased levels of an unspecified drug.
** Decreased valproic acid level decreased tacrolimus level.
††Two cases reported a drug interaction with warfarin, one case reported a drug interaction with tramadol, and one case did not specify the drug product.
Abbreviations: AKI = acute kidney injury, ATN = acute tubular necrosis, VF= ventricular fibrillation, VT = ventricular tachycardia, SVT = supraventricular tachycardia, TdP = Torsades de Pointes, AV = atrioventricular, CPK= creatinine phosphokinase, INR = international normalized ratio, DRESS = drug reaction with eosinophilia and systemic symptoms, RBBB = right bundle branch block, PEA = pulseless electrical activity, SIADH = syndrome of inappropriate antidiuretic hormone; LBBB= left bundle branch block; PRES = posterior reversible encephalopathy syndrome

Key points:

- The majority of the cases occurred in males. The median age in the cases was 64 years, but cases reporting remdesivir use in patients as young as 4 days and as old as 100 years were identified.
- Of the 6,437 total remdesivir cases:
  - 3,593 (56%) have been received after FDA approval of remdesivir.
  - 3,199 (50%) reported use of remdesivir under the EUA. Of these 3,199 cases reporting use under the EUA, 603 (19%) were received after FDA approval of remdesivir.
- There was a fatal outcome in 28% of the cases. About one-third of the cases with a fatal outcome reported no other adverse event besides death. In the remaining cases, the most commonly reported adverse events included acute kidney injury, increased transaminases, cardiac arrest and multiple organ dysfunction, all of which can occur with COVID-19 independent of remdesivir use. Acute kidney injury and increased transaminases were also among the most commonly reported adverse events in cases with non-fatal outcomes.
- Approximately one-third of the IRR cases reported only administration site infiltration or extravasation. Of the remaining IRR cases, the majority described IRR adverse events that are labeled. The most commonly reported IRR adverse events included bradycardia and rash. Cases of anaphylaxis were also reported including cases requiring intubation at the time of the reaction.
- The most commonly reported unlabeled adverse event was acute kidney injury/renal impairment/renal failure (n=1,050) followed by bradycardia occurring outside of infusion-related reactions (n=682).

4 REVIEWERS' COMMENTS

Among the labeled adverse events of interest, we focused on cases reporting IRRs to determine the need for any labeling updates. The adverse events reported in these cases are consistent with the current labeling and no updates are warranted at this time.

Many of the unlabeled adverse events in **Table 4** could also be attributed to COVID-19 (e.g., deep vein thrombosis, myocardial infarction, pulmonary embolism). Other adverse events could

be attributed to concomitant COVID-19 treatments (e.g., intestinal/gastric perforation with concomitant tocilizumab use, hyperglycemia with concomitant corticosteroid use). Adverse events of interest that DPV II assessed as needing active monitoring or further evaluation included:

- **Acute kidney injury (AKI):** AKI was also the most commonly reported adverse event in DPV II's July 2020 remdesivir memorandum. Additionally, cases reporting AKI with remdesivir use were actively monitored for six months post-approval before returning to routine pharmacovigilance with Drug Safety Team (DST) concurrence as no compelling or well documented cases were identified. The cases identified following the initial review and period of active monitoring continue to describe complex AKI but contain limited information (e.g., lack of renal histology data or urine sediment), with the majority having confounding factors that could have contributed to worsening renal function. Therefore, DPV II's assessment of the cases has not changed since the initial assessment. DPV II continues to monitor this adverse event as part of our routine surveillance of treatments used for COVID-19.
- **Bradycardia:** The NISS evaluation team completed an ISA of bradycardia with remdesivir on October 26, 2021 with no regulatory action recommended.[5] DPV II reviewed cases from FAERS, the medical literature and the FACT Pharmacovigilance Project Sub-registry as part of this assessment. From these sources, DPV II identified concerning cases of bradycardia with remdesivir use for the treatment of COVID-19, however, many of these cases lacked important details or had confounding factors so that while remdesivir was assessed as a possible cause of the bradycardia, other causes of the bradycardia could not be ruled out. DPV II continues to monitor this adverse event as part of our routine surveillance of treatments used for COVID-19.
- **Hepatotoxicity:** The increased risk of transaminase elevations is included in the WARNINGS AND PRECAUTIONS section of remdesivir labeling[1]; this does not include a warning for hepatic failure. DPV II completed a review of hepatoxicity with remdesivir use on August 28, 2020 and did not identify any hepatic failure cases at that time. At the data lock of this current memorandum, 36 cases have reported hepatic failure. Of these 36 cases, only 12 described laboratory values (e.g., increased INR, increased total bilirubin levels) or clinical signs or symptoms (e.g., jaundice) suggestive of hepatic failure. Of these 12 cases, only one did not describe concurrent failure of another organ system, use of concomitant hepatotoxic medications, or occur in the setting of shock. The single case without identifiable confounders had an unclear temporal relationship between remdesivir use and the hepatic failure. DPV II will continue to monitor hepatotoxicity, and specifically hepatic failure, as part of our routine surveillance of treatments used for COVID-19.
- **INR/PT increased:** Prothrombin time increased is included in the remdesivir labeling in *6.1 Clinical Trials Experience*.[1] DPV II actively monitored cases of INR and PT elevations with remdesivir for six months post-approval. The cases identified were confounded with liver failure and concomitant medications. There was DST concurrence to return to routine pharmacovigilance. Cases identified since the period of active monitoring have also been confounded. DPV II will continue to monitor this adverse event as part of our routine surveillance of treatments used for COVID-19.
- **QT prolongation:** DPV II actively monitored cases of QT prolongation with remdesivir for six months post-approval. No cases were identified without confounders (e.g.,

comorbidities or concomitant medications). There was DST concurrence to return to routine pharmacovigilance. Cases identified since the period of active monitoring continue to be confounded or lack sufficient information (e.g., an incomplete list of concomitant medications). DPV II will continue to monitor this adverse event as part of our routine surveillance of treatments used for COVID-19.

DPV II did not identify any new safety signals as a result of this safety summary that warrant regulatory action at this time.

5 REFERENCES

[1] Veklury (remdesivir) [package insert]. Gilead Sciences, Inc., Foster City, CA. Revised February 2021. Available at: Drugs@FDA: FDA-Approved Drugs (Accessed on December 22, 2021).
[2] Emergency Use Authorization Letter for Remdesivir. Issued May 1, 2020 and Reissued on October 22, 2020. Available: at https://www.fda.gov/media/137564/download. (Accessed on December 22, 2021).
[3] McCartan K, Swank K, Chehab M, Fanti P. Division of Pharmacovigilance Memorandum for Remdesivir and All Adverse Events in the Setting of COVID-19 Under the EUA. July 9, 2020. Reference ID: 4638219.
[4] Remdesivir Fact Sheet for Health Care Providers Emergency Use Authorization. Gilead Sciences, Inc. Available at: https://www fda.gov/media/137566/download (Accessed on December 22, 2021).
[5] Gada N, Mishra P, et al. Newly Identified Safety Signal (NISS) Integrated Safety Assessment: Remdesivir and Bradycardia. October 26, 2021.

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.2 APPENDIX B. FAERS SEARCH STRATEGY

FAERS Search Strategy (continued)	
Reported Reason for Use	Asymptomatic COVID-19, Asymptomatic SARS-CoV-2 infection, Coronavirus disease 2019, COVID-19;COVID-19 respiratory infection, SARS-CoV-2 acute respiratory disease, SARS-CoV-2 infection, Coronavirus pneumonia, COVID-19 pneumonia, Novel COVID-19-infected pneumonia, Suspected COVID-19, Suspected SARS-CoV-2 infection, SARS-CoV-2 carrier, Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, COVID-19 virus test false negative, SARS-CoV-2 test false negative, COVID-19 antibody test positive, COVID-19 ELISA test positive, COVID-19 molecular test positive, COVID-19 PCR test positive, COVID-19 rapid POC test positive, COVID-19 serology test positive;COVID-19 virus test positive;SARS-CoV-2 antibody test positive, SARS-CoV-2 ELISA test positive, SARS-CoV-2 PCR test positive, SARS-CoV-2 serology test positive, SARS-CoV-2 test positive, COVID-19 prophylaxis, COVID-19 treatment, 2019 novel coronavirus infection, 2019-nCoV infection, COVID-19 aggravated, COVID-19 pneumonia aggravated, COVID-19 pneumonitis, Interstitial pneumonia due to COVID-19, SARS-CoV-2 pneumonia, SARS-CoV-2 sepsis, SARS-CoV-2 viraemia, SARS-CoV-2 viremia, Community-related COVID-19 exposure, Exposure to COVID-19, Occupational exposure to COVID-19, Travel-associated COVID-19 exposure, COVID-19 antigen test positive, SARS-CoV-2 IgG antibody test, SARS-CoV-2 IgM antibody test, SARS-CoV-2 molecular test positive, SARS-CoV-2 rapid antibody test, SARS-CoV-2 rapid POC test positive, Congenital COVID-19, Congenital SARS-CoV-2 infection, Laboratory confirmed SARS-CoV-2 infection without symptoms, COVID-19 recurrent, Long COVID, Post-acute COVID-19 syndrome, Post-COVID syndrome, Vaccine derived SARS-CoV-2 infection, SARS-CoV-2 IgA antibody test, SARS-CoV-2 RNA, SARS-CoV-2 viral load, SARS-CoV-2 RNA decreased, SARS-CoV-2 viral load decreased, SARS-CoV-2 RNA fluctuation, SARS-CoV-2 viral load fluctuation, SARS-CoV-2 RNA increased, SARS-CoV-2 viral load increased, Coronavirus infection
Reporter Narrative	Corona virus, Coronavirus, ncov, COVID, SARS-COV, SARS COV, 2019-NCOV, 2019 NCOV, EUA, Emergency Use Authorization
Medical History Comments	Corona virus, coronavirus, ncov, COVID, SARS-COV, SARS COV, 2019-NCOV, 2019 NCOV

6.3 APPENDIX C. OTHER DATABASE DESCRIPTION

Toxicology Investigators Consortium (ToxIC) Registry

The Toxicology Investigators Consortium (ToxIC) Registry is a multi-center toxico-surveillance and research network overseen by the American College of Medical Toxicology (ACMT). The patients in the registry are manifesting toxicologic symptoms from intentional and unintentional exposures. Data for each case are entered into the registry by the treating medical toxicology team at a participating center. The data source has the potential to detect new and emerging drugs of abuse, adverse effects of new drugs or unapproved products, and associated toxicological syndromes. A strength of the registry is that specific data are collected by the medical toxicologist who is providing direct patient care. Limitations of the registry include the following: lack of representation from certain states (e.g., Wyoming), and a small number of cases relative to other data sources (e.g., poison control data) because each case requires formal bedside medical toxicology consultation. FDA cannot independently verify the causality assessment.

In response to the COVID-19 pandemic, FDA contracted with ACMT to establish the FDA ACMT COVID-19 ToxIC (FACT) Pharmacovigilance Project. FACT is a multi-center active surveillance network designed to capture adverse drug events occurring with COVID-19 treatments and to provide FDA with real-time alerts via email when new cases are documented in the database. FACT enables direct outreach by FDA to site investigators when additional information on reported cases is needed. FACT also develops enhanced data collection forms for some adverse events of special interest to the FDA.

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LABELING AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 30, 2021
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214787/S-010
Product Name, Dosage Form, and Strength:	Veklury (remdesivir) for Injection, 100 mg per vial; Veklury (remdesivir) Injection, 100 mg/20 mL (5 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Gilead Sciences, Inc.
FDA Received Date:	October 21, 2021
OSE RCM #:	2021-2072
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

Gilead submitted a prior approval supplement for Veklury (remdesivir) for injection, 100 mg and Veklury (remdesivir) injection, 100 mg/20 mL to update the prescribing information to include data from Study GS-US-540-9012 to support a 3-day dosing regimen in non-hospitalized patients with COVID-19. Subsequently, the Division of Antivirals (DAV) requested that we review the proposed prescribing information (PI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Labeling and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT AND CONCLUSION

We note that the proposed Veklury PI is being revised to update section 2 (Dosage and Administration) to include a 3-day dosing regimen for non-hospitalized patients with COVID-19. We collaborated with DAV to revise the section 2 of the PI to include an overview section and reduce redundancy of information within this section. We have no additional recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 1 presents relevant product information for Veklury received on October 21, 2021 from Gilead Sciences, Inc.

Table 1. Relevant Product Information for Veklury	
Initial Approval Date	N/A
Active Ingredient	remdesivir
Indication	Indicated for [redacted] (b) (4)
Route of Administration	Intravenous
Dosage Form	For Injection; Injection
Strength	For Injection: 100 mg per vial Injection: 100 mg/20 mL (5 mg/mL)
Dose and Frequency	Loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2
How Supplied	Veklury for Injection: single-dose vial containing 100 mg remdesivir lyophilized powder that is to be reconstituted with 19 mL Sterile Water for Injection and further diluted in 0.9% sodium chloride injection. Veklury Injection: single-dose vial containing 100 mg/20 mL (5 mg/5mL) remdesivir solution for further dilution in 0.9% sodium chloride injection.
Storage	Veklury for Injection: Store below 30°C (86°F) until required for use. After reconstitution, vials can be stored up to (b) (4) hours at room temperature (20°C to 25°C [68°F to 77°F]) or (b) (4) hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]). Dilute within the same day as administration. Veklury Injection: Store vials at refrigerated temperature (2°C to 8°C [36°F to 46°F]) until required for use. Dilute within the same day as administration. Prior to dilution, equilibrate Veklury injection to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.

	Diluted Solution: Store Veklury diluted solution for infusion up to (b) (4) ours at room temperature (20°C to 25°C [68°F to 77°F]) or (b) (4) hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).
Container Closure	Veklury for Injection (b) (4) clear glass vial with 20 mm finish, 20 mm (b) (4) stopper, 20 mm (b) (4) seal with (b) (4) flip-off cap Veklury Injection: (b) (4) clear glass, 20 mL with 20 mm finish, 20 mm (b) (4) stopper, and 20 mm (b) (4) seal with (b) (4) flip-off cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 17, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Veklury. Our search did not identify any relevant previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Veklury labels and labeling submitted by Gilead Sciences, Inc.

- Prescribing Information (Image not shown) received on October 21, 2021, available from \\CDSESUB1\evsprod\NDA214787\0105\m1\us\114-labeling\draft\labeling

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Clinical Inspection Summary

Date	12/21/2021
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Saebyeol Jang, Pharm.D., Regulatory Project Manager Kirk Chan-Tack, M.D., Clinical Reviewer Kimberly Struble, Pharm. D, Clinical Team Leader Division of Antiviral Products (DAV)
NDA #	214787-S010
Applicant	Gilead Sciences, Inc. (Gilead)
Drug	Remdesivir
NME	No
Therapeutic Classification	RNA-dependent RNA Polymerase Inhibitor
Proposed Indication	Outpatient Treatment of Coronavirus Disease 2019
Consultation Request Dates	10/29/2021
Summary Goal Date	03/04/2022
Action Goal Date	01/21/2022
PDUFA Date	04/21/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEBLATIONS

The clinical investigators Drs. Hidalgo, Mera, and Hill were inspected in support of this application. Despite some regulatory deviations found at Drs. Hidalgo's and Hill's site, based on the results of these inspections, the study (GS-US-540-9012) appears to have been conducted adequately, and the data generated by the clinical investigator sites appear acceptable in support of the respective indication.

II. BACKGROUND

Remdesivir, a broad-spectrum nucleotide prodrug, is an RNA-dependent RNA polymerase inhibitor. It was developed by Gilead Sciences, Inc. (Gilead) and was approved by FDA in October 2020 for the treatment of COVID-19 in hospitalized adults and pediatric patients (12 years of age and older and weighing at least 40 kg).

The applicant (Gilead) conducted a study (Protocol GS-US-540-9012) in subjects with confirmed COVID-19 at high risk for disease progression for the treatment of COVID-19 in an outpatient setting. Gilead submitted the study data to support the indication for remdesivir (Veklury®) for the treatment of non-hospitalized adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with confirmed SARS-CoV-2 infection who were at high risk for COVID-19 disease progression, including hospitalization or death. The review division requested clinical investigator (CI) inspections for this study. The following is a brief description of the study. For more detailed information, please refer to the background packages.

Protocol GS-US-540-9012

Title: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (remdesivir, GS-5734™) Treatment of COVID-19 in an Outpatient Setting"

Subjects: 584 subjects were randomized

Study Start Date: 18 September 2020 (first participant screened)

Study End Date: 06 May 2021 (last subject last observation for the primary endpoint and for this report)

Study Centers: 64 centers: 55 in the United States (US), 5 in Denmark, 2 in Spain, and 2 in the United Kingdom.

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of remdesivir therapy for outpatients with early stage COVID-19 who were at higher risk of disease progression. Subjects who met all eligibility criteria were randomized in a 1:1 ratio to remdesivir treatment or placebo group. In the remdesivir treatment group, subjects received a single dose of intravenous (IV) remdesivir 200 mg on Day 1 followed by IV remdesivir 100 mg on Days 2 and 3. In placebo group, subjects received IV placebo-to-match remdesivir on Days 1 to 3. Randomization was stratified by subjects who resided in a skilled nursing facility, by subject's age (< 60 vs ≥ 60 years), and by region (US vs. outside US).

The primary efficacy endpoint was total subjects with COVID-19-related hospitalization or all-cause death by Day 28. Hospitalization was defined as ≥ 24 hours of acute care.

Rationale for Site Selection

All three CIs had large enrollment and no prior FDA inspections.

III. RESULTS

1. **Ausberto B. Hidalgo, M.D.**
   Site #20152
   302 NW 179th Ave., Suite 103
   Pembroke Pines, Florida 33029
   Inspection dates: November 29, 2021 to December 3, 2021

At this site for GS-US-540-9012, a total of 45 subjects were screened, 41 were enrolled, and 37 subjects completed the study. Four subjects discontinued the study. Three subjects withdrew consent. One subject (# (b) (6)) was enrolled and randomized into the placebo group, but the subject's eligibility expired after she failed to complete the Day 1 Visit due to her anxiety.

The inspection included the review of the following documents for all 41 enrolled subjects: the informed consent forms, the primary efficacy endpoint data, adverse events, study eligibility, and protocol compliance. Other records reviewed included, but were not limited to, protocols, clinical investigator oversight of the study, site training activities and implementation of study procedures, sub-investigator direct involvement, Institutional Review Board (IRB) submission and correspondence, adherence to and documentation of protocol required visits, other source documents, case report forms, Form FDA 1572s, schedule of assessments, subject discontinuations, concomitant medications, study test article accountability, and sponsor monitoring activities.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

The inspection had the following findings related to protocol non-compliance:

- Two subjects (# (b) (6) and # (b) (6), both in remdesivir treatment group) did not meet Inclusion Criteria #4, which required the presence of at least one symptom consistent with COVID-19 for 7 days or less prior to randomization. Both subjects had COVID symptoms for 8 days prior to randomization.

Reviewer's comment: Since both subjects (# (b) (6) and # (b) (6)) were ineligible according to Inclusion Criteria #4, we recommend removing these two subjects from the per protocol set analysis. Of note, these protocol deviations were not reported to the FDA.

- The protocol required nasopharyngeal (NP) swabs collected on Day 1, 2, 3, 7 and 14 for SARS-CoV-2 polymerase chain reaction (PCR) testing. Eight subjects had missed at least one NP swab as shown in the table below. "Yes" indicates NP swab was collected and "no" indicates not collected.

Subject #/ Treatment Assignment	Day 1	Day 2	Day 3	Day 7	Day 14	Number of Missing NP Swab(s)
(b) (6) /Placebo	Yes	No	Yes	Yes	No	2 of 5
(b) (6) /Remdesivir	Yes	Yes	No	Yes	Yes	1 of 5
(b) (6) /Placebo	No	Yes	Yes	Yes	Yes	1 of 5
(b) (6) /Placebo	Yes	Yes	Yes	Yes	No	1 of 5
(b) (6) /Placebo	Yes	No	Yes	Yes	Yes	1 of 5
(b) (6) /Placebo	Yes	Yes	No	Yes	Yes	1 of 5
(b) (6) /Placebo	Yes	No	No	No	Yes	3 of 5
(b) (6) /Placebo	No	No	No	Yes	Yes	3 of 5

Reviewer's comments: According to the protocol, SARS-CoV-2 PCR testing results from NP swabs were related to exploratory endpoints only. Therefore, the protocol deviation of not collecting NP swabs for PCR should not impact the study primary efficacy result or subject safety.

The CI has responded to the FDA Form 483. He acknowledged the above protocol deviations and stated that he has taken corrective and preventive actions.

2. **Jorge Mera, M.D.**
   Site #1806
   19600 E Ross St
   Tahlequah, Oklahoma 74464
   Inspection dates: November 15 to 19, 2021

At this site for Protocol GS-US-540-9012, 35 subjects were screened, 33 were enrolled, and 31 subjects completed the study. Two subjects withdrew consent.

The inspection included the review of the following documents for all 33 enrolled subjects: the informed consent forms, the primary efficacy endpoint data, adverse events, and study eligibility. Other records reviewed included, but were not limited to, protocols with their amendments, signed investigator statements (Form FDA 1572), deviation reports, study drug accountability, training, protocol deviations, IRB documentation, other subject records, financial disclosures, and study monitoring.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

3. **Joshua A. Hill, M.D.**
   Site #19752
   820 Minor Ave North
   Seattle, Washington 98109-1024
   Inspection dates: November 15 to 19, 2021

At this site for Protocol GS-US-540-9012, 41 subjects were screened and 36 were enrolled, and 32 subjects completed the study. Four subjects withdrew consent and discontinued the study.

The inspection included the review of informed consent forms for all 41 screened subjects and the primary efficacy endpoint data, adverse events, and study eligibility for all 36 enrolled subjects. Other records reviewed included, but were not limited to, randomization; vital signs and physical examinations; concomitant medications; laboratory reports; visit documentation; information collected on medically attended visits, hospitalizations, and deaths; protocol deviations; study drug administration, accountability, and storage.

There was no evidence of underreporting of adverse events. The primary efficacy endpoint data were all verifiable except for one subject (# (b) (6) in remdesivir treatment group). Subject # (b) (6) had a routine primary care physician visit on one day according to the source records. However, this medically attended visit was documented in the case report form as “hospitalization ongoing”. The sponsor’s line listing for this subject also had hospitalization as “ongoing”. Therefore, this visit was counted as an event of hospitalization.

Reviewer’s comment: This discrepancy between the source document and the case report form was likely due to a transcription error. As a result, this subject, who was in the remdesivir treatment group, had a false event of hospitalization, which was not in favor of remdesivir.

One subject's concomitant medication was not reported. Subject # (b) (6) (in remdesivir treatment group) was noted to be taking aspirin in the source documents, but aspirin was not documented as a concomitant medication in the electronic case report form.

One subject's COVID-19 vaccine was not reported. Subject # (b) (6) (in remdesivir treatment group) reported at Day 28 Visit on (b) (6) that he received his second dose of COVID-19 vaccine on (b) (6) during the study, which was documented in the source records. However, it was not documented in the electronic case report form.

Reviewer's comment: we recommend the review division consider including the unreported aspirin use and COVID-19 vaccine in the review.

The protocol was amended on January 14, 2021 (Amendment 4) to make administration of any SARS-CoV-2 (or COVID-19) vaccine an exclusion criterium. Therefore, Subject # (b) (6) should have been discontinued from the study according to Protocol Amendment 4.

{See appended electronic signature page}

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