CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214787Orig1s011

Trade Name:	Veklury
Generic or Proper Name:	remdesivir
Sponsor:	Gilead Sciences, Inc.
Approval Date:	April 25, 2022
Indication:	for the use of Veklury (remdesivir) for injection, for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients (28 days of age and older and weighing at least 3 kg to less than 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 214787/S-11

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 November 30, 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) for injection, for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients (28 days of age and older and weighing at least 3 kg to less than 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.

In addition, the Patient Information was updated with pediatric information.

The carton labeling and container label for Veklury (remdesivir) for injection, 100 mg/vial were revised to minimize the risk for medication error.

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 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).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214787/S-11**." Approval of this submission by FDA is not required before the labeling is used.

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

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

the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirement for ages 28 days and older and weighing at least 3 kg 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 SARS-CoV-2 substitutions identified as treatment-emergent or associated with reduced response to remdesivir treatment in Study GS-US-540-5823 that require additional evaluation for their potential to reduce SARS-CoV-2 susceptibility to remdesivir. 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 resistance to remdesivir.

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:

4265-1 Evaluate substitutions meeting the following criteria for their impact on remdesivir susceptibility of virus in cell culture, or, if virus is unable to be recovered, in a replicon assay or biochemical assay of RdRp activity:

Substitutions identified in replication complex subunits as treatment-emergent at a frequency of ≥15% of the virus population or are polymorphisms associated with viral RNA rebound in more than one subject, including different amino acid substitutions at the same position:
nsp9: N95D;
nsp10: D64Y, T101I;
nsp12: V495F, A656P, G670V, A656P+G670V;
nsp13: R248I, S259L, V266F;
nsp14: N129D.

The timetable you submitted on March 31, 2022 states that you will conduct this study according to the following schedule:

Study Completion:	02/2023
Final Report Submission:	03/2023

Submit 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 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.

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.*[3]

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.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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

REPORTING REQUIREMENTS

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

If you have any questions, contact Saebyeol Jang, PhD, RAC-US, 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
- Carton and Container Labeling for Veklury (remdesivir) for injection, 100 mg/vial

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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/

YODIT BELEW
04/25/2022 10:36:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s011

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)	04/2022
Dosage and Administration	
Dosage and Administration Overview (2.1)	04/2022
Recommended Dosage in Adults and Pediatric Patients 28 Days of Age and Older and Weighing at Least 3 kg (2.3)	04/2022
Dosage Preparation and Administration in Adults and Pediatric Patients Weighing At Least 40 kg (2.5)	04/2022
Dosage Preparation and Administration in Pediatric Patients 28 Days of Age and Older and Weighing 3 kg to Less Than 40 kg (2.6)	04/2022
Warnings and Precautions, Hypersensitivity Including Infusion-related and Anaphylactic Reactions (5.1)	01/2022

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

VEKLURY is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleotide analog RNA polymerase inhibitor indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct 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----------

- The only approved dosage form of VEKLURY for pediatric patients weighing 3 kg to less than 40 kg is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial). (2.1)
- 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:
  - Adults and pediatric patients 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. (2.3)
  - Pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg: a single loading dose of VEKLURY 5 mg/kg on Day 1 followed by once-daily maintenance doses of VEKLURY 2.5 mg/kg from Day 2 via intravenous infusion. (2.3)
- Hospitalized patients: 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)
- 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. (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).
- Renal impairment: VEKLURY is not recommended in patients with eGFR less than 30 mL/min. (2.4)
- Administer VEKLURY via intravenous (IV) infusion over 30 to 120 minutes. (2.5, 2.6)
- Dose preparation and administration: Refer to the full prescribing information for further details for both formulations. (2.5, 2.6)
- Storage of prepared dosages: VEKLURY contains no preservative. (2.7)

---------- 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: 04/2022

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 (28 days of age and older and weighing at least 3 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 Dosage and Administration (2.5, 2.6), Warnings and Precautions (5.1)]*.
- Administer VEKLURY for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 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 with 0.9% sodium chloride injection.
    - **The only approved dosage form of VEKLURY for pediatric patients weighing 3 kg to less than 40 kg is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial).**
  - VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial) must be further diluted in 250 mL of 0.9% sodium chloride injection 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, 2.6)].*

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 28 Days of Age and Older and Weighing at Least 3 kg

- The recommended dosage for adults and pediatric patients 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.
- The recommended dosage for pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg is a single loading dose of VEKLURY 5 mg/kg on Day 1 via intravenous infusion followed by once-daily maintenance doses of VEKLURY 2.5 mg/kg 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, 2.6) 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 (8.4, 8.6)].*

2.5 Dosage Preparation and Administration in Adults and Pediatric Patients Weighing at Least 40 kg

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 (2.7)].*

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 injection infusion bag. Refer to Table 1 for instructions.

Table 1 Recommended Dilution Instructions—Reconstituted VEKLURY for Injection Lyophilized Powder in Adults and Pediatric Patients Weighing at Least 40 kg

VEKLURY dose	0.9% sodium chloride injection infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride injection 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 injection 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 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 injection only. Refer to Table 3 for instructions.

Table 3 Recommended Dilution Instructions—VEKLURY Injection (Supplied as Solution in Vial) in Adults and Pediatric Patients Weighing at Least 40 kg

VEKLURY dose	0.9% sodium chloride injection infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride injection 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 injection 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 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 Dosage Preparation and Administration in Pediatric Patients 28 Days of Age and Older and Weighing 3 kg to Less Than 40 kg

The only approved dosage form of VEKLURY for pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial). Carefully follow the product-specific preparation instructions below.

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

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 (2.7)].*

Dilution Instructions

- For pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg, the 100 mg/20 mL (5 mg/mL) remdesivir reconstituted solution should be further diluted to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride injection.
- The final required infusion volume concentration of 1.25 mg/mL remdesivir diluted solution for infusion is based on the pediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride injection infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for pediatric dosing. The recommended dose is administered via

intravenous infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe and syringe pump may be used for infusion volumes less than 50 mL.

Infusion with IV Bag

- Determine the total infusion volume needed to achieve a final infusion volume concentration of 1.25 mg/mL of remdesivir diluted solution based on the patient's calculated dose.
- Select an appropriately sized infusion bag (either prefilled with 0.9% sodium chloride injection or empty) to prepare VEKLURY diluted solution.
- If using a prefilled 0.9% sodium chloride injection infusion bag, withdraw and discard the amount of diluent equal to the volume of reconstituted VEKLURY solution needed per patient's dose plus a quantity sufficient to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- Withdraw the required volume of reconstituted VEKLURY solution into an appropriately sized syringe.
- Transfer the required volume of reconstituted VEKLURY solution to the 0.9% sodium chloride injection infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- If using an empty infusion bag, transfer the required volume of reconstituted VEKLURY solution to the bag, followed by a volume of 0.9% sodium chloride injection sufficient to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- 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]).

Infusion with Syringe

- Determine the total infusion volume needed to achieve a final infusion volume concentration of 1.25 mg/mL of remdesivir diluted solution based on patient's calculated dose.
- Select an appropriately sized syringe equal to or larger than the calculated total infusion volume of 1.25 mg/mL remdesivir solution needed.
- Withdraw the required volume of reconstituted VEKLURY solution from the vial into the syringe based on patient's calculated dose, followed by the required volume of 0.9% sodium chloride injection needed to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- Gently invert the syringe 20 times to mix the solution in the syringe. Do not shake.
- The prepared diluted solution should be used immediately.

Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of VEKLURY with IV solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer VEKLURY via intravenous infusion over 30 to 120 minutes. The rate of infusion (mL/min) should be calculated based on the total infusion volume and total infusion time.

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)]*.

2.7 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.

Clinical Trials in Adult Subjects

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 Adults 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 in Adults from Clinical Trials

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

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.

Clinical Trials in Pediatric Subjects

Study GS-US-540-5823 was a Phase 2/3, single-arm, open-label clinical trial in hospitalized subjects 28 days of age and older and weighing at least 3 kg with mild, moderate, and severe COVID-19 treated with weight-based VEKLURY (n=53) for up to 10 days *[see Clinical Studies (14.6)]*:

- Subjects ≥12 years and weighing ≥40 kg (n=12) and subjects <12 years and weighing ≥40 kg (n=5): Received 200 mg on Day 1 and 100 mg once daily on subsequent days.
- Subjects ≥28 days and weighing ≥20 to <40 kg (n=12); subjects ≥28 days and weighing ≥12 to <20 kg (n=12); and subjects ≥28 days and weighing ≥3 to <12 kg (n=12): Received 5 mg/kg on Day 1 and 2.5 mg/kg once daily on subsequent days.

The adverse reactions observed were consistent with those observed in clinical trials of VEKLURY in adults. Adverse reactions (all grades) were reported in 8 (15%) subjects. The most common adverse reaction occurring in at least 5% of subjects was ALT increased (6%). No subjects experienced serious adverse reactions. Two (4%) subjects permanently discontinued treatment due to adverse

reactions (ALT increased [n=1], ALT increased and AST increased and hyperbilirubinemia [n=1]). Laboratory abnormalities (Grades 3-4) occurring in at least 3% of subjects with COVID-19 receiving VEKLURY in Trial 5823 and who had at least one post-baseline value for the specified test were hemoglobin decreased (18%, 9/51), eGFR decreased (18%, 7/40), creatinine increased (10%, 5/52), direct bilirubin increased (9%, 2/23), prothrombin time increased (7%, 3/46), APTT increased (7%, 3/45), lymphocytes decreased (6% 2/33), proteinuria (6%, 2/36), WBC decreased (4%, 2/51), ALT increased (4%, 2/51), glucose increased (4%, 2/52), glycosuria (4%, 2/46), potassium decreased (4%, 2/52).

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

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 28 days of age and older and weighing at least 3 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 supported by the following:

- trials in adults *[see Clinical Studies (14.1, 14.2, 14.3, 14.4, 14.5)]*
- an open-label trial (Study 5823) in 53 hospitalized pediatric subjects *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6)].*

Use of VEKLURY in pediatric patients 28 days of age and older and weighing at least 3 kg is supported by Study 5823 where 53 hospitalized pediatric subjects were treated with weight-based VEKLURY for up to 10 days in the following cohorts: subjects ≥12 years and weighing ≥40 kg (n=12); subjects <12 years and weighing ≥40 kg (n=5); subjects ≥28 days and weighing ≥20 to <40 kg (n=12); subjects ≥28 days and weighing ≥12 to <20 kg (n=12); and subjects ≥28 days and weighing ≥3 to <12 kg (n=12). The safety and pharmacokinetic results in pediatric subjects in this group were similar to those in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.6)].*

Use of VEKLURY in pediatric patients weighing at least 40 kg is further supported by a clinical trial of VEKLURY in non-hospitalized subjects that included 3 pediatric subjects 12 years and older, and by clinical trials in hospitalized subjects that 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 *[see Adverse Reactions (6.1) and Clinical Studies (14)].*

All pediatric patients 28 days of age and older and weighing at least 3 kg must have eGFR determined before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.2, 2.4), Adverse Reactions (6.1), Use in Specific Populations (8.6)].*

The safety and effectiveness of VEKLURY have not been established in pediatric patients younger than 28 days of age or weighing less than 3 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.

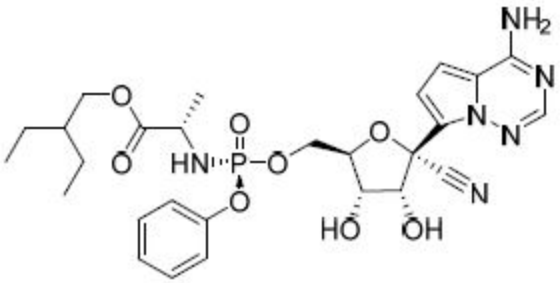
Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)].*

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 (2.5, 2.6)]*. 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, 2.6)]*. 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 adults with COVID-19 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 Adults with COVID-19

Parameter Mean[b] (95% CI)	Remdesivir	GS-441524	GS-704277
C_{max} (nanogram per mL)	2700 (2440, 2990)	143 (135, 152)	198 (180, 218)
AUC_{tau} (nanogram•h per mL)	1710 (1480, 1980)	2410 (2250, 2580)	392 (348, 442)
C_{trough} (nanogram per mL)	ND	61.5 (56.5, 66.8)	ND

CI=Confidence Interval; ND=Not detectable (at 24 hours post-dose)

a. Population PK estimates for 30-minute IV infusion of remdesivir for 3 days (Study GS-US-540-9012, n=147).

b. Geometric mean estimates.

Specific Populations

Pharmacokinetic differences based on sex, race, age, renal function, and hepatic function on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Sex and race did not affect the pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524).

Pediatric Patients

Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy subjects and in adult and pediatric patients with COVID-19, were used to estimate pharmacokinetic exposures in pediatric patients aged ≥28 days to <18 years and weighing ≥3 kg (Study 5823). Geometric mean estimated exposures (AUC_{tau}, C_{max}, and C_{tau}) for these patients at the doses administered were higher for remdesivir (33% to 129%), GS-441524 (0% to 60%), and GS-704277 (37% to 124%) as compared to those in adult patients with COVID-19; however, the increases were not considered clinically significant *[see Use in Specific Populations (8.4)].*

The multiple dose PK parameters of remdesivir and metabolites in pediatric patients with COVID-19 are provided in Table 14.

Table 14 Multiple Dose PK Parameters[a] of Remdesivir and Metabolites (GS-441524 and GS-704277) Following Intravenous Administration of VEKLURY 100 mg (Cohorts 1 and 8) or 2.5 mg/kg (Cohorts 2-4) to Pediatric Patients with COVID-19

Parameter Mean[b] (95% CI)	Cohort 1	Cohort 8	Cohort 2	Cohort 3	Cohort 4
	12 to <18 Years and Weighing ≥40 kg (N=12)	<12 Years and Weighing ≥40 kg (N=5)	28 Days to <18 Years and Weighing 20 to <40 kg (N=12)	28 Days to <18 Years and Weighing 12 to <20 kg (N=11)	28 Days to <18 Years and Weighing 3 to <12 kg (N=10)
Remdesivir					
C_{max} (nanogram per mL)	3910 (3140, 4870)	3920 (2270, 6790)	5680 (4660, 6930)	5530 (4240, 7210)	4900 (3790, 6340)
AUC_{tau} (nanogram•h per mL)	2470 (1940, 3150)	2280 (1200, 4300)	3500 (2570, 4780)	3910 (2140, 7160)	2930 (1900, 4520)
GS-441524					
C_{max} (nanogram per mL)	197 (123, 316)	162 (57.4, 458)	181 (132, 248)	158 (116, 215)	202 (171, 238)
AUC_{tau} (nanogram•h per mL)	3460 (2010, 5960)	2640 (772, 9030)	2870 (2020, 4080)	2400 (1740, 3320)	2770 (2230, 3450)
C_{tau} (nanogram per mL	98.3 (59.0, 164)	76.2 (24.0, 242)	73.8 (49.9, 109)	69.4 (48.1, 100)	78.4 (58.5, 105)
GS-704277					
C_{max} (nanogram per mL)	307 (212, 443)	278 (145, 532)	423 (309, 578)	444 (336, 585)	390 (305, 500)
AUC_{tau} (nanogram•h per mL)	815 (474, 1400)	537 (203, 1420)	754 (547, 1040)	734 (513, 1050)	691 (494, 966)

CI=Confidence Interval

a. Population PK estimates for 30-minutes IV infusion of remdesivir for up to 10 days (Study GS-US-540-5823).

b. Geometric mean estimates.

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

Cell Culture 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 virus yield reduction assay and/or N protein ELISA assay, remdesivir retained similar antiviral activity (<2.5-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), Gamma (P.1), Epsilon (B.1.429), Kappa (B.1.617.1), Lambda (C.37), Iota (B.1.526), and Zeta (P.2) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates. For the clinical isolates of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants, remdesivir maintained antiviral activity (<0.6-fold change).

Clinical Antiviral Activity

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

Cell Culture 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.

Treatment-Emergent Resistance

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 Description of Clinical Trials

The efficacy and safety of VEKLURY were evaluated in the trials summarized in Table 15.

Table 15 Trials Conducted with VEKLURY in Subjects with COVID-19

Trial	Population	Trial Arms (N)	Timepoint
NIAID ACTT-1[a] (NCT04280705)	Hospitalized with mild/moderate and severe COVID-19	VEKLURY 10 Days (532) Placebo (516)	29 Days after Randomization
GS-US-540-5773[b] (NCT04292899)	Hospitalized with severe COVID-19	VEKLURY 5 Days (200) VEKLURY 10 Days (197)	Day 14
GS-US-540-5774[b] (NCT04292730)	Hospitalized with moderate COVID-19	VEKLURY 5 Days (191) VEKLURY 10 Days (193) Standard of care (200)	Day 11
GS-US-540-9012[a] (NCT04501952)	Non-hospitalized with mild-to-moderate COVID-19 and at high risk for progression to severe disease	VEKLURY 3 Days (279) Placebo (283)	Day 28
GS-US-540-5823 (Cohorts 1-4, 8)[c] (NCT04431453)	Hospitalized pediatric subjects 28 days to <18 years of age and weighing at least 3 kg with COVID-19	VEKLURY up to 10 Days (53)	Day 10

COVID-19: coronavirus disease 2019

a. Randomized, double-blind, placebo-controlled trial.
b. Randomized, open-label trial.
c. Open-label trial, descriptive outcome analyses.

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

A randomized, double-blind, placebo-controlled clinical trial (ACTT-1) 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]).

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

A randomized, open-label multi-center clinical trial (Study 5773) 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.

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

A randomized, open-label multi-center clinical trial (Study 5774) 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.

14.5 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) 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.

14.6 Study GS-US-540-5823 in Hospitalized Pediatric Subjects with COVID-19

The primary objectives of this Phase 2/3 single-arm, open-label clinical study (Study GS-US-540-5823) were to evaluate pharmacokinetics and safety of up to 10 days of treatment with VEKLURY in pediatric subjects. A total of 53 pediatric subjects at least 28 days of age and weighing at least 3 kg with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19 was evaluated in five cohorts: subjects ≥12 years and weighing ≥40 kg (n=12); subjects <12 years and weighing ≥40 kg

(n=5); subjects ≥28 days and weighing ≥20 to <40 kg (n=12); subjects ≥28 days and weighing ≥12 to <20 kg (n=12); and subjects ≥28 days and weighing ≥3 to <12 kg (n=12). Subjects weighing ≥40 kg received 200 mg of VEKLURY on Day 1 followed by VEKLURY 100 mg once daily on subsequent days; subjects weighing ≥3 kg to <40 kg received VEKLURY 5 mg/kg on Day 1 followed by VEKLURY 2.5 mg/kg once daily on subsequent days. Assessments occurred at the following intervals: Screening; Day 1 (Baseline); Days 2-10, or until discharge, whichever came earlier; Follow-Up on Day 30 (±5). Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

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

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

Recovery (defined as an improvement from a baseline clinical status score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7) was reported for 62% of subjects on Day 10; median (Q1, Q3) time to recovery was 7 (5, 16) days.

Overall, 60% of subjects were discharged by Day 10, and 83% of subjects were discharged by Day 30. Three subjects (6%) died during the study.

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)]*.

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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 28 days of age and older and weighing at least 7 pounds (3 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 28 days of age or weighing less than 7 pounds (3 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:
  - o changes in your heart rate
  - o fever
  - o shortness of breath, wheezing
  - o swelling of the lips, face, or throat
  - o rash
  - o nausea
  - o sweating
  - o 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
VEKLURY is a trademark of Gilead Sciences, Inc., or its related companies. All other trademarks referenced herein are the property of their respec ive owners.
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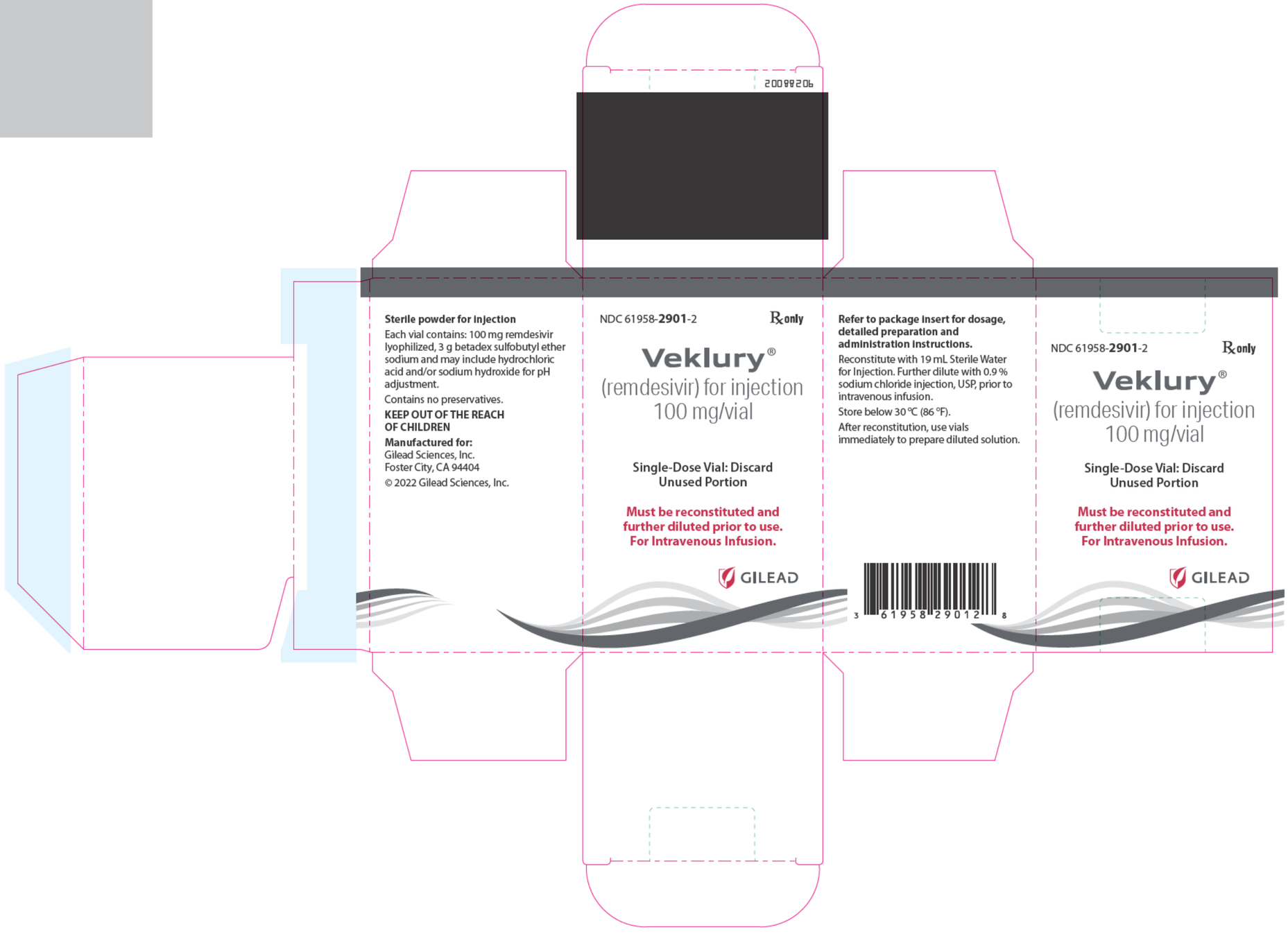
214787-GS-005
For more information, call 1-800-445-3235 or go to www.VEKLURY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 04/2022

(b) (4)



Reference ID: 4970886

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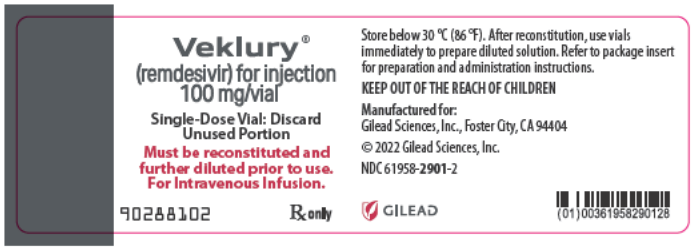
Veklury®
(remdesivir) for injection
100 mg/vial
Single-Dose Vial: Discard Unused Portion
Must be reconstituted and further diluted prior to use. For Intravenous Infusion.
90288102
℞only
GILEAD
(01)00361958290128
Store below 30 °C (86 °F). After reconstitution, use vials immediately to prepare diluted solution. Refer to package insert for preparation and administration instructions.
KEEP OUT OF THE REACH OF CHILDREN
Manufactured for:
Gilead Sciences, Inc., Foster City, CA 94404
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NDC 61958-2901-2

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s011

OFFICER/EMPLOYEE LIST

MEMORANDUM

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

DATE: April 21, 2022

TO: Administrative file for NDA 214787, Supplement 11

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

SUBJECT: Officer/Employee List for NDA 214787, Supplement 11

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
Cho, Seongeun
Diak, Ida-Lina
Donaldson, Eric
Griffiths, LaShawn
Ince, William
Jang, Saebyeol
Javidnia, Monica
Kapoor, Rachna
Kolejian, Sevan
Lewin, Amanda
Lewis, David
McCartan, Kate
Mills, Sharon
Min, Stacey
Mishra, Poonam
O'Rear, Julian
Ossareh, Nima
Redwood, Susan

Sampson, Mario
Struble, Kimberly
Thakur, Rishi
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/s/

SAEBYEOL JANG
04/21/2022 05:42:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s011

MULTI-DISCIPLINE REVIEW

Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology, and Division Director Review

Application Type	Supplemental New Drug Application (sNDA), S-11
Application Number(s)	214787
Priority or Standard	Priority
Submit Date(s)	November 30, 2021
Received Date(s)	November 30, 2021
PDUFA Goal Date	May 30, 2022
Division/Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)	Division of Antivirals Yodit Belew, MD, Deputy Director (Acting) Kimberly Struble, PharmD, CDTL Kirk Chan-Tack, MD, Medical Officer Division of Infectious Disease Pharmacology /Office of Clinical Pharmacology/Office of Translational Sciences Mario Sampson, PharmD, Clinical Pharmacology Reviewer Justin Earp, PhD, Pharmacometrics Reviewer Vikram Arya, PhD, Associate Director for Therapeutic Review
Review Completion Date	April 11, 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 5 mg/kg on Day 1, followed by once-daily maintenance doses of RDV 2.5 mg/kg from Day 2 via IV infusion. The treatment duration depends upon the patient population, is unchanged from the currently approved label: • The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation (IMV) and/or extracorporeal membrane oxygenation (ECMO) is 10 days. • The recommended treatment duration for hospitalized patients not requiring IMV 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. • 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.

Applicant Proposed Indication(s)/Population(s)	Treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 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
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 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. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Remdesivir (RDV) is an intravenous (IV) antiviral drug approved 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.

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, 485,243,022 confirmed cases of COVID-19 have been reported, including 6,137,553 deaths as of March 30, 2022. In the United States, according to the Centers for Disease Control and Prevention, 79,904,464 confirmed cases of COVID-19 have been reported, including 977,495 deaths as of March 30, 2022. RDV is currently the only approved treatment for COVID-19.

In this supplemental new drug application (sNDA), the Applicant's proposed indication is treatment of adults and pediatric patients (28 days and older and weighing at least 3 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.

The Applicant's proposed expansion of the population to include pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg is based on the results from the completed cohorts of GS-US-540-5823, an ongoing Phase 2/3, single-arm, open-label study to investigate the safety, tolerability, pharmacokinetics (PK), and efficacy of RDV in pediatric subjects birth to < 18 years of age who are hospitalized with laboratory-confirmed COVID-19.

The Division of Antivirals (DAV) has determined that adult and pediatric populations with mild, moderate, or severe COVID-19 generally

display similar symptoms, and virologic response to an antiviral drug, such as RDV, is expected to be similar in adult and pediatric patients. These determinations allow extrapolation of efficacy from the adult clinical trials to pediatric patients if they achieve similar drug exposures. Therefore, efficacy in pediatric patients will be supported by: extrapolation of efficacy from the adult trials (three randomized clinical trials [RCTs] in hospitalized subjects [reviewed under the original NDA; action date October 22, 2020]; one RCT in non-hospitalized adult and adolescent subjects [reviewed under sNDA-10; action date January 21, 2022]) that evaluated the efficacy of RDV; and the pharmacokinetic/pharmacodynamic and safety data from pediatric patients.

Pediatric exposures in GS-US-540-5823 were within the range of exposures observed in adults.

The overall safety profile in the GS-US-540-5823 pediatric population is consistent with the known safety profile of RDV.

The overall benefit-risk profile of RDV is favorable to support extending the indicated population to include pediatric patients 28 days and older and weighing at least 3 kg to less than 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.

In pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg, the recommended dosage is a single loading dose of RDV 5 mg/kg on Day 1 via IV infusion followed by once-daily maintenance doses of RDV 2.5 mg/kg from Day 2 via IV infusion. The treatment duration depends upon the patient population, is unchanged from the currently approved label, and is summarized below:

<u>Hospitalized patients:</u>
The treatment course of RDV 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 (IMV) and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
• The recommended treatment duration for hospitalized patients not requiring IMV 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.

<u>Non-hospitalized patients:</u>
The treatment course of RDV 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.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Analysis of Condition</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, 485,243,022 confirmed cases of COVID-19 have been reported as of March 30, 2022, including 79,904,464 people in the United States (US).
• Globally, 6,137,553 deaths due to COVID-19 have been reported as of March 30, 2022, including 977,495 deaths in the US.</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>Current Treatment Options</td><td>• RDV is currently the only approved treatment for COVID-19. The current RDV approval encompasses pediatric patients 12 years of age and older and weighing at least 40 kg.
• The following products are authorized for emergency use for the treatment of COVID-19 in the following hospitalized patient populations:
<table>
<tr><th>Hospitalized Patient Population</th><th>EUA</th></tr>
<tr><td>Pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age and weighing at least 3.5 kg with positive results of direct SARS-CoV-2 viral testing and who are hospitalized</td><td>Remdesivir</td></tr>
<tr><td>Hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)</td><td>Baricitinib</td></tr>
<tr><td>Adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO</td><td>Tocilizumab</td></tr>
</table>
• The following products are authorized for emergency use for the treatment of mild-to moderate COVID-19 in the following nonhospitalized patient populations:</td><td>An unmet medical need exists for effective antiviral regimens for pediatric patients with COVID-19, including younger ages/lower weights.</td></tr>
</table>

Dimension	Evidence and Uncertainties		Conclusions and Reasons
	Nonhospitalized Patient Population	**EUA**	
	Pediatric patients weighing 3.5 kg to less than 40 kg ***or*** pediatric patients less than 12 years of age and weighing at least 3.5 kg with positive results of direct SARS-CoV-2 viral testing and 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.	Remdesivir	
	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 Sotrovimab‡ Casirivimab and imdevimab*	
	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	Bamlanivimab and etesevimab*	
	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 approved or authorized by FDA are not accessible or clinically appropriate	Molnupiravir	
	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, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate	Bebtelovimab	
	*Not susceptible against the Omicron B.1.1.529 variant. On January 24, 2022, FDA issued a statement that, due to the high frequency of the Omicron variant, the following products are not currently authorized in any US region: casirivimab and imdevimab bamlanivimab and etesevimab. ‡Substantially decreased in vitro activity against the Omicron BA.2 subvariant. On April 5, 2022, FDA issued a statement that sotrovimab is no longer authorized to treat COVID-19 in any U.S. region due to increases in the proportion of COVID-19 cases caused by		

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the Omicron BA.2 sub-variant. • Due to the mortality and severe morbidity associated with COVID-19, there is an urgent need to develop effective treatments.	
Benefit	• The efficacy of RDV was assessed in three Phase 3 clinical trials in hospitalized patients and one Phase 3 clinical trial in non-hospitalized patients who are at high risk for progression to severe COVID-19, including hospitalization or death. • Despite the inherent limitations of its small sample size and single-arm, open-label design, GS-US-540-5823 provided supportive evidence for the efficacy of RDV in pediatric patients hospitalized with COVID-19. A total of 32 subjects (60%) were discharged alive by Day 10, and a total of 44 subjects (83%) were discharged alive by Day 30. Three subjects (6%) died during the study.	Based on the totality of the data, including extrapolation of efficacy from the four Phase 3 clinical trials in the approved label, and the pharmacokinetic/pharmacodynamic and safety data from GS-US-540-5823, it is reasonable to extend the indication to include the pediatric population 28 days and older and weighing at least 3 kg to less than 40 kg, with positive results of direct 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. RDV fills an important unmet medical need for pediatric patients with COVID-19, including 28 days and older and weighing at least 3 kg to less than 40 kg.
Risk	• No major safety issues were encountered during this review. • ALT increased (6%) was the most commonly reported adverse drug reaction (ADR) reported in GS-US-540-5823. All other ADRs occurred in less than 5% of subjects.	The overall safety profile in the GS-US-540-5823 pediatric population is consistent with the known safety profile of RDV as observed from adult and adolescent subjects in the hospitalized and non-hospitalized Phase 3 clinical trials.
Risk Management	• No significant safety signals were identified in this trial conducted in pediatric patients.	Safety concerns associated with RDV are adequately addressed in product labeling.

2. Background

COVID-19 can result in pneumonia, respiratory failure, multi-organ failure, and death. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic.[1] Globally, according to the WHO, as of March 30, 2022, 485,243,022 confirmed cases of COVID-19 have been reported, including 6,137,553 deaths. In the US, according to the Centers for Disease Control and Prevention (CDC), as of March 30, 2022, 79,904,464 confirmed cases of COVID-19 have been reported, including 977,495 deaths.[2]

The predominant signs and symptoms of COVID-19 include fever, cough, and shortness of breath. Clinical severity ranges widely, from asymptomatic infection to critical illness. 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, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation (IMV), or extra-corporeal membrane oxygenation (ECMO). Risk factors for hospitalization include, but are not limited to, age > 65 years, hypertension, obesity, diabetes, cardiovascular disease, and chronic lung disease.[3]

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

RDV, a direct acting antiviral drug that inhibits viral RNA synthesis, is currently the only approved antiviral treatment regimen for COVID-19 caused by SARS-CoV-2 virus. 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. The original NDA approval was based on efficacy and safety data from three Phase 3 randomized clinical trials in hospitalized adult subjects with COVID-19 treated with 5-10 days of RDV. The initial indication included patients 12 years of age and older and weighing at least 40 kg. The inclusion of this pediatric sub-population in the indication was supported by the following: 1) the systemic exposure and clearance of drugs are generally similar in adolescent

[1] World Health Organization -- Coronavirus disease (COVID-19) pandemic – https://covid19.who.int/. Accessed on March 30, 2022.
[2] CDC – Cases and Deaths in the U.S. -- https://covid.cdc.gov/covid-data-tracker/. Accessed on March 30, 2022.
[3] COVID-NET: COVID-19-Associated Hospitalization Surveillance Network, CDC. https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html. Accessed on March 30, 2022.
[4] Feldstein, L.R., Rose, E.B, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *NEJM*. June 29, 2020. DOI: 10.1056/NEJMoa2021680.
[5] CDC – Information for Pediatric Healthcare Providers – https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html. Accessed on March 30, 2022.

and adult patients after accounting for the effect of body size on pharmacokinetics;[6] 2) using physiologically-based pharmacokinetic (PBPK) modeling and population pharmacokinetic (popPK) modeling, the to-be-marketed dosing regimen was expected to result in comparable steady-state plasma exposures of RDV and metabolites in patients 12 years of age and older and weighing at least 40 kg as observed in healthy adults; 3) the safety profile in adult subjects weighing 40-50 kg in clinical trials was comparable to adult subjects weighing greater than 50 kg and; 4) Thirty-nine pediatric patients 12 years and older and weighing at least 40 kg received RDV in a compassionate use program; however, the available clinical data from these patients were limited. Importantly, confirmatory PK and safety information would be collected in patients 12 to 17 years of age in the ongoing RDV pediatric trial.

On January 21, 2022, the indication was expanded to include treatment of COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct 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. The outpatient sNDA approval was based on efficacy and safety data from a Phase 3 randomized, double-blind, placebo-controlled clinical trial evaluating 3 days of RDV in non-hospitalized adults and adolescents with mild-to-moderate COVID-19 who are at high risk of progression to severe COVID-19, including hospitalization or death.[7] The inclusion of this pediatric sub-population (12 years of age and older and weighing at least 40 kg) in the non-hospitalized indication is based on extrapolation of pediatric efficacy from the aforementioned adequate and well-controlled study.

In this supplemental new drug application (sNDA), the Applicant's proposes to expand the indication to encompass treatment of pediatric patients (28 days and older and weighing at least 3 kg to less than 40 kg) with positive results of direct 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.

There are currently no approved therapies for treatment of COVID-19 in pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg. RDV would provide an approved antiviral drug to address this unmet medical need.

This review will summarize and focus only on the notable events which directly impacted the current RDV supplemental NDA (sNDA).

3. Product Quality

Changes to the commercial product were not made in this sNDA. Please refer to the Office of Product Quality (OPQ) reviews of the original NDA for further details on manufacturing

[6] Momper JD, Mulugeta Y, Green DJ, et al. Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. *JAMA Pediatr*. 2013;167(10):926-932. doi:10.1001/jamapediatrics.2013.465
[7] Veklury® [package insert]. Foster City, CA: Gilead Sciences, Inc.; 2022 – https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214787s013lbl.pdf.

processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for RDV.

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.

5. Clinical Pharmacology

Background

Study GS-US-540-5823 (study 5823) evaluated the pharmacokinetics (PK), safety, and efficacy of RDV in pediatric subjects. The interim CSR (dated October 4, 2021) in this submission contains data for Cohorts 1-4 and 8, i.e., pediatric subjects ≥ 28 days of age and weighing ≥ 3 kg. The inspection of clinical sites was favorable (NDA 214787, ORA review dated February 15, 2022). The bioanalytical site was not inspected due to a recent favorable inspection (NDA 214787, OSIS review dated January 19, 2022).

The Clinical Pharmacology review focused on a comparison of exposures in pediatrics vs adults. As described in the section below (Exposure comparison in pediatric subjects vs adults), pediatric exposures were within the range of adult exposures. The Clinical Pharmacology review team supports approval of the studied pediatric dosing regimen for pediatric subjects ≥28 days of age and weighing ≥3 kg.

Exposure comparison in pediatric subjects vs adults

The Applicant conducted two PK comparisons. First, a comparison of exposures from enrolled pediatric subjects vs enrolled adults. Second, a comparison of simulated exposures in a virtual pediatric population to a virtual adult population.

Exposure comparison in pediatric subjects vs adults: enrolled subjects

The Applicant's initial analysis used an adult reference consisting of study 540-9012 (study 9012) in adult outpatients with COVID-19 and study REMDACTA (also known as WA42511) in hospitalized adults with COVID-19. As the CSR has not been submitted for REMDACTA, we requested the Applicant to repeat the analysis using an adult reference consisting of study 9012 only.

Geometric mean exposures of RDV and its metabolites were generally higher in pediatric subjects vs adults (33-129% for RDV, 0-60% for GS-441524, 37-124% for GS-704277) (calculated from geometric mean values in Table 1). However, the distribution of RDV and metabolite exposures in pediatric subjects were within the range observed in adults (AUC shown

Reference ID: 4971782

in Figure 1, Figure 2, and Figure 3; the conclusions are the same for Cmax and Ctau; see NDA 214787 SDN 268).

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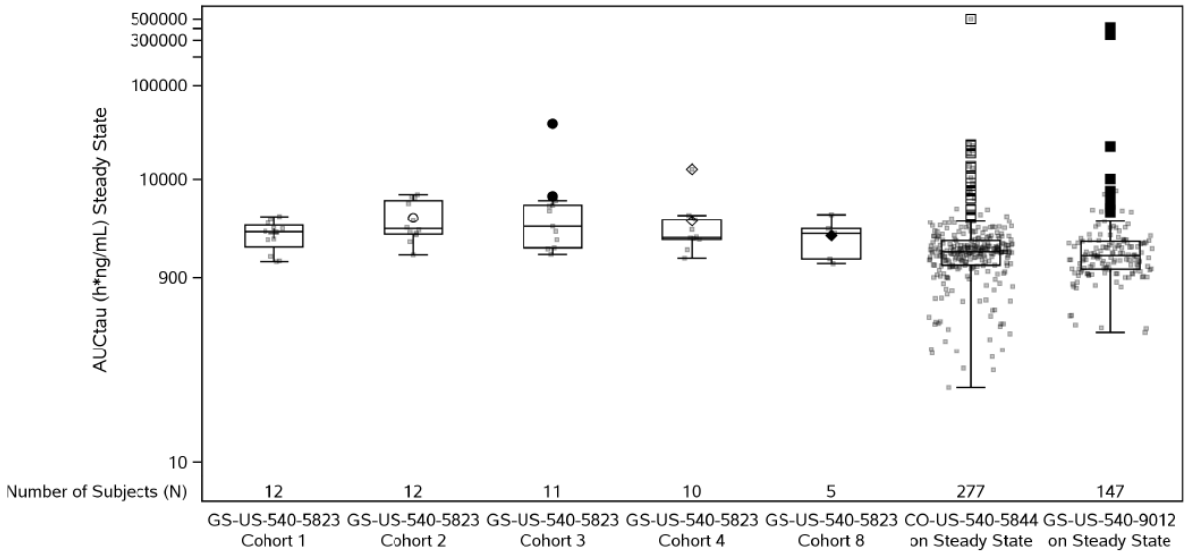
Table 1. RDV and metabolite exposures in enrolled pediatric subjects (study 5823) and adults (study 9012)

Geometric Mean (95% CI)	Cohort 1 12-<18 Years and ≥40 kg (N=12)	Cohort 8 <12 Years and ≥40 kg (N=5)	Cohort 2 28 Days-<18 Years and 20-<40 kg (N=12)	Cohort 3 28 Days-<18 Years and 12-<20 kg (N=11)	Cohort 4 28 Days-<18 Years and 3-<12 kg (N=10)	Adults (n=147)
Remdesivir						
C_{max} (ng/mL)	3910 (3140, 4870)	3920 (2270, 6790)	5680 (4660, 6930)	5530 (4240, 7210)	4900 (3790, 6340)	2700 (2440, 2990)
AUC_{tau} ng*h/mL)	2470 (1940, 3150)	2280 (1200, 4300)	3500 (2570, 4780)	3910 (2140, 7160)	2930 (1900, 4520)	1710 (1480, 1980)
GS-441524						
C_{max} (ng/mL)	197 (123, 316)	162 (57.4, 458)	181 (132, 248)	158 (116, 215)	202 (171, 238)	143 (135, 152)
AUC_{tau} ng*h/mL)	3460 (2010, 5960)	2640 (772, 9030)	2870 (2020, 4080)	2400 (1740, 3320)	2770 (2230, 3450)	2410 (2250, 2580)
C_{tau} (ng/mL)	98.3 (59.0, 164)	76.2 (24.0, 242)	73.8 (49.9, 109)	69.4 (48.1, 100)	78.4 (58.5, 105)	61.5 (56.5, 66.8)
GS-704277						
C_{max} (ng/mL)	307 (212, 443)	278 (145, 532)	423 (309, 578)	444 (336, 585)	390 (305, 500)	198 (180, 218)
AUC_{tau} ng*h/mL)	815 (474, 1400)	537 (203, 1420)	754 (547, 1040)	734 (513, 1050)	691 (494, 966)	392 (348, 442)

(b) (4) CI=Confidence Interval; ND=Not detectable (at 24 hours post-dose). Study 5823: Population PK estimates for 30-minutes IV infusion of remdesivir 100 mg (Cohort 1 and 8) or 2.5 mg/kg (Cohort 2-4) for up to 10 days. Study 9012: Population PK estimates for 30-minute IV infusion of remdesivir 100 mg for 3 days.

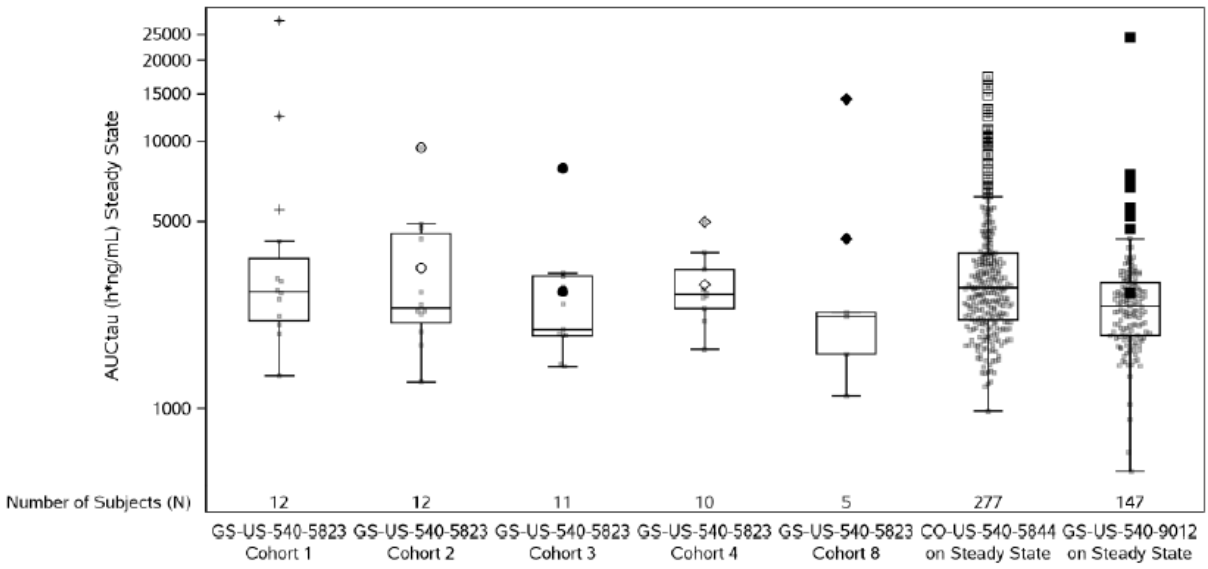
Figure 1. RDV AUC in enrolled pediatric subjects (study 5823) and adults (study 9012)



COVID-19 = coronavirus disease 2019; IV = intravenous PK = pharmacokinetic(s); RDV = remdesivir; TCZ = tocilizumab
Lines are medians and interquartile ranges; dots are individual values.
In Study GS-US-540-5823, participants assigned to Cohort 1 (≥ 12 to < 18 years, weight ≥ 40 kg) received 200 mg RDV on the first day (loading dose) followed by 100 mg daily for up to 10 days. Cohorts 2 to 4 (weight 3 to < 40 kg) received RDV 5 mg/kg on the first day (loading dose) followed by RDV 2.5 mg/kg daily for up to 10 days (steady state). Participants in Cohort 8 (< 12 years, weight ≥ 40 kg) received RDV 200 mg on the first day (loading dose) followed by 100 mg daily for up to 10 days (steady state).
In Study CO-US-540-5844, participants assigned to RDV + placebo received a 200-mg IV RDV loading dose and placebo infusion on Day 1 followed by 100 mg RDV on Days 2-10 (steady state). Participants in Study CO-US-540-5844 assigned to RDV + TCZ received a 200-mg IV RDV loading dose and a TCZ 8-mg/kg infusion on Day 1 followed by 100 mg RDV on Days 2-10 (steady state).

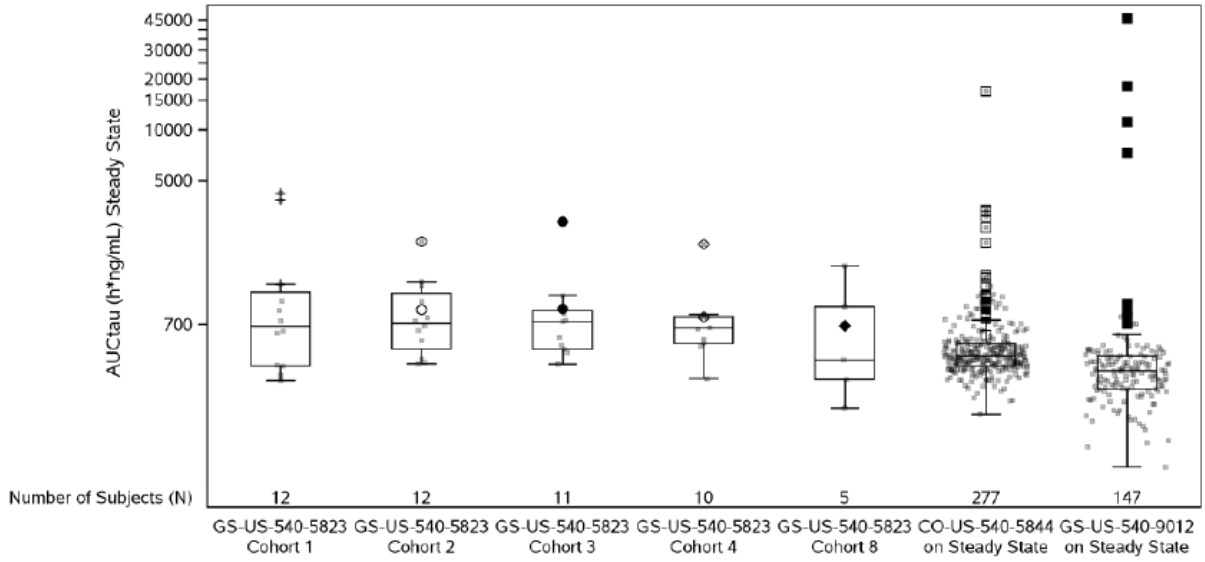
Source: Clinical Pharmacology Summary, p18. Note adult study 5844 was not included in the FDA analysis; however, is included in Figures 1-3 as provided by the Applicant.

Figure 2. GS-441524 AUC in enrolled pediatric subjects (study 5823) and adults (study 9012)



Source: Clinical Pharmacology Summary, p20. Abbreviations and dosing are as described in the footnote to Figure 1. Note adult study 5844 was not included in our analysis.

Figure 3. GS-704277 AUC in enrolled pediatric subjects (study 5823) and adults (study 9012)



Source: Clinical Pharmacology Summary, p19. Abbreviations and dosing are as described in the footnote to Figure 1. Note adult study 5844 was not included in our analysis.

Exposure comparison in pediatric subjects vs adults: virtual population

Due to uncertainty associated with individual subject exposures estimated for enrolled subjects using population PK modeling (later resolved; described in more detail in section Population PK models), the Applicant also compared exposures in pediatric subjects vs adults using virtual populations. Virtual pediatric subjects were generated by sampling age and body weight from CDC growth charts. Virtual adults were generated by sampling age and body weight from study 9012. A total of 1000 subjects per pediatric cohort and 1000 adults were generated. Observations were the same as for enrolled subjects, namely higher geometric mean exposures in pediatric subjects vs adults, with the range of exposures in pediatric subjects being within the range in adults (Table 2; box plots on p10-16 in NDA 214787 SDN 247).

Table 2. Statistical comparison of RDV and metabolite exposures in a virtual population of hospitalized pediatric subjects and a virtual population of hospitalized adults

Analyte/ PK Parameter	Cohort 1 Age 12 to < 18 Years and Weight ≥ 40 kg (N=1000)	Cohort 2 Age 28 Days to < 18 Years and Weight 20 to < 40 kg (N=1000)	Cohort 3 Age 28 Days to < 18 Years and Weight 12 to < 20 kg (N=1000)	Cohort 4 Age 28 Days to < 18 Years and Weight 3 to < 12 kg (N=1000)	Cohort 8 Age < 12 years and Weight ≥ 40 kg (N=1000)
	%GMR (90% CI)				
RDV					
AUC_{tau} (h•ng/mL)	145.65 (134.99, 157.15)	171.34 (158.8, 184.88)	157.19 (145.69, 169.61)	188.63 (174.83, 203.53)	148.91 (138.01, 160.68)
C_{max} (ng/mL)	189.47 (178.22, 201.44)	227.76 (214.23, 242.15)	210.90 (198.37, 224.22)	241.01 (226.69, 256.23)	195.93 (184.29, 208.3)
GS-704277					
AUC_{tau} (h•ng/mL)	205.79 (191.11, 221.61)	247.52 (229.86, 266.54)	236.95 (220.04, 255.15)	266.28 (247.28, 286.74)	221.96 (206.12, 239.01)
C_{max} (ng/mL)	215.16 (200.37, 231.01)	282.73 (263.31, 303.57)	280.00 (260.77, 300.64)	281.09 (261.78, 301.81)	220.05 (204.94, 236.28)
GS-441524					
AUC_{tau} (h•ng/mL)	159.22 (149.48, 169.6)	183.98 (172.72, 195.97)	164.59 (154.52, 175.31)	141.65 (132.98, 150.88)	164.74 (154.66, 175.48)
C_{max} (ng/mL)	150.16 (142.56, 158.17)	184.23 (174.9, 194.06)	170.67 (162.04, 179.78)	147.45 (139.99, 155.32)	154.93 (147.09, 163.2)
C_{tau} (ng/mL)	189.39 (176.59, 203.15)	222.55 (207.5, 238.71)	204.60 (190.76, 219.45)	180.33 (168.14, 193.43)	196.43 (183.14, 210.7)

% GMR = % geometric mean ratio; AUC = area under the concentration-versus-time curve over the dosing interval (AUC_{tau}); CI = confidence interval; C_{max} = maximum observed concentration; C_{tau} = observed drug concentration at the end of the dosing interval; max = maximum; min minimum; PK = pharmacokinetic; RDV = remdesivir; SD = standard deviation.
Reference are virtual adults representing the population of Study GS-US-540-9012.

PK parameters from the GS-US-540-5823 study were simulated using population PK modeling with 0.5 hour of duration for RDV infusions. GS-US-540-5823 Cohort 1 (≥ 12 to < 18 years, weight ≥ 40 kg) received 200 mg RDV on first day followed by 100 mg daily for 4 days (steady state). Cohorts 2 to 4 (weight 3 to < 40 kg) received 5 mg/kg on first day followed by 2.5 mg/kg daily for 4 days (steady state). Cohort 8 (< 12 years, weight ≥ 40 kg) received 200 mg on first day followed by 100 mg daily for 4 days (steady state).
Source: Exposure-Summary.html

Source: NDA 214787 SDN 247, p17.

Study GS-US-540-5823 summary

Methods

Ongoing study 5823 is enrolling hospitalized pediatric subjects with SARS-CoV-2 infection (Table 3). The interim CSR submitted in this application contains data for Cohorts 1-4 and 8.

Table 3. Cohort age and weight definitions and dosing for study 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[a]
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[a]
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[b]	4	≥ 14 days to < 28 days of age, gestational age > 37 weeks and weight at Screening ≥ 2.5 kg	
6[b]	d, e	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[a]
7[c]	d, e	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[a]
8	5[e]	< 12 years and weight ≥ 40 kg	200 mg IV on Day 1 followed by 100 mg IV QD for up to 10 days[a]

[a]Treatment with RDV was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.
[b]Cohorts 5 and 6 will enroll term neonates.
[c]Cohort 7 will enroll preterm neonates and infants.
[d]Subjects in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined.
[e]No minimum number; TBD, to be determined.
Exploratory cohort 8 was added in the September 22, 2020 protocol amendment

In Cohorts 1-4 and 8, PK samples were to be collected at timepoints below from each participant if feasible:

- Day 2: end of infusion (± 15 minutes) and 4 hours (±30 minutes) post end of infusion
- Day 3: pre-infusion (≤ 60 minutes) and 2 hours (± 15 minutes) post end of infusion
- Day 5: middle of infusion and 6 hours (± 60 minutes) post end of infusion (optional)

Prohibited concomitant medications included unapproved COVID-19 treatments with direct antiviral effect such as LPV/RTV, chloroquine, interferon, etc. in addition to P-gp inducers (e.g. rifampin, rifabutin, carbamazepine, phenytoin or herbal medications).

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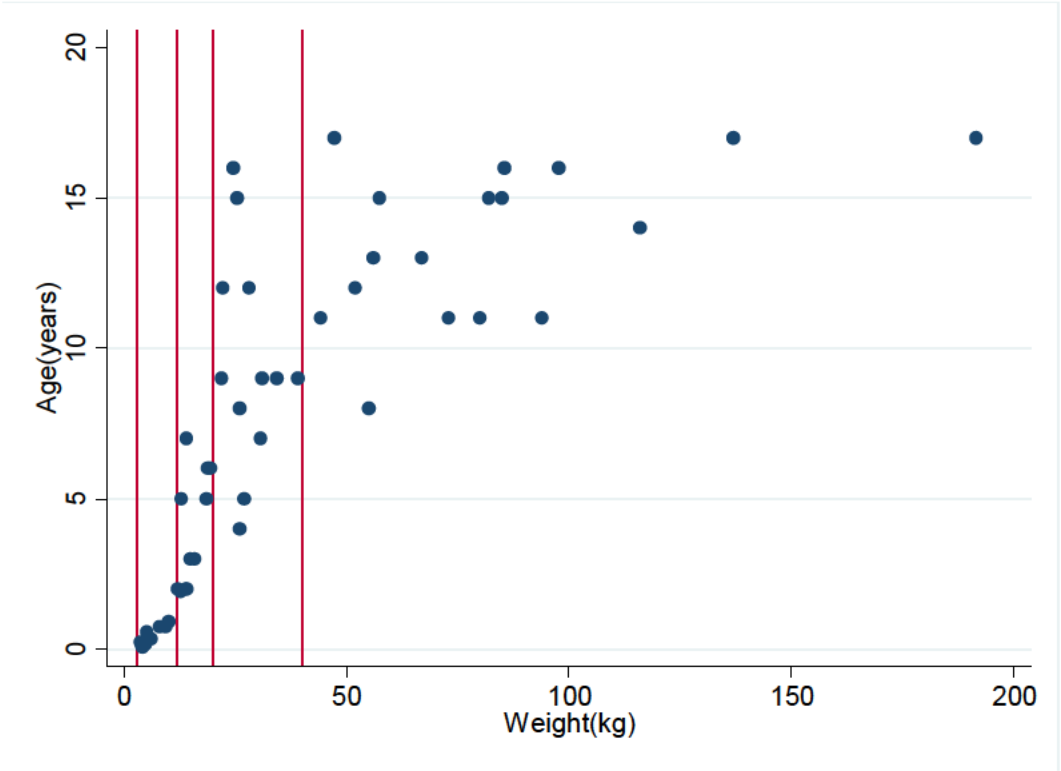
Results

Concentrations of RDV (calibration curve: 4-4000 ng/mL), GS-441524 (2-2000 ng/mL), and GS-704277 (2-2000 ng/mL) were measured in human plasma using validated LC/MS-MS method 60-15117 (study sample analysis report). Most validation and study sample analysis runs were acceptable with calibration curve, QC sample, and incurred sample reanalysis assessments meeting acceptance criteria. Study samples were analyzed within the documented duration of stability. No significant protocol deviations were reported.

A total of 50 pediatric subjects with at least one PK sample with a detectable concentration of RDV and/or metabolites were enrolled in study 5823. Enrollment was approximately continuous within the 3-<12 kg (Cohort 4), 12-<20 kg (Cohort 3), 20-<40 kg (Cohort 2), and ≥40 kg (Cohorts 1 and 8) weight ranges (Figure 4).

Figure 4. Baseline age vs weight among pediatric subjects in study 5823 with at least one PK sample with a detectable concentration

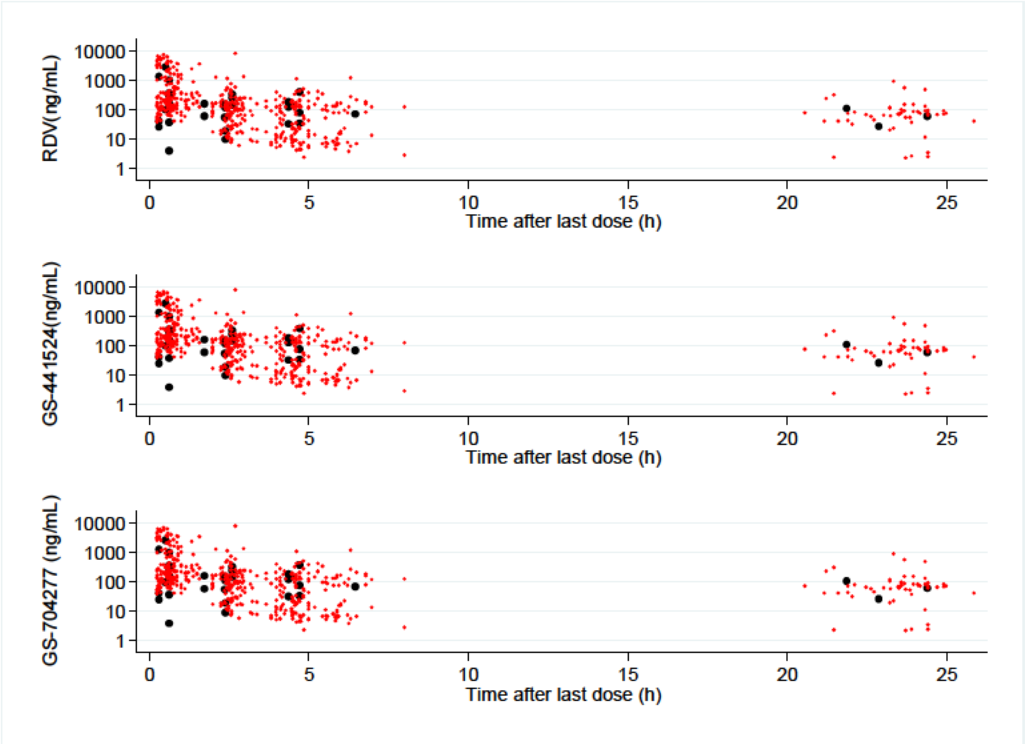


Source: Plotted by reviewer from Applicant's pharmacokinetic concentration (pc), demographic (dm), and vital signs (vs) datasets. Red lines = weight limits separating cohorts, i.e. 3, 12, 20, and 40 kg.

Use of prohibited concomitant medications included phenobarbital (n=3, all in cohort 2), hydroxychloroquine (n=1) and ganciclovir (n=1) (CSR, Table 15.8.5.1.1). Of these, only phenobarbital is expected to potentially affect RDV exposures. However, RDV and metabolite exposures did not differ by concomitant phenobarbital use (Figure 5).

Reference ID: 4971782

Figure 5. RDV and metabolite concentration-time profiles in study 5823 by reported phenobarbital use



Source: Plotted by reviewer from concomitant medication (cm) and population PK datasets (RDV, GS-441524, GS-704277). Black dots = concomitant phenobarbital; red dots = no concomitant phenobarbital.

RDV and metabolite exposures are tabulated by cohort in Table 1.

Population PK models

Population PK models of RDV, GS-441524, and GS-704277 were initially developed using PK data from three intensive PK studies in healthy adults (studies 399-1812, 399-1954, and 399-5505) (RDV new NDA popPK report). Plasma concentrations were described following a sequential modeling approach by 2-compartment models for RDV and GS-704277, and a 3-compartment model for GS-441524 with first-order elimination (Table 4). No covariates were identified. At the time of the RDV original NDA, FDA assessed the popPK models to be acceptable for the purpose of predicting exposures in pediatric patients ≥12 years of age and weighing ≥40 kg (NDA 214787, Clinical Pharmacology review dated September 18, 2020).

Table 4. Initial popPK model parameters

Parameter - Model	Parameter Description	Population Estimate [RSE%]
θ_1 - RDV	Clearance RDV (L/h)	48.2 [2%]
θ_2 - RDV	Central volume RDV (L)	6.34 [3%]
θ_3 - RDV	Peripheral volume RDV (L)	6 [4%]
θ_4 - RDV	Intercompartment clearance RDV (L/h)	5.04 [4%]
θ_1 - GS-704277	Clearance GS-704277 (L/h)	210 [3%]
θ_2 - GS-704277	Central volume GS-704277 (L)	242 [3%]
θ_3 - GS-704277	Peripheral volume GS-704277 (L)	46 [6%]
θ_4 - GS-704277	Intercompartment clearance GS-704277 (L/h)	20.5 [9%]
θ_1 - GS-441524	Clearance GS-441524 (L/h)	17.6 [2%]
θ_2 - GS-441524	Central volume GS-441524 (L)	104 [5%]
θ_3 - GS-441524	First peripheral volume GS-441524 (L)	236 [5%]
θ_4 - GS-441524	Intercompartment clearance to first periph. cmt. GS-441524 (L/h)	379 [6%]
θ_9 - GS-441524	Second peripheral volume GS-441524 (L)	233 [4%]
θ_{10} - GS-441524	Intercompartment clearance to second periph. cmt. GS-441524 (L/h)	31.6 [6%]
ω^2_{11} - RDV	IIV on CL-RDV (%CV)	15% [28%]
ω^2_{22} - RDV	IIV of Vc-RDV (%CV)	32% [69%]

Parameter - Model	Parameter Description	Population Estimate [RSE%]
ω^2_{33} - RDV	IIV of Vp-RDV (%CV)	15% [31%]
ω^2_{11} - GS-704277	IIV on CL-GS-704277 (%CV)	32% [18%]
ω^2_{21} - GS-704277	Correlation CL/Vc GS-704277	0.113 [17%]
ω^2_{22} - GS-704277	IIV of Vc-GS-704277 (%CV)	39% [17%]
ω^2_{33} - GS-704277	IIV of Vp-GS-704277 (%CV)	26% [28%]
ω^2_{11} - GS-441524	IIV on CL-GS-441524 (%CV)	24% [20%]
ω^2_{21} - GS-441524	Correlation CL/Vc GS-441524	0.0527 [36%]
ω^2_{31} - GS-441524	Correlation CL/Vp1 GS-441524	0.0872 [20%]
ω^2_{22} - GS-441524	IIV of Vc-GS-441524 (%CV)	45% [19%]
ω^2_{32} - GS-441524	Correlation Vc/Vp1 GS-441524	0.0356 [75%]
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524 (%CV)	43% [18%]
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524 (%CV)	25% [21%]
sqrt(θ_5) - RDV	Proportional residual error - RDV (%CV)	45% [1%]
θ_6 - RDV	Additive residual error - RDV (ng/mL)	0.884 [11%]
sqrt(θ_5) - GS-704277	Proportional residual error - GS-704277 (%CV)	44% [1%]
θ_6 - GS-704277	Additive residual error - GS-704277 (ng/mL)	0.604 [5%]
sqrt(θ_7) - GS-441524	Proportional residual error - GS-441524 (%CV)	31% [0%]
θ_8 - GS-441524	Additive residual error - GS-441524 (ng/mL)	0.511 [16%]

θ = absolute value of the estimate; %CV = percentage coefficient of variation; IIV = interindividual variability; OFV = objective function value; periph. cmt. = peripheral compartment; PK = pharmacokinetic; RDV = remdesivir (GS-5734™); RSE = relative standard error.
Minimum OFV = 30760.
Source: vek-pmm-tab-base-seq-20200713.R

Source: RDV new NDA popPK report, p35.

The revised popPK models were developed from a dataset consisting of three healthy adult studies (studies 399-1812, 399-1954, and 399-5505), study 9012 in adult outpatients with COVID-19, study REMDACTA (also known as WA42511) in hospitalized adults with COVID-19, and study 540-5823 in hospitalized pediatric subjects with COVID-19 (RDV popPK report for revised models). Of note, REMDACTA data were used for model development but not included in the FDA analysis.

The starting point for development of the revised popPK models were the initial popPK models, which did not describe the newly added data. Several changes were made:

- Removal of interindividual variability (IIV) on peripheral compartments because PK data were sparse in study 9012
- Change of methods used to estimate concentrations of samples that were below the limit of quantification from M3 to M6
- Addition of maturation functions for clearance of RDV and GS-704277

- Several changes to better estimate variability (estimating correlation between V1 and CL, reincorporating IIV on V2, estimating variance of residual errors, estimating different variance of residual errors and IIVs for Phases 1 and 2/3 and Phase 3)

The revised models (Table 4) demonstrated acceptable goodness-of-fit (GOF) (Figure 6, Figure 7, Figure 8). Acceptable GOF was also demonstrated via age-stratified visual predictive check plots, which show overlap of observed vs model-predicted RDV and metabolite exposures (RDV popPK report for revised models, p421-426).

One main purpose of the popPK models was to estimate individual subject exposures for pediatric subjects in study 5823 and adult outpatients with COVID-19 in study 9012. All IIV shrinkage parameters were <30% for the initial popPK models (RDV new NDA popPK report, p99). However, for the revised models, shrinkages for 14 of 16 IIV parameters were >30% (Table 5). In response to our IR concerning high shrinkage values, the Applicant proposed re-calculating shrinkage values based on estimates from patients where data were available to evaluate the model completely, avoiding including values from sparsely sampled subjects. When shrinkages were re-calculated using the changed methods, 4 of 16 shrinkage values for IIV parameters were >30% (Table 6). Considering the updated shrinkage calculation, the Clinical Pharmacology review team finds the final model acceptable for simulation of pediatric exposures.

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Table 5. Final model parameters for the revised models

Parameter – Model	Parameter Description	Population Estimate	RSE%
Structural Model Parameters			
θ_1 – remdesivir	CL - remdesivir (L/h)	49.4	3.1
θ_2 – remdesivir	Central volume - remdesivir (L)	7.09	6.09
θ_3 – remdesivir	Peripheral volume - remdesivir (L)	6.38	4.82
θ_4 – remdesivir	Intercompartment clearance - remdesivir (L/h)	5.12	4.88
θ_1 - GS-704277	CL - GS-704277 (L/h)	287	4.67
θ_2 - GS-704277	Central volume - GS-704277 (L)	285	6.66
θ_3 - GS-704277	Peripheral volume - GS-704277 (L)	167	28.1
θ_4 - GS-704277	Intercompartment clearance - GS-704277 (L/h)	11.4	13.4
θ_7 - GS-704277	Effect of baseline ferritin for pediatric subjects on clearance	−0..201	42.4
θ_8 - GS-704277	Effect of hospitalization for patients on clearance	−0..281	18.7
θ_9 - GS-704277	Effect of age for subjects 60 years or older on central volume	−0..324	21.7
θ_1 - GS-441524	Clearance - GS-441524 (L/h)	26	2.62
θ_2 - GS-441524	Central volume - GS-441524 (L)	150	6.53
θ_3 - GS-441524	First peripheral volume - GS-441524 (L)	373	3.77
θ_4 - GS-441524	Intercompartment clearance to first periph. Cmt. GS-441524 (L/h)	529	5.41
θ_5 - GS-441524	Second peripheral volume - GS-441524 (L)	298	5.94
θ_6 - GS-441524	Intercompartment clearance to second periph. Cmt. GS-441524 (L/h)	46	6.8
θ_9 - GS-441524	Effect of age for subjects 60 years or older on clearance	−0..341	10.2
θ_{10} - GS-441524	Effect of baseline bilirubin for pediatric subjects on clearance	−0..25	56
Interindividual Variability Parameters			
ω^2_{11} – remdesivir	IIV on CL-remdesivir, Phases 1 and 2/3 (%CV)	15.7%	36.9
ω^2_{22} – remdesivir	IIV of V_c -remdesivir, Phases 1 and 2/3 (%CV)	15.2%	78.9
ω^2_{33} – remdesivir	IIV of CL-remdesivir, Phase 3 (%CV)	111%	38
ω^2_{44} – remdesivir	IIV of V_c -remdesivir, Phase 3 (%CV)	157%	25.3
ω^2_{11} - GS-704277	IIV on CL-GS-704277, Phases 1 and 2/3 (%CV)	17.2%	19.6
ω^2_{22} - GS-704277	IIV of V_c -GS-704277, Phases 1 and 2/3 (%CV)	28.6%	27.3
ω^2_{33} - GS-704277	IIV of CL-GS-704277, Phase 3 (%CV)	53%	32.9
ω^2_{44} - GS-704277	IIV of V_c -GS-704277, Phase 3 (%CV)	123%	22.1
ω^2_{11} - GS-441524	IIV on CL-GS-441524, Phases 1 and 2/3 (%CV)	17.5%	20.7
ω^2_{22} - GS-441524	IIV of V_c -GS-441524, Phases 1 and 2/3 (%CV)	88%	20.7
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524, Phases 1 and 2/3 (%CV)	21.6%	20.1

Parameter – Model	Parameter Description	Population Estimate	RSE%
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524, Phases 1 and 2/3 (%CV)	30.3%	40.1
ω^2_{55} - GS-441524	IIV on CL-GS-441524, Phase 3 (%CV)	32.8%	15.5
ω^2_{66} - GS-441524	IIV of V_c -GS-441524, Phase 3 (%CV)	98.2%	25.9
ω^2_{77} - GS-441524	IIV of Vp1-GS-441524, Phase 3 (%CV)	128%	21
ω^2_{88} - GS-441524	IIV of Vp2-GS-441524, Phase 3 (%CV)	187%	20.2
Residual Variability Parameters			
σ_1 – remdesivir	Variance of residual error - remdesivir, Phases 1 and 2/3	0.6	14.1
σ_2– remdesivir	Variance of residual error - remdesivir, Phase 3	1.78	8.28
σ_1 – GS-704277	Variance of residual error - GS-704277, Phases 1 and 2/3	0.125	29.1
σ_2– GS-704277	Variance of residual error - GS-704277, Phase 3	0.782	45
σ_1 – GS-441524	Variance of residual error - GS-441524, Phases 1 and 2/3	0.231	8.59
σ_2– GS-441524	Variance of residual error - GS-441524, Phase 3	0.929	10.5
sqrt(θ5) – remdesivir	Proportional residual error - remdesivir (%CV)	40.4%	7.11
θ6 – remdesivir	Additive residual error - remdesivir (ng/mL)	1.78	1.64
sqrt(θ5) - GS-704277	Proportional residual error - GS-704277 (%CV)	75.8%	15.6
θ6 - GS-704277	Additive residual error - GS-704277 (ng/mL)	1	
sqrt(θ7) - GS-441524	Proportional residual error - GS-441524 (%CV)	21.9%	0.56
θ8 - GS-441524	Additive residual error - GS-441524 (ng/mL)	1	

θ = absolute value of the estimate; %CV = percentage coefficient of variation; IIV = interindividual variability; OFV = objective function value; periph. Cmt. = peripheral compartment; PK = pharmacokinetic; RDV = remdesivir; RSE = relative standard error; σ = variance of residual error; ω = interindividual variability; V_c = central volume; Vp1 = first peripheral volume; Vp2 = second peripheral volume.

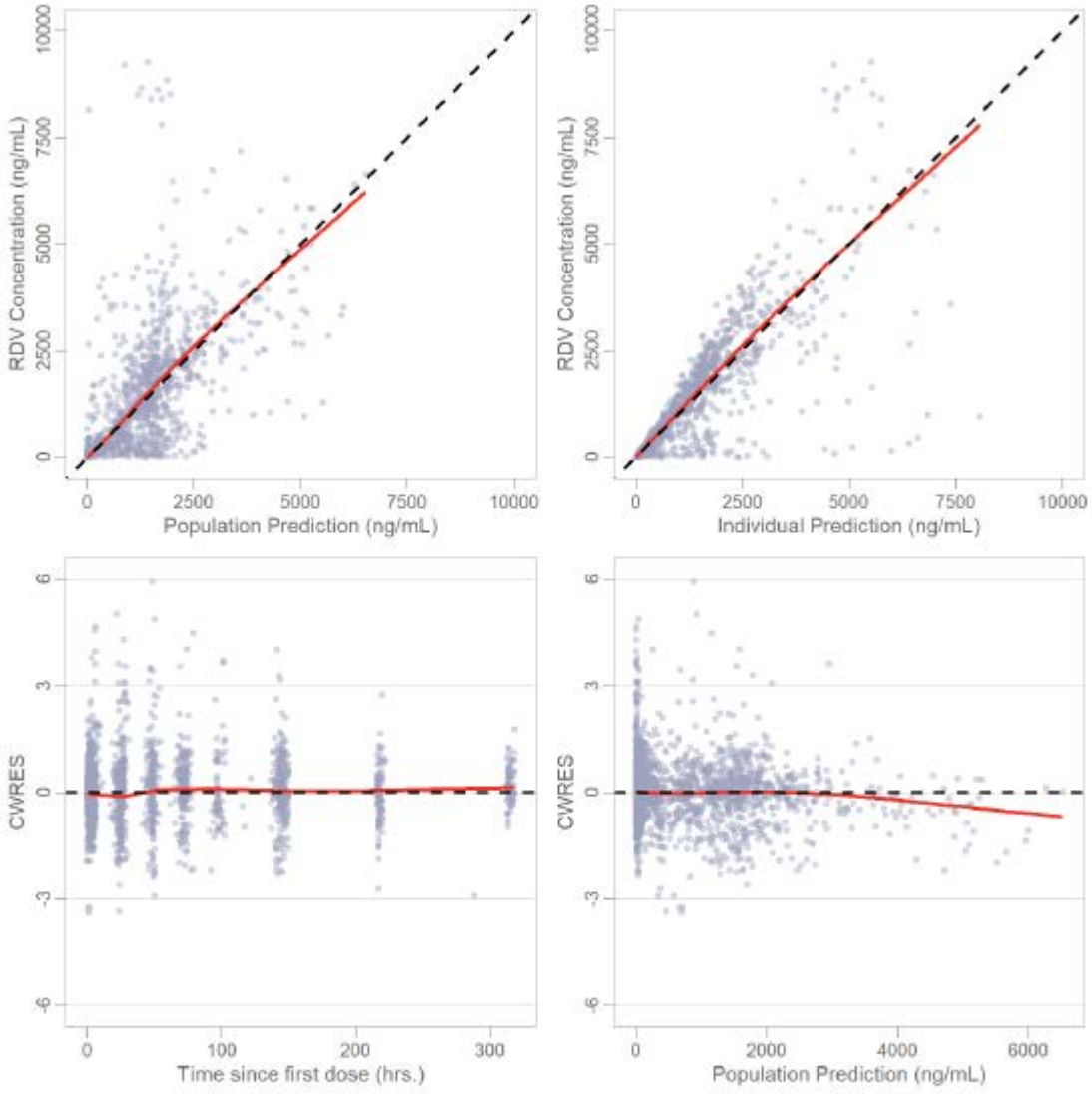
OFV–remdesivir = 25248.242, OFV–GS-704277= 20924.235, OFV–GS-441524 = 26379.828

Condition number– Remdesivir = 58.56, Condition number – GS-704277= 993.9, Condition number – GS-441524 = 119.4

Source: PPK-Diagnostics.html

Source: RDV popPK report for revised models, p60.

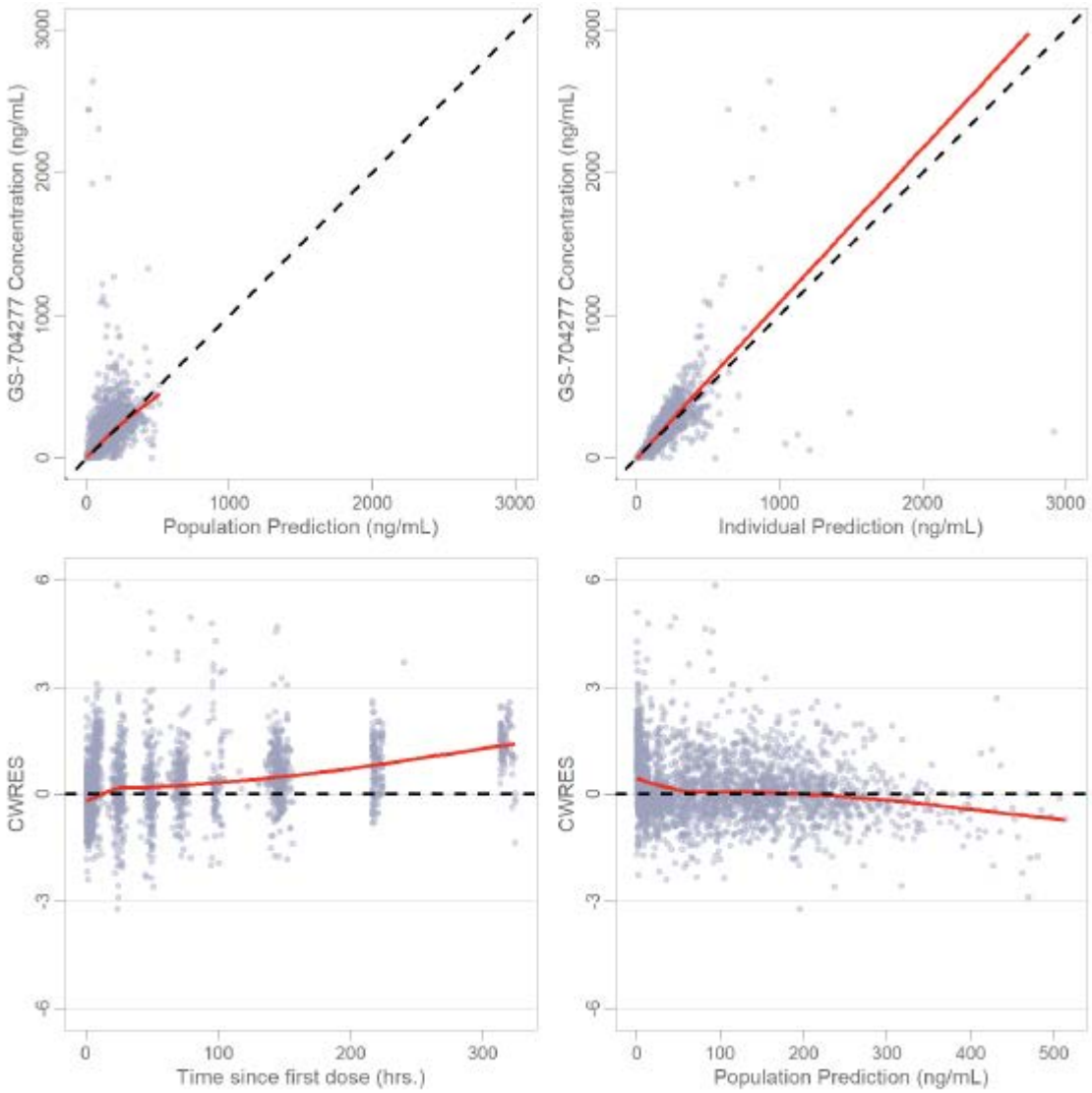
Figure 6. RDV final model GOF plots



Note: Base model and final model are the same for RDV as no significant covariates were identified during the stepwise covariate analysis (SCA) step.
CWRES = conditional [cond.] weighted residuals; The circles represent individual data points; the red lines represent lowess smooth curves; and the dashed lines represent either the line of unity (y = x), the unity line at 0 (y = 0).

Source: Response to IR (NDA 214787 SDN 276), p11.

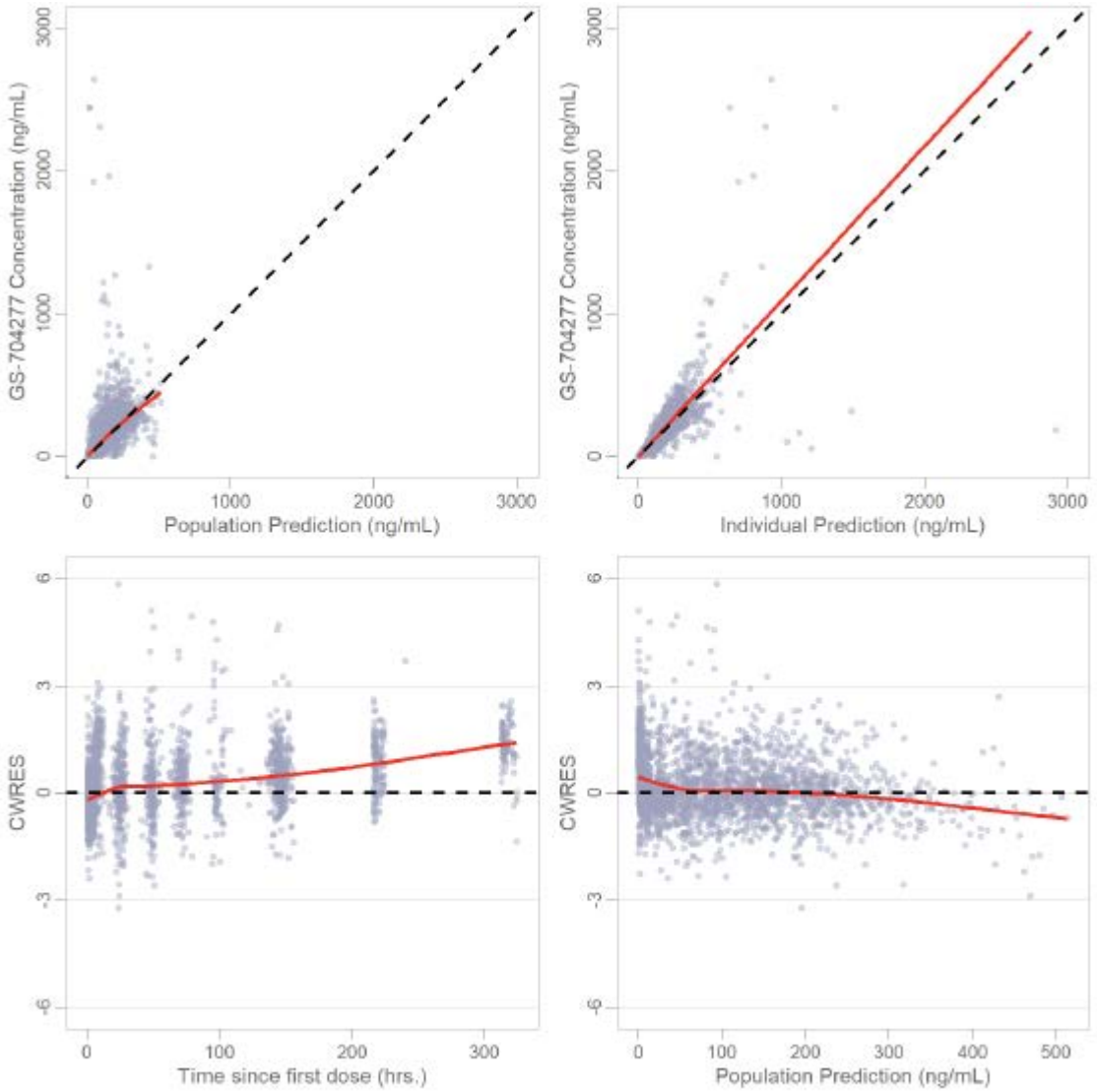
Figure 7. GS-441524 final model GOF plots



CWRES = conditional [cond.] weighted residuals; The circles represent individual data points; the red lines represent lowess smooth curves; and the dashed lines represent either the line of unity (y = x), the unity line at 0 (y = 0).

Source: Response to IR (NDA 214787 SDN 276), p15.

Figure 8. GS-704277 final model GOF plots



CWRES = conditional [cond.] weighted residuals; The circles represent individual data points; the red lines represent lowess smooth curves; and the dashed lines represent either the line of unity (y = x), the unity line at 0 (y = 0).

Source: Response to IR (NDA 214787 SDN 276), p13.

Table 6. Shrinkage values for the revised popPK models

Parameter	Parameter Description	Shrinkage (%)
ω^2_{11} – remdesivir	IIV on CL-remdesivir, Phases 1 and 2/3 (%CV)	48
ω^2_{22} – remdesivir	IIV of V_c -remdesivir, Phases 1 and 2/3 (%CV)	58
ω^2_{33} – remdesivir	IIV of CL -remdesivir, Phase 3 (%CV)	28
ω^2_{44} – remdesivir	IIV of V_c -remdesivir, Phase 3 (%CV)	63
ω^2_{11} - GS-704277	IIV on CL-GS-704277, Phases 1 and 2/3 (%CV)	48
ω^2_{22} - GS-704277	IIV of V_c -GS-704277, Phases 1 and 2/3 (%CV)	51
ω^2_{33} - GS-704277	IIV of CL-GS-704277, Phase 3 (%CV)	32
ω^2_{44} - GS-704277	IIV of V_c -GS-704277, Phase 3 (%CV)	33
ω^2_{11} - GS-441524	IIV on CL-GS-441524, Phases 1 and 2/3 (%CV)	49
ω^2_{22} - GS-441524	IIV of V_c -GS-441524, Phases 1 and 2/3 (%CV)	52
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524, Phases 1 and 2/3 (%CV)	53
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524, Phases 1 and 2/3 (%CV)	58
ω^2_{55} - GS-441524	IIV on CL-GS-441524, Phase 3 (%CV)	26
ω^2_{66} - GS-441524	IIV of V_c -GS-441524, Phase 3 (%CV)	58
ω^2_{77} - GS-441524	IIV of Vp1-GS-441524, Phase 3 (%CV)	61
ω^2_{88} - GS-441524	IIV of Vp2-GS-441524, Phase 3 (%CV)	61
σ_1 – remdesivir	Variance of residual error - remdesivir, Phases 1 and 2/3	6
σ_2– remdesivir	Variance of residual error - remdesivir, Phase 3	10
σ_1 – GS-704277	Variance of residual error - GS-704277, Phases 1 and 2/3	7
σ_2– GS-704277	Variance of residual error - GS-704277, Phase 3	19
σ_1 – GS-441524	Variance of residual error - GS-441524, Phases 1 and 2/3	9
σ_2– GS-441524	Variance of residual error - GS-441524, Phase 3	26

σ = standard deviation of residual variability; ω = standard deviation of between-subject variability; %CV = percentage coefficient of variation; IIV = interindividual variability; PopPK = population pharmacokinetic; RDV = remdesivir; σ = variance of residual error; ω = interindividual variability; V_c = central volume; Vp1 = first peripheral volume; Vp2 = second peripheral volume.
Source: PPK-Diagnostics.html

Source: RDV popPK report for revised models, p171.

Table 7. Re-calculated shrinkage values for the revised popPK models

Parameter	Parameter Description	Previously Reported Shrinkage Value (%)	Recalculated Shrinkage Value (%)	Shrinkage Value without REMDACTA (%)
ω^2_{11} – remdesivir	IIV on CL-remdesivir, Phases 1 and 2/3 (%CV)	48	6	3
ω^2_{22} – remdesivir	IIV of V_c -remdesivir, Phases 1 and 2/3 (%CV)	58	24	21
ω^2_{33} – remdesivir	IIV of CL -remdesivir, Phase 3 (%CV)	28	15	8
ω^2_{44} – remdesivir	IIV of V_c -remdesivir, Phase 3 (%CV)	63	57	34
ω^2_{11} - GS-704277	IIV on CL-GS-704277, Phases 1 and 2/3 (%CV)	48	7	3
ω^2_{22} - GS-704277	IIV of V_c -GS-704277, Phases 1 and 2/3 (%CV)	51	13	8
ω^2_{33} - GS-704277	IIV of CL-GS-704277, Phase 3 (%CV)	32	20	19
ω^2_{44} - GS-704277	IIV of V_c -GS-704277, Phase 3 (%CV)	33	21	18
ω^2_{11} - GS-441524	IIV on CL-GS-441524, Phases 1 and 2/3 (%CV)	49	7	3
ω^2_{22} - GS-441524	IIV of V_c -GS-441524, Phases 1 and 2/3 (%CV)	52	13	11
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524, Phases 1 and 2/3 (%CV)	53	16	12
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524, Phases 1 and 2/3 (%CV)	58	25	22
ω^2_{55} - GS-441524	IIV on CL-GS-441524, Phase 3 (%CV)	26	12	11
ω^2_{66} - GS-441524	IIV of V_c -GS-441524, Phase 3 (%CV)	58	50	29
ω^2_{77} - GS-441524	IIV of Vp1-GS-441524, Phase 3 (%CV)	61	55	41
ω^2_{88} - GS-441524	IIV of Vp2-GS-441524, Phase 3 (%CV)	61	54	51
σ_1 – remdesivir	Variance of residual error - remdesivir, Phases 1 and 2/3	6	6	7
σ_2– remdesivir	Variance of residual error - remdesivir, Phase 3	10	10	11
σ_1 – GS-704277	Variance of residual error - GS-704277, Phases 1 and 2/3	7	7	7
σ_2– GS-704277	Variance of residual error - GS-704277, Phase 3	19	19	16
σ_1 – GS-441524	Variance of residual error - GS-441524, Phases 1 and 2/3	9	9	9
σ_2– GS-441524	Variance of residual error - GS-441524, Phase 3	26	26	26

Notes: Red represents shrinkage > 30 %. Corrected shrinkage was calculated by adding ETASTYPE=1 in the estimation block. When removing REMDACTA, all parameters were re-estimated.

Source: Response to IR (NDA 214787 SDN 247), p7.

6. Clinical Virology

Dr. William Ince recommended approval of this sNDA based on his review of the virology information provided in the application. Please refer to the Supplement 11 virology review by Dr. Ince for a detailed assessment of the clinical virology data. There were no nonclinical virology data submitted to support Supplement S-011. Key nonclinical and clinical virology characteristics, including mechanism of action, antiviral activity against SARS-CoV-2, 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., Reference ID in DARRTS: 4672246 (N214787.000), Clinical Virology Review for NDA 214787, Supplement 9 by E. Donaldson Ph.D., Reference ID in DARRTS: 4919868 (N214787.S-009.MI.219); and Clinical Virology Review for NDA 214787, Supplement 13 by W. Ince Ph.D., Reference ID in DARRTS: 4957456 (N214787.S-013.265)].

Clinical Virology
Interim clinical virology data from the single-arm trial GS-US-540-5823 submitted to support this supplement included longitudinal quantitative viral RNA shedding and baseline and post-baseline sequence data from respiratory samples. A total of 54 subjects were enrolled, and 53 subjects were positive for SARS-CoV-2 at baseline and included in the Full Analysis Set and virologic analyses.

Viral RNA shedding
Nasopharyngeal/oropharyngeal, nasal/oropharyngeal, and/or endotracheal samples were collected at baseline (Day 1) and Days 3, 5, 7, and 10. Viral RNA quantified by RT-PCR exhibited a general declined in all sample types for most subjects over the observation period; however, <50% of subjects were confirmed viral RNA negative (based on two consecutive negative RT-PCR results) through Day 10. While a placebo comparator arm was not included in this trial, the results are consistent with the lack of a significant impact of RDV treatment on viral RNA shedding that was observed in adult, placebo controlled trials (Supplement 10 Clinical Virology Review [reference ID in DARRTS: 4672246; N214787.SE-010.190]).

Resistance analyses
SARS-CoV-2 whole-genome sequence analysis was attempted for all subjects in the Full Analysis Set who had respiratory samples with viral RNA >LLOQ of the viral RNA load assay. Of the 53 subjects in the FAS, sequencing was attempted for baseline and/or post-baseline samples for 39 subjects with evaluable samples. Sequence data at any time point were obtained for 34 subjects. Baseline sequencing was obtained for 30 subjects, post-baseline sequencing was obtained for 27 subjects, and sequence data were successfully obtained at baseline and post-baseline for 23 subjects.

Virus genotype based on baseline or post-baseline sequence data was determined for 34 subjects. The most common variant represented was B.1.2 (5 subjects), followed by B.1.1.7 (Alpha; 4 subjects) and B.1.429 (Epsilon; 3 subjects). All other variants were identified in ≤2 subjects. SARS-CoV-2 Variants of Concern including Delta and Omicron were not represented in this trial, which completed enrollment of the cohorts included in the interim

analysis prior to widespread circulation of Delta and Omicron variants. Data were inadequate to draw a conclusion regarding the association between the SARS-CoV-2 genotype and a treatment effect or clinical outcome.

SARS-CoV-2 replication complex genes nsp8, nsp9, nsp10, nsp12, nsp13, and nsp14 were evaluated for baseline and treatment-emergent substitutions potentially associated with reduced susceptibility to RDV. Substitutions meeting the following criteria were identified as requiring evaluation for their impact on RDV susceptibility (see PMR 1):

i. Identified as treatment-emergent at a frequency of ≥15% of the virus population, or
ii. Baseline substitutions associated with viral RNA rebound in more than one subject, including different amino acid substitutions at the same position; rebound was defined as an increase RNA from the previous time point to a level greater than the median viral RNA level for the time point and sample type.

A PMR will be issued for additional clinical virology information regarding the evaluation of potential RDV resistance-associated substitutions (see Section 13).

7. Clinical – Descriptive Efficacy

Use of RDV in pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg is based on extrapolation of efficacy from adequate and well-controlled studies in adults (three, Phase 3 clinical trials in hospitalized adults of varying disease severity), one Phase 3 clinical trial in non-hospitalized adults and adolescents with mild-to-moderate COVID-19 (who are at high risk of progression to severe COVID-19, including hospitalization or death). Study GS-US-540-5823 provided pharmacokinetic/pharmacodynamic and safety data from pediatric patients.

Please refer to the original NDA review (action date October 22, 2020) and the sNDA-10 review (action date January 21, 2022) for full details of the aforementioned adequate and well-controlled studies in adults.

This section summarizes the descriptive efficacy analyses of Study GS-US-540-5823 Cohorts 1-4 and Cohort 8. The study design, subject characteristics, and descriptive efficacy results are summarized below.

Study design, baseline characteristics, and key efficacy results

Study GS-US-540-5823 (clinicaltrials.gov identifier NCT04431453) is an ongoing Phase 2/3, single-arm, open-label study to investigate the safety, tolerability, pharmacokinetics (PK), and efficacy of RDV in pediatric subjects birth to < 18 years of age who are hospitalized with laboratory-confirmed COVID-19. The following table displays the study cohorts (age/weight groups) and dosing regimens. Treatment with RDV was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment. Cohorts 1-5 and Cohort 8 were enrolled in parallel. Cohorts 1-4 and Cohort 8 are submitted in this sNDA.

Table 8: 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[a]
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[a]
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[b]	4	≥ 14 days to < 28 days of age, gestational age > 37 weeks and weight at Screening ≥ 2.5 kg	
6[b]	d, e	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[a]
7[c]	d, e	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[a]
8	5[e]	< 12 years and weight ≥ 40 kg	200 mg IV on Day 1 followed by 100 mg IV QD for up to 10 days[a]

[a]Treatment with RDV was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.
[b]Cohorts 5 and 6 will enroll term neonates.
[c]Cohort 7 will enroll preterm neonates and infants.
[d]Subjects in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined.
[e]No minimum number; TBD, to be determined.
Exploratory cohort 8 was added in the September 22, 2020 protocol amendment.

Inclusion criteria specified that subjects are aged < 18 years who met one of the study's weight criteria (where permitted according to local law and approved nationally and by relevant IRB or IEC); had laboratory-confirmed SARS-CoV-2 infection as determined by reverse transcription polymerase chain reaction (RT-PCR) assay; and are hospitalized and requiring medical care for COVID-19.

Exclusion criteria disallowed subjects with any of the following:
• Concurrent treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing
• ALT or AST > 5 times the upper limit of normal (ULN)
• Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 using Schwartz formula for individuals ≥ 1 year of age
• Creatinine above protocol specified thresholds for < 1 year of age
• If < 28 days of age, any major congenital renal anomaly
• If < 24 hours of age, Apgar score < 5 when last recorded
• Known hypersensitivity to the study drug, the metabolites, or formulation excipient
• Positive pregnancy test at Screening only for female of child-bearing potential *(Note: If female subjects who become pregnant during the study or are discovered to be pregnant after receiving at least one dose may continue study drug, after discussion with the investigator.)*
• On renal replacement therapies (intermittent hemodialysis [iHD], peritoneal dialysis [PD], continuous renal replacement therapy [CRRT])

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Routine clinical tests

In GS-US-540-5823, routine clinical evaluation and laboratory testing occurred at pre-specified intervals: Screening; Day 1 (Baseline); Days 2-10, or until discharge, whichever comes earlier; Follow-Up on Day 30 (±5). 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 Endpoints

The primary endpoints are as follows:

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

The secondary endpoints are as follows:

- Oxygen usage and ventilation modality and settings
- Clinical improvement based on scoring using the 7-point ordinal scale; the ordinal scale consisted of the following categories:
    1. Death
    2. Hospitalized, on IMV or ECMO
    3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
    4. Hospitalized, requiring low-flow supplemental oxygen
    5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (related or not to COVID-19)
    6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than that specified in the protocol for RDV administration)
    7. Not hospitalized
- Time (days) to discharge from hospital
- Days to the first confirmed negative PCR result, where confirmed is defined by 2 consecutive negative PCR results
- Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)
- Bilirubin concentrations in < 14-day-old subjects
- Clinical improvement based on scoring using the Pediatric Early Warning Score (PEWS) Improvement Scale
- Plasma concentrations of SBECD (where possible)
- Proportion of subjects with concomitant use of medications other than RDV for treatment of COVID-19

Reviewer Comment: Study GS-US-540-5823 was not powered to demonstrate efficacy.

Statistical Analysis Plan (SAP)

Efficacy was to be assessed using the Full Analysis Set (FAS), which included all randomized subjects who received at least one dose of study medication. Efficacy endpoints were summarized using descriptive statistics for each cohort and overall.

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Clinical improvement based on scoring using the 7-point ordinal scale was evaluated as follows:
• Clinical status by study day and last available assessment.
• Change in clinical status by study day and last available assessment.
• Time to clinical improvement (days): Clinical improvement is defined as a ≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale. Time to clinical improvement was modelled using a competing risk analysis. Subjects not achieving clinical improvement at the last assessment were censored on the day of the last clinical assessment. Subjects who died were considered to have experienced a competing event.
• Time to recovery based on the 7-point ordinal scale, where recovery is defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7. Time to recovery was modelled using a competing risk analysis. Subjects not achieving recovery at the last assessment were censored on the day of the last clinical assessment. Subjects who died were considered to have experienced a competing event.

Reviewer Comment: The ordinal scale assessment on Day 10 was not prespecified as the primary efficacy endpoint in the protocol or the SAP for Study GS-US-540-5823. The protocol and SAP did not prespecify Day 10 as the timepoint for any of the efficacy assessments.

Safety was to be assessed using the Safety Analysis Set (SAS), which was defined identically to the FAS.

The SAP pre-specified the following analyses:
• Independent data monitoring committee (IDMC) reviewed safety, PK (if available), and efficacy data when approximately 50% of subjects across the age range of 0 days to < 18 years reached the Day 10 visit or were discharged, whichever came first.
• Interim Analysis was performed after (i) all subjects in Cohort 1-4 were enrolled and completed the study or prematurely discontinued from the study; (ii) subjects in Cohort 8 as of the last date of enrolment into Cohorts 1-4 completed the study or prematurely discontinued from the study; (iii) outstanding data queries were resolved or adjudicated as unresolvable; and (iv) the data had been finalized.

(b) (4)

Protocol Amendments
Three protocol amendments were made. Other than the addition of Cohort 8 and revised toxicity management (both in Amendment 2), none of these amendments significantly impact the conduct of this trial. Key changes in these amendments are summarized below.

Amendment 1 (dated June 18, 2020)
• Added Exclusion criterion #8 for positive pregnancy at Screening for females of child-bearing potential.

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• Updated the SARS-CoV-2 PCR testing and viral sequencing to include nasal and oropharyngeal samples (combined)
• Updated the eGFR units to (mL/min/1.73 m^2)
• Updated the collection of Apgar score at 10 min to last recorded score
• Clarified the Prohibited Concomitant Medications to include Investigational agents for COVID-19 with direct antiviral effect and added rifabutin, carbamazepine, phenytoin
• Added Contraceptive requirement for participating females of child-bearing potential at Screening and during the study
• Added instructions to use smallest possible blood vials for sample collection for subjects <15kg

Amendment 2 (dated September 22, 2020)
• Number of sites: Increased from 30 to 35 globally.
• Clarified the number of subjects planned for the study as at least 52
• Added Exploratory cohort 8 (< 12 years and weight ≥ 40 kg); outlined that Cohort 8 is an exploratory cohort, there is no minimum number of subjects to be enrolled in Cohort 8, and Cohort 8 will be enrolled in parallel with Cohorts 1-5
• Clarified the PK collection windows
• Added exclusion criterion for subjects on renal replacement therapies (iHD, PD, CRRT)
• Updated renal replacement therapies (iHD, PD, CRRT) as a criterion for discontinuation
• Added the following to Toxicity Management: "Remdesivir infusions will be administered to participants at the site under close supervision. Healthcare professionals administering RDV infusions should have the appropriate medication available for immediate use in case of hypersensitivity or infusion-related reactions. The participant should be treated according to the standard of care for management of hypersensitivity reaction or infusion-related reactions. Participants should be monitored for at least 2 hours after the RDV infusion is completed."

Amendment 3 (dated February 16, 2021)
• Updated the routine coagulation test for Cohorts 5, 6 and 7
• Revised the blood volume tables for Cohorts 5, 6 and 7

Disposition
The first subject was screened on July 22, 2020, and the last subject visit for this sNDA was completed on May 24, 2021. A total of 53 subjects were randomized and treated. Subjects were enrolled across 15 centers in the United States, 2 in Spain, 1 in Italy, and 1 in the United Kingdom.

Of the 54 subjects who were screened for Cohorts 1-4 and Cohort 8, 53 subjects were enrolled and received at least one dose of study medication, and consequently were included in the full analysis set. One subject met all eligibility criteria but was not enrolled in the study due to investigator discretion.

Reviewer Comment: Of the 54 subjects, 42 subjects were from the US, 12 subjects were ex-US.

A total of 95 important protocol deviations occurred in 41 subjects. Of the 41 subjects, 16 subjects had a single protocol deviation, 9 subjects had 2 protocol deviations, 9 subjects had 3

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protocol deviations, 3 subjects had 4 protocol deviations, 2 subjects had 5 protocol deviations and 2 subjects had 6 protocol deviations. The largest number of protocol deviations (46 of 95) were due to missed data related to primary and secondary end points or discontinuation criteria through the study. These protocol violations had no bearing on the interpretability of the trial results.

In this study the full analysis set (FAS) used for efficacy assessments exactly coincided with the safety analysis set (SAS).

Table 9: Subject Disposition, FAS

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Age/weight groups	**≥ 12 years to < 18 years and weight ≥ 40 kg**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg**	**< 12 years and weight ≥ 40 kg**	
Subjects enrolled	12	12	12	12	5	53
Subjects treated (FAS)	12	12	12	12	5	53
Subjects completed study drug	3 (25%)	2 (17%)	2 (17%)	4 (33%)	2 (40%)	13 (25%)
Subjects prematurely discontinuing study drug	9 (75%)	10 (83%)	10 (83%)	8 (67%)	3 (60%)	40 (75%)
Adverse Event	2 (17%)	0	0	0	0	2 (4%)
Hospital Discharge	2 (17%)	7 (58%)	7 (58%)	4 (33%)	2 (40%)	22 (42%)
Investigator's Discretion	5 (42%)	2 (17%)	3 (25%)	2 (17%)	1 (20%)	13 (31%)
Subject Decision	0	1 (8%)	0	0	0	1 (2%)
Parent/Guardian Decision	0	0	0	2 (17%)	0	2 (4%)
Subjects still on study up to the data cut date*	0	0	1 (8%)	0	0	1 (2%)
Subjects completed study	11 (92%)	11 (92%)	10 (83%)	9 (75%)	4 (80%)	45 (85%)
Subjects prematurely discontinuing from study	1 (8%)	1 (8%)	1 (8%)	3 (25%)	1 (20%)	7 (13%)
Death	1 (8%)	0	0	0	1 (20%)	2 (4%)
Withdrew Consent	0	1 (8%)	0	2 (17%)	0	3 (6%)
Lost to Follow-Up	0	0	1 (8%)	1 (8%)	0	2 (4%)

*Subject had completed both the study drug and the Day 30 follow-up visit as of the data cut-off date. Disposition is as of the Day 30 follow-up visit.
Source: ADSL dataset; Study GS-US-540-5823 Clinical Study Report, Table 9.
Notes: The denominator for percentages is the number of subjects in the full analysis set (FAS).

Reviewer Comment: Of the 53 subjects, 40 subjects (75%) prematurely discontinued RDV. The four most common reasons for premature discontinuation of RDV were:
- *Hospital discharge: 22 subjects (42%)*
- *Investigator discretion: 13 subjects (31%)*

- *Parent-Guardian decision: 2 subjects (4%)*
- *Adverse event: 2 subjects (4%)*

Baseline demographics

The table below summarizes baseline demographics.

Table 10: Demographics, FAS

Cohort	1	2	3	4	8	Total
Age/weight groups	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Age (years)						
Mean (SD)	15 (1.7)	9.6 (3.6)	3.9 (1.8)	0.4 (0.3)	10.4 (1.3)	7.5 (5.0)
Median	15.0	9.0	3.5	0.5	11.0	7.0
Q1, Q3	13.5, 16.5	7.5, 12.0	2.0, 5.5	0.2, 0.7	11.0, 11.0	2.0, 12.0
Minimum, maximum	12.0, 17.0	4.0, 16.0	1.9, 7.0	0.1, 0.9	9.0, 11.0	0.1, 17.0
Sex at birth						
Male	4 (33%)	5 (42%)	7 (58%)	5 (42%)	2 (40%)	23 (43%)
Female	8 (67%)	7 (58%)	5 (42%)	7 (58%)	3 (60%)	30 (57%)
Race						
Black	5 (42%)	2 (17%)	4 (33%)	2 (17%)	1 (20%)	14 (26%)
White	7 (58%)	9 (75%)	6 (50%)	8 (67%)	3 (60%)	33 (62%)
Other	0	1 (8%)	2 (17%)	2 (17%)	1 (20%)	6 (11%)
Ethnicity						
Hispanic or Latino	3 (25%)	7 (58%)	7 (58%)	3 (25%)	3 (60%)	23 (43%)
Not Hispanic or Latino	8 (67%)	5 (42%)	5 (42%)	9 (75%)	2 (40%)	29 (55%)
Not Permitted	1 (8%)	0	0	0	0	1 (2%)
Baseline weight (kg)						
Mean (SD)	89.5 (42.0)	28.1 (5.0)	15.4 (2.6)	6.2 (2.3)	69.0 (20.2)	38.0 (38.6)
Median	83.5	26.5	14.6	5.0	73.0	24.6
Q1, Q3	56.8, 106.9	25.0, 30.9	13.4, 18.2	4.4, 8.5	55.1, 80.0	12.8, 55.1
Minimum, maximum	47.3, 191.6	22.0, 39.1	12.0, 19.4	3.7, 10.4	42.9, 94.0	3.7, 191.6

Source: ADSL dataset; Study GS-US-540-5823 Clinical Study Report, Table 11.

Reviewer Comment: The median age was 7 years; 57% of subjects were female, 62% of subjects were White and 26% of subjects were Black; 44% of subjects were Hispanic or Latino; median weight was 25 kg (range: 4 to 192 kg).

Baseline disease characteristics

The table below summarizes baseline disease characteristics.

Table 11: Baseline disease characteristics, FAS

Cohort	1	2	3	4	8	Total
Age/weight groups	**≥ 12 years to < 18 years and**	**≥ 28 days to < 18 years and weight ≥**	**≥ 28 days to < 18 years and weight ≥**	**≥ 28 days to < 18 years and weight**	**< 12 years and weight ≥ 40 kg**	

	weight ≥ 40 kg (n=12)	**20 kg to < 40 kg (n=12)**	**12 kg to < 20 kg (n=12)**	**≥ 3 kg to < 12 kg (n=12)**	**(n=12)**	**53**
Duration of symptoms prior to first dose of RDV (days)						
Mean (SD)	21 (49.4)	5 (2.7)	5 (3.0)	5 (3.3)	7 (3.0)	9 (23.8)
Median	7	5	3	5	5	5
Q1, Q3	3, 11	3, 7	3, 7	2, 8	5, 7	3, 7
Minimum, maximum	1, 177	2, 11	1, 11	0, 9	5, 12	0, 177
Oxygen support status (ordinal scale)						
Room air (OS-5)	3 (25%)	2 (17%)	6 (50%)	1 (8%)	1 (20%)	13 (25%)
Low-flow oxygen (OS-4)	2 (17%)	3 (25%)	0	3 (25%)	2 (40%)	10 (19%)
High-flow oxygen (OS-3)	6 (50%)	4 (33%)	3 (25%)	3 (25%)	2 (40%)	18 (34%)
IMV (OS-2)	1 (8%)	3 (25%)	3 (25%)	5 (42%)	0	12 (23%)
Duration of hospitalization prior to first dose of RDV (days)						
Mean (SD)	8 (25.1)	2 (1.1)	2 (1.4)	13 (26.3)	5 (9.2)	6 (17.6)
Median	1	1	2	2	1	1
Q1, Q3	0, 3	1, 2	1, 3	1, 7	0, 1	1, 3
Minimum, maximum	0, 88	0, 4	0, 5	1, 82	0, 21	0, 88

Source: ADSL dataset; Study GS-US-540-5823 Clinical Study Report, Table 12.
Abbreviations: OS, ordinal scale; IMV, invasive mechanical ventilation.

Reviewer Comment: The median duration of symptoms prior to treatment initiation was 5 days. The median duration of hospitalization prior to treatment initiation was one day.

Baseline clinical status (7-point ordinal scale) reflected the severity of baseline disease:

- *13 subjects (25%) had a clinical status of 5 (hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care [related or not to COVID-19])*
- *10 subjects (19%) had a clinical status of 4 (hospitalized, requiring supplemental oxygen)*
- *18 subjects (34%) had a clinical status of 3 (hospitalized, receiving noninvasive ventilation or high-flow oxygen devices)*
- *12 subjects (23%) had a clinical status of 2 (hospitalized, receiving IMV or ECMO)*

Treatment duration

The table below summarizes the treatment duration.

Table 12: Treatment Duration, SAS

Cohort	1	2	3	4	8	Total
Age/weight groups	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Number of doses						
Mean (SD)	7 (2.4)	6 (2.3)	5 (2.5)	6 (3.5)	6 (3.6)	6 (2.8)
Median	5	5	5	5	5	5
Q1, Q3	5, 9	4, 7	4, 5	3, 10	3, 10	4, 8
Minimum, maximum	3, 10	3, 10	2, 10	1, 10	3, 10	1, 10
Number of doses						
1	0	0	0	1	0	1
2	0	0	1	2	0	3
3	1	1	2	1	2	7
4	0	3	2	1	0	6
5	6	4	5	3	1	19
6	0	1	0	0	0	1
7	1	0	0	0	0	1
8	1	1	0	0	0	2
9	0	0	0	0	0	0
10	3	2	2	4	2	13

Source: ADAE dataset, Study GS-US-540-5823

Reviewer Comment: The median duration of treatment was 5 days, and this observation was consistent across all cohorts. However, limitations of this trial included the open-label design and its possible influence on the timing of discharge decisions.

Hospital discharge

The table below summarizes clinical outcomes for hospitalization.

Table 13: Proportion of subjects who were hospitalized, FAS

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Age/weight groups	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Day 10						
Number of subjects discharged alive by Day 10	3 (25%)	9 (75%)	11 (92%)	6 (50%)	3 (60%)	32 (60%)
Number of subjects still hospitalized at Day 10	9 (75%)	3 (25%)	1 (8%)	6 (50%)	2 (40%)	21 (40%)
Number of subjects who died on or prior to Day 10	0	0	0	0	0	0
Day 30						
Number of subjects discharged alive by Day 30	9 (75%)	10 (83%)	12 (100%)	9 (75%)	4 (80%)	44 (83%)
Number of subjects still hospitalized at Day 30	2 (17%)	2 (17%)	0	3 (25%)	0	7 (13%)
Number of subjects who died on or prior to Day 30	1 (8%)	0	0	0	1 (20%)	2 (4%)
Duration of hospitalization (days) from Study Day 1* for subjects who were discharged alive by Day 30 (n=44)						
Mean (SD)	12 (5.5)	7 (4.1)	8 (6.3)	9 (6.9)	9 (6.9)	9 (5.9)
Median	12	7	6	7	7	7
Q1, Q3	8, 15	5, 9	4, 9	4, 17	4, 14	5, 12
Minimum, maximum	6, 24	4, 18	2, 26	3, 19	3, 18	2, 26
Total Duration of hospitalization (days) for subjects who were discharged alive by Day 30 (n=44)						
Mean (SD)	14 (5.2)	9 (4.0)	10 (7.3)	17 (21.5)	15 (16.7)	12 (11.8)
Median	14	8	8	8	8	9
Q1, Q3	9, 16	6, 10	5, 11	5, 21	4, 25	6, 14
Minimum, maximum	7, 24	5, 19	4, 31	4, 71	4, 39	4, 71

*Study Day 1 is the date of RDV initiation
Source: ADEFF dataset, Study GS-US-540-5823

Reviewer Comment: A total of 32 subjects (60%) were discharged alive by Day 10, and a total of 44 subjects (83%) were discharged alive by Day 30.

For the 44 subjects who were discharged alive by Day 30, the median total duration of hospitalization was 9 days, and the median duration of hospitalization following RDV initiation was 7 days.

Clinical status
The table below summarizes the clinical status (based on the 7-point ordinal scale) on Day 10 and on the last available assessment, respectively.

Reference ID: 4971782

Table 14: Clinical status (based on the 7-point ordinal scale), FAS

Cohort	1	2	3	4	8	Total
Age/weight groups	≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)	< 12 years and weight ≥ 40 kg (n=12)	53
Clinical status (based on the 7-point ordinal scale) on Day 10						
1 (Death)	0	0	0	0	0	0
2 (IMV or ECMO)	3 (25%)	1 (8%)	0	3 (25%)	1 (20%)	8 (15%)
3 (Noninvasive ventilation or high-flow oxygen devices)	1 (8%)	0	0	0	0	1 (2%)
4 (Hospitalized, requiring low-flow supplemental oxygen)	0	1 (8%)	0	1 (8%)	0	2 (4%)
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	5 (42%)	1 (8%)	1 (8%)	2 (17%)	0	9 (17%)
6 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, other than per protocol RDV administration)	0	0	0	0	1 (20%)	1 (2%)
7 (Not hospitalized)	3 (25%)	9 (75%)	11 (92%)	6 (50%)	3 (60%)	32 (60%)
Clinical status (based on the 7-point ordinal scale) on the last available assessment						
1 (Death)	2 (17%)	1 (8%)	0	0	1 (20%)	4 (8%)
2 (IMV or ECMO)	1 (8%)	0	0	3 (25%)	0	4 (8%)
3 (Noninvasive ventilation or high-flow oxygen devices)	0	0	0	0	0	0
4 (Hospitalized, requiring low-flow supplemental oxygen)	0	0	0	0	0	0
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	0	1 (8%)	0	0	0	1 (2%)
6 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, other than per protocol RDV administration)	0	0	0	0	0	0
7 (Not hospitalized)	9 (75%)	10 (83%)	12 (100%)	9 (75%)	4 (80%)	44 (83%)

Source: ADEFF dataset, Study GS-US-540-5823
Abbreviations: IMV, invasive mechanical ventilation.

Reviewer Comment: A total of 32 subjects (60%) achieved an ordinal scale score of 7 (i.e. not hospitalized) on Day 10. A total of 44 subjects (83%) achieved an ordinal scale score of 7 (i.e. not hospitalized) on the last available assessment.

Change from baseline in clinical status

The table below summarizes the change from baseline in clinical status (based on the 7-point ordinal scale) on Day 10 and at the last available assessment, respectively.

Table 15: Change from baseline in clinical status (based on the 7-point ordinal scale), FAS

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Age/weight groups	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Change from baseline in clinical status (based on the 7-point ordinal scale) on Day 10						
Mean (SD)	1.0 (1.6)	2.8 (1.2)	3.1 (1.2)	2.1 (1.7)	2.0 (1.9)	2.2 (1.6)
Median	0.5	3.0	2.5	3.0	2.0	2.0
Q1, Q3	0.0, 2.0	2.0, 4.0	2.0, 4.0	0.0, 3.5	2.0, 3.0	2.0, 4.0
Minimum, maximum	-1, 4	0, 4	2, 5	0, 4	-1, 4	-1, 5
Change from baseline in clinical status (based on the 7-point ordinal scale) on the last available assessment						
Mean (SD)	2.0 (2.2)	3.0 (1.5)	3.3 (1.4)	2.7 (1.9)	2.0 (2.4)	2.7 (1.8)
Median	2.5	3.0	3.0	3.0	3.0	3.0
Q1, Q3	0.5, 4.0	2.5, 4.0	2.0, 4.5	0.5, 4.0	2.0, 3.0	2.0, 4.0
Minimum, maximum	-2, 4	-1, 5	2, 5	0, 5	-2, 4	-2, 5

Source: ADEFF dataset,

Reviewer Comment: On Day 10, the median change from baseline in clinical status (based on the 7-point ordinal scale) on Day 10 was a 2-point improvement. On the last assessment, the median change from baseline in clinical status (based on the 7-point ordinal scale) was a 3-point improvement.

Clinical improvement (≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale)

Of the 52 subjects with baseline ordinal score of ≤ 5 points, 39 subjects (75%) had a ≥ 2-point improvement in clinical status on Day 10, and 44 subjects (85%) had a ≥ 2-point improvement in clinical status on the last assessment.

Reviewer Comment: Of the 39 subjects with ≥ 2-point improvement in clinical status on Day 10, 32 subjects had been discharged and 7 subjects were improving but remained hospitalized.

Of the 44 subjects with ≥ 2-point improvement in clinical status on the last assessment, all had been discharged.

Recovery (improvement from a baseline ordinal score of 2 through 5 to a score of 6 or 7 or an improvement from a baseline ordinal score of 6 to an ordinal score of 7)

A total of 33 subjects (62%) met the definition for recovery on Day 10. A total of 44 subjects (83%) met the definition for recovery on the last available assessment. For these 44 subjects, the median time to recovery was 7 days.

Reviewer Comment: Of the 33 subjects who met the definition for recovery on Day 10, 32 subjects had been discharged (i.e. achieved an ordinal scale score of 7) and 1 subject was improving but remained hospitalized (i.e. achieved an ordinal scale score of 6).

Of the 44 subjects who met the definition for recovery on the last assessment, all had been discharged (i.e. achieved an ordinal scale score of 7).

Conclusions on effectiveness

The disease process from acute COVID-19 is considered to be generally similar between adults and children; further, SARS-CoV-2 is expected to respond similarly to RDV regardless of host (i.e. adults or children). Therefore, the effectiveness of RDV in pediatric patients can be extrapolated from adequate and well-controlled studies in adults. The efficacy of the proposed RDV dose in pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg is demonstrated by establishing that, RDV exposures in pediatric subjects are within the range of RDV exposures that were observed in adults at the approved dose(s). In summary, the use of RDV in pediatric patients is supported by:

- extrapolation of efficacy from adequate and well-controlled studies in adults (three Phase 3 clinical trials in hospitalized adults of varying disease severity),
- extrapolation of efficacy from adequate and well-controlled Phase 3 clinical trial in non-hospitalized adults and adolescents with mild-to-moderate COVID-19 who are at high risk of progression to severe COVID-19, including hospitalization or death),
- pharmacokinetic data from pediatric patients enrolled in Study GS-US-540-5823, which was compared to the adult PK data,
- safety and pharmacodynamic data from pediatric patients

Despite the inherent limitations of its small sample size and single-arm, open-label design, the descriptive outcome analyses in Study GS-US-540-5823 provided supportive evidence for the efficacy of RDV in pediatric patients hospitalized with COVID-19.

Based on the totality of data, the review team supports expanding the indication to encompass treatment of pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg with positive results of direct 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.

8. Safety

This section summarizes the safety findings of Study GS-US-540-5823 Cohorts 1-4 and Cohort 8.

Reference ID: 4971782

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

The safety database is considered adequate to assess the safety of RDV for the proposed indication, dosage regimen, duration of treatment, and patient population – pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg with positive results of direct 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.

The Applicant provided a basic assessment of safety as a component of the sNDA submission. No substantive issues with data integrity were identified.

Categorization of adverse events (AEs)
No issues were identified with respect to recording, coding, and categorizing AEs. The Applicant categorized AEs and SAEs in accordance with standard regulatory definitions. AEs were graded using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, which is derived from the Division of AIDS (DAIDS) toxicity grading criteria.

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

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

An overall summary of safety events in Study GS-US-540-5823 is presented in the following table. The reviewer assessments and conclusions are similar to those of the Applicant. Limitations of the safety analyses result from the small sample size and lack of a placebo arm.

Table 16. Overview of Adverse Events, GS-US-540-5823

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Subjects Experiencing Event	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Any AE	11 (92%)	7 (58%)	9 (75%)	7 (58%)	4 (80%)	38 (72%)
Related AE	4 (33%)	1 (8%)	0	1 (8%)	2 (40%)	8 (15%)
Grade 3 or 4 AE	6 (50%)	2 (17%)	1 (8%)	4 (33%)	2 (40%)	15 (28%)
Related Grade 3 or 4 AE	3 (25%)	0	0	0	0	3 (6%)
SAE	5 (42%)	2 (17%)	0	3 (25%)	1 (20%)	11 (21%)
Related SAE	0	0	0	0	0	0
Death*	2* (17%)	1 (8%)	0	0	1 (20%)	4 (8%)
Related deaths	0	0	0	0	0	0

Discontinuation of study drug due to AE	2 (17%)	0	0	0	0	2 (4%)
D/c of study drug due to related AEs	2 (17%)	0	0	0	0	2 (4%)

*Includes one nontreatment-emergent death (i.e. death occurred after Day 30±5).
Source: ADAE dataset, Study GS-US-540-5823
Abbreviations: AE, adverse event; SAE, serious adverse event

Reviewer Comment: The majority of AEs and Grade 3/4 AEs were assessed as unrelated to study drug by the study investigators. All deaths and SAEs were assessed as unrelated to study drug by the study investigators.

Deaths
In GS-US-540-5823, deaths were overall consistent with those observed in a hospitalized patient population. A total of 4 deaths (3 treatment-emergent and 1 nontreatment-emergent) occurred, and all deaths were assessed as unrelated to study drug by the study investigators. All of the SAEs in these 4 patients were assessed by investigators as unrelated to study drug.

Treatment-emergent deaths
• Subject (b) (6) (Cohort 1) was a 16-year-old white female with a history of bone marrow transplant, recurrent acute lymphoblastic leukemia, venoocclusive disease, seizure disorder, posterior reversible encephalopathy syndrome, hypertension, iron overload, pulmonary hemorrhage, respiratory failure, cholelithiasis, adrenal insufficiency, myopathy, CMV viremia (treated with ganciclovir), neuralgia, viral hemorrhagic cystitis, cholestatic liver disease, hyperbilirubinemia, transaminases increased, acute kidney injury, upper gastrointestinal hemorrhage, graft-versus-host-disease in GI tract, thrombotic microangiopathy, disseminated aspergillus (treated with voriconazole), subcutaneous emphysema, pneumomediastinum.
- Subject received five doses of RDV and discontinued RDV due to the development of the following AEs (assessed as related to study drug by the study investigators) on Day 6: Grade 3 AE of ALT increased, Grade 3 AE of AST increased, Grade 4 AE of hyperbilirubinemia.
- On Day 6, subject also developed Grade 4 AE of blood sodium increased and SAE of Grade 5 multiple organ dysfunction syndrome – both assessed as not related to study drug.
- On Day 14, subject died due to multi-system organ failure; this AE was considered Grade 5, fatal, and not related to study drug.

• Subject (b) (6) (Cohort 2) was a 16-year-old white female with a history of Rett syndrome, developmental delay, seizure disorder, long QT syndrome, vagal nerve stimulator implantation. Subject received ten doses of RDV. On Day 14, subject developed SAE of Grade 4 hypotension. On Day 30, subject developed SAE of Grade 4 cardiopulmonary arrest. On Day 35, subject developed SAE of Grade 5 respiratory failure and subject died that day due to family's decision to remove life support. The AE of respiratory failure was considered Grade 5, fatal, and not related to study drug.

• Subject (b) (6) (Cohort 8) was an 8-year-old white male with a history of asthma, obesity (BMI 27 kg/m^2). Subject received ten doses of RDV. Subject developed the following SAEs:

- Day 3: Grade 5 hemodynamic instability, Grade 4 pneumoperitoneum, Grade 5 respiratory distress
- Day 6: Grade 5 gastrointestinal necrosis
- Day 16: Grade 5 cardiac failure
- Day 18: Grade 5 multiple organ dysfunction syndrome

On Day 18, subject died due to respiratory, cardiac, and renal failure; these AEs were considered Grade 5, fatal, and not related to study drug.

Nontreatment-emergent deaths

• Subject (b) (6) (Cohort 1) was a 13-year-old white female with a history of lupus, lupus nephritis, CMV pneumonitis. Subject received ten doses of RDV. On Day 12, subject developed SAE of Grade 4 septic shock. On Day 35, subject developed SAE of Grade 5 pulmonary hemorrhage. On Day 42, subject died due to respiratory failure due to worsening COVID-19 and CMV pneumonitis. The AEs of COVID-19 and CMV pneumonitis were considered Grade 5, fatal, and not related to study drug.

Reviewer Comment: The clinical narratives were reviewed, and the FDA clinical reviewer agrees with the investigators' assessments that these deaths were unrelated to study medication. No specific drug-related safety concern has been identified from the range of deaths reported in GS-US-540-5823. There were no treatment-related deaths.

Serious Adverse Events (SAEs)

In GS-US-540-5823, SAEs were overall consistent with those observed in a hospitalized patient population. SAEs occurred in 21% of subjects. These SAEs were assessed by investigators as not related to study drug. The following table provides a summary of SAEs by Preferred Term (PT).

Table 17: SAEs

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Preferred Term	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Total subjects	5 (42%)	2 (17%)	0	3 (25%)	1 (20%)	11 (21%)
Cardiorespiratory arrest	0	1 (8%)	0	1 (8%)	0	2 (4%)
MODS	1 (8%)	0	0	0	1 (20%)	2 (4%)
Pyrexia	1 (8%)	0	0	1 (8%)	0	2 (4%)
Respiratory distress	1 (8%)	0	0	0	1 (20%)	2 (4%)
Septic shock	1 (8%)	0	0	1 (8%)	0	2 (4%)
Thrombosis	1 (8%)	0	0	1 (8%)	0	2 (4%)
Acute kidney injury	1 (8%)	0	0	0	0	1 (2%)
Cardiac failure	0	0	0	0	1 (20%)	1 (2%)
Cardiogenic shock	0	1 (8%)	0	0	0	1 (2%)
Cellulitis	0	1 (8%)	0	0	0	1 (2%)
Empyema	1 (8%)	0	0	0	0	1 (2%)
Enterococcal bacteremia	0	0	0	1 (8%)	0	1 (2%)

Gastrointestinal necrosis	0	0	0	0	1 (20%)	1 (2%)
Hemodynamic instability	0	0	0	0	1 (20%)	1 (2%)
Hyperkalemia	0	0	0	1 (8%)	0	1 (2%)
Hypocalcemia	0	0	0	1 (8%)	0	1 (2%)
Hypotension	0	1 (8%)	0		0	1 (2%)
Negative pressure pulmonary edema	1 (8%)	0	0	0	0	1 (2%)
Pneumoperitoneum	0	0	0	0	1 (20%)	1 (2%)
Pulmonary hemorrhage	1 (8%)		0	0	0	1 (2%)
Respiratory failure	0	1 (8%)	0	0	0	1 (2%)
Supraventricular tachycardia	0	0	0	1 (8%)	0	1 (2%)
Vomiting	1 (8%)	0	0		0	1 (2%)

Source: ADAE dataset, Study GS-US-540-5823
Abbreviations: MODS, multiple organ dysfunction syndrome

Reviewer Comment: The narratives were reviewed and the FDA clinical reviewer agrees with the investigators' assessments. No specific drug-related safety concern has been identified from the SAEs reported in GS-US-540-5823. There were no treatment-related SAEs.

Discontinuations due to AEs

Discontinuations due to AEs were infrequent, occurring in 2 subjects, and both were assessed by investigators as related to RDV:

• Subject (b) (6) (described under the Deaths subsection above).
• Subject (b) (6) (Cohort 1) was a 17-year-old Black or African American male with a history of asthma, obesity (BMI 54 kg/m^2), autism, attention deficit hyperactivity disorder, hypothyroidism, Grade 1 AE of ALT increased, Grade 1 AE of AST increased. On Day 5, subject experienced non-serious Grade 3 AE of ALT increased. Study drug was discontinued. Duration of treatment was 4 days. The event was resolved on Day 144.
- Day 1 (pre-dose): ALT 105 U/L; AST 95 U/L
- Day 2: ALT 111 U/L; AST 76 U/L
- Day 5: ALT 324 U/L; AST 103 U/L
- Day 8: ALT 185 U/L; AST 31 U/L

Reviewer Comment: The narratives were reviewed and the FDA clinical reviewer agrees with the investigators' assessments.

Significant AEs

This section describes Grades 3 and 4 events that occurred in the treatment-emergent period (during treatment and through Day 30 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 the SAE subsection (above).

In GS-US-540-5823, Grade 3/4 AEs were overall consistent with those observed in a hospitalized patient population. Grade 3/4 AEs occurred in 28% of subjects. The majority of Grade 3/4 AEs were assessed by investigators as not related to study drug.

Grade 3/4 AEs considered related to study drug by the study investigators (i.e. ADRs) occurred in 6% of subjects. These Grade 3/4 ADRs are summarized below (*note: subjects could have more than one event*):

- ALT increased (n=2), AST increased (n=1), hyperbilirubinemia (n=1), hemoglobin decreased (n=1)

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

Treatment-emergent AEs (TEAEs)

In GS-US-540-5823, TEAEs were overall consistent with those observed in a hospitalized patient population. TEAEs occurred in 72% of subjects. The majority of these AEs were assessed by investigators as not related to study drug.

Table 18: Treatment-Emergent AEs by Preferred Term, All Grade and All Causality, Occurring in ≥ 2 subjects

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Preferred Term	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Total subjects	11 (92%)	7 (58%)	9 (75%)	7 (58%)	4 (80%)	38 (72%)
Constipation	3 (25%)	1 (8%)	1 (8%)	1 (8%)	3 (60%)	9 (17%)
Acute kidney injury	4 (33%)	0	0	1 (8%)	1 (20%)	6 (11%)
Abdominal pain[1]	3 (25%)	0	0	1 (8%)	2 (40%)	6 (11%)
Hyperglycemia	1 (8%)	1 (8%)	1 (8%)	2 (17%)	0	5 (9%)
Pyrexia	1 (8%)	2 (17%)	1 (8%)	1 (8%)	0	5 (9%)
ALT increased	2 (17%)	0	0	1 (8%)	1 (20%)	4 (8%)
Hypertension	2 (17%)	1 (8%)	0	0	1 (20%)	4 (8%)
Hypomagnesemia	0	1 (8%)	0	1 (8%)	2 (40%)	4 (8%)
Rash[2]	0	1 (8%)	0	2 (17%)	1 (20%)	4 (8%)
Vomiting	1 (8%)	1 (8%)	1 (8%)	0	1 (20%)	4 (8%)
Nausea	1 (8%)	0	0	1 (8%)	1 (20%)	3 (6%)
Agitation	0	1 (8%)	2 (17%)	0	0	3 (6%)
Anemia	1 (8%)	1 (8%)	0	1 (8%)	0	3 (6%)
Bradycardia	0	2 (17%)	0	1 (8%)	0	3 (6%)
ARDS	1 (8%)	1 (8%)	0	0	0	2 (4%)
Cardiorespiratory arrest	0	1 (8%)	0	1 (8%)	0	2 (4%)
AST increased	1 (8%)	0	0	1 (8%)	0	2 (4%)
Hypoalbuminemia	1 (8%)	1 (8%)	0	0	0	2 (4%)
Hypocalcemia	0	0	0	1 (8%)	1 (20%)	2 (4%)
Hypokalemia	1 (8%)	0	0	0	1 (20%)	2 (4%)
Hypoxia	1 (8%)	0	1 (8%)	0	0	2 (4%)
Infusion site extravasation	0	2 (17%)	0	0	0	2 (4%)
Insomnia	0	0	1 (8%)	0	1 (20%)	2 (4%)
MODS	1 (8%)	0	0	0	1 (20%)	2 (4%)
Pleural effusion	0	1 (8%)	0	0	1 (20%)	2 (4%)
Respiratory distress	1 (8%)	0	0	0	1 (20%)	2 (4%)

Respiratory failure	1 (8%)	1 (8%)	0	0	0	2 (4%)
Septic shock	1 (8%)	0	0	1 (8%)	0	2 (4%)
Thrombosis	1 (8%)	0	0	1 (8%)	0	2 (4%)

Source: ADAE dataset, Study GS-US-540-5823
[1] Includes abdominal pain, abdominal pain upper, abdominal distension.
[2] Includes rash, rash maculo-papular.
Abbreviations: ARDS, acute respiratory distress syndrome

The majority of AEs were Grade 1 in severity. The three most commonly reported AEs were constipation (17%), acute kidney injury (11%), and abdominal pain (11%).
Reviewer Comment: No new or unexpected findings were observed compared to the events noted in the hospitalized trials in adults. TEAEs were overall consistent with those observed in a hospitalized patient population.

ADRs occurred in 15% of subjects. ADRs that occurred in ≥ 2% of subjects were ALT increased (6%), AST increased (4%).

Reviewer Comment: ALT increased was the only ADR that occurred in ≥ 5% of subjects; this will be displayed in product labeling.

Laboratory abnormalities
Graded laboratory abnormalities occurred in 90% of subjects. Grade 3/4 laboratory abnormalities occurred in 42% of subjects.

The following table summarizes graded chemistry and urinalysis results.

Table 19: Chemistry and Urinalysis Laboratory Results, All Grade

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Parameter and Max Analysis Toxicity Grade	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Increased alanine aminotransferase (U/L)						
N	12	12	12	10	5	51
Grade 1 (1.25 to <2.5x ULN)	4 (33%)	0	2 (17%)	1 (10%)	2 (40%)	9 (18%)
Grade 2 (2.5 to <5x ULN)	1 (8%)	1 (8%)	0	1 (10%)	0	3 (6%)
Grade 3 (5 to <10x ULN)	1 (8%)	0	0	1 (10%)	0	2 (4%)
Grade 4 (>10x ULN)	0	0	0	0	0	0
Increased aspartate aminotransferase (U/L)						
N	12	12	12	11	5	52
Grade 1 (1.25 to <2.5x ULN)	1 (8%)	1 (8%)	0	1 (9%)	1 (20%)	4 (8%)
Grade 2 (2.5 to <5x ULN)	1 (8%)	3 (25%)	0	2 (18%)	0	6 (12%)
Grade 3 (5 to <10x ULN)	1 (8%)	0	0	0	0	1 (2%)
Grade 4 (>10x ULN)	0	0	0	0	0	0
Increased total bilirubin (mg/dL)						
N	12	12	12	10	5	51
Grade 1 (1.1 to <1.6x ULN)	0	1 (8%)	0	0	0	1 (2%)

Grade 2 (1.6 to <2.6x ULN)	0	1 (8%)	0	0	0	1 (2%)
Grade 3 (2.6 to <5x ULN)	0	0	0	0	0	0
Grade 4 (≥5x ULN)	0	0	0	0	0	0
Increased direct bilirubin (mg/dL)						
N	7	7	4	3	2	23
Grade 1 (NA)	0	0	0	0	0	0
Grade 2 (NA)	0	0	0	0	0	0
Grade 3 (> ULN with other signs and symptoms of hepatotoxicity)	1 (14%)	1 (14%)	0	0	0	2 (9%)
Grade 4 (> ULN with life-threatening consequences [e.g., signs and symptoms of liver failure])	0	0	0	0	0	0
Increased creatinine (mg/dL)						
N	12	12	12	11	5	52
Grade 1 (1.1 to 1.3x ULN)	0	0	0	0	1 (20%)	1 (2%)
Grade 2 (>1.3 to 1.8x ULN *OR* increase to 1.3 to <1.5x subject's baseline)	1 (8%)	1 (8%)	4 (33%)	1 (9%)	0	7 (13%)
Grade 3 (>1.8 to <3.5x ULN *OR* increase to 1.5 to <2.0x subject's baseline)	1 (8%)	0	1 (8%)	1 (9%)	1 (20%)	4 (8%)
Grade 4 (≥3.5x ULN *OR* increase of ≥2.0x subject's baseline)	1 (8%)	0	0	0	0	1 (2%)
Decreased eGFR (mL/min/1.73m^2)						
N	12	12	11	0	5	40
Grade 1 (NA)	0	0	0	0	0	0
Grade 2 (<90 to 60 mL/min/1.73m^2 *OR* 10 to <30% decrease from subject's baseline)	3 (25%)	2 (17%)	2 (18%)	0	1 (20%)	8 (20%)
Grade 3 (<60 to 30 mL/min/1.73m^2 *OR* 30 to <50% decrease from subject's baseline)	1 (8%)	0	4 (36%)	0	1 (20%)	6 (15%)
Grade 4 (<30 mL/min/1.73m^2 *OR* ≥50% decrease from subject's baseline or dialysis needed)	1 (8%)	0	0	0	0	1 (3%)
Increased glucose (mg/dL)						
N	12	12	12	11	5	52
Grade 1 (116 to 160 mg/dL)	3 (25%)	1 (8%)	1 (8%)	1 (9%)	1 (20%)	7 (13%)
Grade 2 (>160 to 250 mg/dL)	3 (25%)	3 (25%)	2 (17%)	1 (9%)	3 (60%)	12 (2%)
Grade 3 (>250 to 500 mg/dL)	1 (8%)	0	1 (8%)	0	0	2 (4%)
Grade 4 (≥500 mg/dL)	0	0	0	0	0	0
Decreased potassium (mEq/L)						
N	12	12	12	11	5	52
Grade 1 (3.0 to 3.4 mEq/L)	2 (17%)	0	2 (17%)	1 (9%)	1 (20%)	6 (12%)
Grade 2 (2.5 to <3.0 mEq/L)	1 (8%)	1 (8%)	0	1 (9%)	0	3 (6%)
Grade 3 (2.0 to 2.5 mEq/L)	0	1 (8%)	0	0	1 (20%)	2 (4%)
Grade 4 (<2.0 mEq/L)	0	0	0	0	0	0

Urine glucose (mg)						
N	11	11	11	9	4	46
Grade 1 (≤250 mg)	1 (9%)	2 (18%)	0	0	0	3 (7%)
Grade 2 (250 to ≤500 mg)	0	0	0	0	0	0
Grade 3 (>500 mg)	1 (9%)	0	0	1 (11%)	0	2 (4%)
Grade 4 (NA)	0	0	0	0	0	0
Urine protein						
N	8	9	10	7	2	36
Grade 1 (1+)	3 (38%)	0	1 (10%)	0	0	4 (11%)
Grade 2 (2+)	0	1 (11%)	0	1 (14%)	0	2 (6%)
Grade 3 (3+ or higher)	1 (13%)	0	0	0	1 (50%)	2 (6%)
Grade 4 (NA)	0	0	0	0	0	0

Source: ADLB dataset, Study GS-US-540-5823
eGFR calculated using Bedside Schwartz formula for 1 to <18 year-old children.
For each laboratory parameter, N represents the number of subjects who had at least one post-baseline value for the specified test.
Abbreviations: ULN, upper limit of normal; NA, not applicable

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 (SBECD) excipient. Similar effects were seen in humans in Study GS-US-540-5823 with Grade 3/4 creatinine clearance decreased (18%) and Grade 3/4 increased creatinine (10%) observed in this hospitalized trial in pediatric subjects. None of these renal laboratory abnormalities resulted in RDV discontinuation. These laboratory abnormalities were also noted in the hospitalized trials in adults but occurred at similar or slightly higher rates in the PBO or SOC groups compared to the RDV group.

Rates of Grade 3/4 ALT elevations (4%) and Grade 3/4 AST elevations (2%) were low. Two subjects discontinued RDV due to ALT/AST elevations (please refer to the Deaths subsection and to the Discontinuations due to AEs subsection above).

There were no Grade 3/4 bilirubin elevations.

The following table summarizes graded hematology and coagulation results.

Table 20: Hematology and Coagulation Laboratory Results, All Grade

Cohort	**1**	**2**	**3**	**4**	**8**	**Total**
Parameter and Max Analysis Toxicity Grade	**≥ 12 years to < 18 years and weight ≥ 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg (n=12)**	**≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg (n=12)**	**< 12 years and weight ≥ 40 kg (n=12)**	**53**
Decreased hemoglobin (g/dL)						
N	12	12	12	10	5	51
Grade 1 (10 to <10.9 g/dL)	1 (8%)	1 (8%)	1 (8%)	1 (10%)	0	4 (8%)
Grade 2 (9 to <10 g/dL)	1 (8%)	3 (25%)	2 (17%)	0	0	6 (12%)
Grade 3 (7 to <9 g/dL)	4 (33%)	1 (8%)	0	2 (20%)	1 (20%)	8 (16%)
Grade 4 (<7 g/dL)	0	0	0	0	1 (20%)	1 (2%)

Decreased neutrophils (cells/mm^3)						
N	12	12	12	10	5	51
Grade 1 (800 to 1000/mm^3)	0	0	2 (17%)	1 (10%)	0	3 (6%)
Grade 2 (600 to 799/mm^3)	0	0	0	0	1 (20%)	1 (2%)
Grade 3 (400 to 599/mm^3)	0	0	0	0	0	0
Grade 4 (<400/mm^3)	0	0	1 (8%)	0	0	1 (2%)
Decreased lymphocytes (cells/mm^3)						
N	12	11	5	0	5	33
Grade 1 (600 to 650/mm^3)	0	1 (9%)	0	0	0	1 (3%)
Grade 2 (500 to <600/mm^3)	0	0	2 (40%)	0	0	2 (6%)
Grade 3 (350 to <500/mm^3)	0	0	0	0	0	0
Grade 4 (<350/mm^3)	1 (8%)	0	0	0	1 (20%)	2 (6%)
Decreased platelets (cells/mm^3)						
N	12	12	12	10	5	51
Grade 1 (100,000 to <125,000/mm3)	1 (8%)	0	1 (8%)	0	1 (20%)	3 (6%)
Grade 2 (50,000 to <100,000/mm^3)	0	1 (8%)	0	1 (10%)	0	2 (4%)
Grade 3 (25,000 to <50,000/mm^3)	1 (8%)	0	0	0	0	1 (2%)
Grade 4 (<25,000/mm3)	0	0	0	0	0	0
Decreased WBC (cells/mm^3)						
N	12	12	12	10	5	51
Grade 1 (2000 to 2499/mm^3)	0	0	1 (8%)	0	0	1 (2%)
Grade 2 (1500 to <1999/mm^3)	0	0	0	0	0	0
Grade 3 (1000 to <1499/mm^3)	1 (8%)	0	0	0	1 (20%)	2 (4%)
Grade 4 (<1000/mm^3)	0	0	0	0	0	0
Prothrombin time increased						
N	12	12	10	8	4	46
Grade 1 (1.1 to <1.25x ULN)	1 (8%)	2 (17%)	1 (10%)	2 (25%)	0	6 (13%)
Grade 2 (1.25 to <1.5x ULN)	2 (17%)	0	2 (20%)	0	1 (25%)	5 (11%)
Grade 3 (1.5 to <3x ULN)	1 (8%)	1 (8%)	0	1 (13%)	0	3 (7%)
Grade 4 (≥3x ULN)	0	0	0	0	0	0
Activated Partial Thromboplastin Time (aPTT) increased						
N	11	11	9	9	5	45
Grade 1 (1.1 to <1.66x ULN)	0	0	3 (33%)	2 (22%)	1 (20%)	6 (13%)
Grade 2 (1.66 to <2.33x ULN)	1 (9%)	0	0	1 (11%)	1 (20%)	3 (7%)
Grade 3 (2.33 to <3x ULN)	1 (9%)	1 (9%)	0	0	0	2 (4%)
Grade 4 (≥3x ULN)	0	1 (9%)	0	0	0	1 (2%)

Source: ADLB dataset, Study GS-US-540-5823
eGFR calculated using Bedside Schwartz formula for 1 to <18 year-old children.
For each laboratory parameter, N represents the number of subjects who had at least one post-baseline value for the specified test.
Abbreviations: ULN, upper limit of normal

Reviewer Comment: None of these hematologic or coagulation laboratory abnormalities resulted in RDV discontinuation.

Of the above Grade 3/4 laboratory abnormalities, those that occurred in ≥ 3% of subjects were hemoglobin decreased (18%), prothrombin time increased (7%), activated partial thromboplastin time increased (7%), lymphocytes decreased (6%), and WBC decreased (4%).

Overall Assessment: The laboratory abnormalities observed in pediatric subjects were consistent with those observed in clinical trials in adults. Acknowledging the caveats associated with cross-study comparisons, the small sample size of Study GS-US-540-5823 (further decreased due to the varying number of subjects who had at least one post-baseline value for a given laboratory parameter), these laboratory abnormalities occurred at comparable rates to those observed in the hospitalized trials in adults.

In GS-US-540-5823, Grade 3/4 laboratory abnormalities that occurred in ≥ 3% of subjects were hemoglobin decreased (18%), eGFR decreased (18%), creatinine increased (10%), direct bilirubin increased (9%), prothrombin time increased (7%), activated partial thromboplastin time increased (7%), lymphocytes decreased (6%), proteinuria (6%), WBC decreased (4%), ALT increased (4%), glucose increased (4%), potassium decreased (4%), and glycosuria (4%). These findings will be displayed in product labeling. Of note, the approved label already outlines that monitoring of renal function, hepatic function, and prothrombin time are recommended while receiving RDV.

Submission-specific safety issues

Nephrotoxicity:

- Renal AEs (all causality) occurred in 6 subjects. Renal events that occurred in at least 2 subjects were acute kidney injury (n=6).

There were no renal ADRs.

- Grade 3/4 renal AEs of acute kidney injury occurred in two subjects; these were assessed as not related to RDV.
- A total of one renal SAE (acute kidney injury) occurred; this renal SAE was assessed as not related to RDV.
- No renal AEs led to RDV discontinuation.
- Grade 3/4 creatinine clearance decreased occurred in 7 subjects and Grade 3/4 increased creatinine occurred in 5 subjects; these laboratory abnormalities occurred at comparable rates to those observed in the hospitalized trials in adults.
- No renal laboratory abnormalities led to RDV discontinuation.

Overall Assessment: Based on these findings, no additional labeling is warranted aside from displaying GS-US-540-5823 renal laboratory data in Section 6. Routine pharmacovigilance will be in place to detect postmarketing signals.

Hepatotoxicity:

- In GS-US-540-5823, the only hepatic AEs were laboratory events: ALT increased (n=4), AST increased (n=2), hyperbilirubinemia (n=1).
- Hepatic ADRs were the same laboratory events outlined above.
- Grade 3/4 hepatic AEs occurred in two subjects:
    - Subject (b) (6) had Grade 3 AE of ALT increased, Grade 3 AE of AST increased, Grade 4 AE of hyperbilirubinemia at Day 6; these were also assessed as Grade 3/4 ADRs; RDV was discontinued.
    - Subject (b) (6) had Grade 3 AE of ALT increased at Day 5; these were also assessed as Grade 3 ADR; RDV was discontinued.

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- There were no hepatic SAEs.
- Hepatic AEs or hepatic ADRs led to RDV discontinuation in two subjects, as noted above.
- Grade 3/4 ALT elevations occurred in two subjects. Grade 3/4 AST elevations occurred in one subject. There were no Grade 3/4 bilirubin elevations.
- Grade 3/4 transaminase elevations led to RDV discontinuation in two subjects, as noted above.

Overall Assessment: Based on these findings, no additional labeling is warranted aside from displaying GS-US-540-5823 hepatic laboratory data in Section 6. Routine pharmacovigilance will be in place to detect postmarketing signals.

Hypersensitivity Reactions

- Hypersensitivity or infusion-related reactions occurred in 11 subjects (21%). The majority of events were Grade 1 in severity. No RDV infusions were paused for these events.
- All of these events were assessed as not related to RDV.
- No SAEs or Grade 3/4 events were observed in GS-US-540-5823.
- No subjects discontinued RDV due to hypersensitivity or infusion-related reactions.

Overall Assessment: Based on these findings, no additional labeling is warranted at this time. Routine pharmacovigilance will be in place to detect postmarketing signals.

Hemorrhagic events:

- A total of two hemorrhagic AEs (pulmonary hemorrhage [n=1]; gastrointestinal hemorrhage [n=1]) occurred.
- There were no hemorrhagic ADRs.
- There was one Grade 3 hemorrhagic AE (gastrointestinal hemorrhage) and one Grade 5 hemorrhagic AE (pulmonary hemorrhage); these were assessed as not related to RDV.
- A total of one hemorrhagic SAEs (pulmonary hemorrhage) occurred; this hemorrhagic SAE was assessed as not related to RDV.
- No hemorrhagic AEs led to RDV discontinuation.
- Grade 3/4 PT elevations occurred in three subjects.
- No coagulation laboratory abnormalities led to RDV discontinuation.

Overall Assessment: Based on these findings, no additional labeling is warranted aside from displaying GS-US-540-5823 coagulation laboratory data in Section 6. Routine pharmacovigilance will be in place to detect postmarketing signals.

Rash events

- Rash events occurred in 4 subjects (8%). All rash events were Grade 1 in severity.
- There were no rash ADRs.
- No subjects discontinued RDV due to rash.
- No SAEs or Grade 3/4 events were observed in GS-US-540-5823.
- No Grade 3/4 events, and no events of Stevens Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme were observed in Study GS-US-540-5823.

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Overall Assessment: 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.

Conclusions on safety

The overall safety profile in the GS-US-540-5823 pediatric population is consistent with the known safety profile of RDV.

9. Advisory Committee Meeting

As there were no issues identified that would necessitate an Advisory Committee meeting, an Advisory Committee was not convened to discuss this application.

10. Pediatrics

The Applicant submitted an initial Pediatric Study Plan (iPSP) for RDV in advance of the original NDA submission. The document was reviewed by the Division of Pediatrics and Maternal Health (DPMH), the Division of Antivirals, and the Pediatric Review Committee (PeRC). The Applicant proposed to use an extrapolation approach leveraging PK, safety, and efficacy data, wherever applicable, in adults and adolescents to guide dosing and assessment of RDV efficacy in the pediatric population. The Agency concurred that SARS-CoV-2 is expected to respond similarly to RDV in pediatric patients as it does in adults, and therefore pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, supplemented with information obtained in pediatric patients, such as PK and safety from Study GS-US-540-5823. 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's recommendations. The Agency's recommendations for revisions were conveyed to the Applicant. The Applicant accepted the Agency's recommendations, and the Agency issued a formal notice of agreement in July 2020.

As outlined in Section 2 of this review, the initial indication included patients 12 years of age and older and weighing at least 40 kg. 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. Due to limitations of the PBPK and popPK models and the absence of PK data in the pediatric population at the time of the original NDA, the initial indication for RDV did not include pediatric patients younger than 12 years of age or weighing < 40 kg. The Applicant requested, and the Agency granted, a deferral of pediatric studies for patients younger than 18 years of age or weighing < 40 kg on the basis that the drug is ready for approval for use in adults before pediatric studies are complete (section 505B(a)(3)(A)(i) of the Act).

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The proposed pediatric development plan (as outlined in the iPSP) comprises a broad range of pediatric patients including the following: 1) preterm neonates and infants 0 days to < 56 days old; 2) term neonates 0 days to < 28 days old and; 3) pediatric patients ≥ 28 days to < 18 years old. Patients in all age ranges are enrolled in parallel, except for preterm neonates and infants < 56 days old and a subset of term neonates. As outlined in this review, Cohorts 1-4 and Cohort 8 are submitted in this sNDA.

The Applicant is planning a (b) (4)

11. Other Relevant Regulatory Issues

- *Financial disclosures*

Financial disclosures were provided and reviewed for investigators involved in GS-US-540-5823. There were no financial disclosures of significant concern, individually or collectively. The financial disclosures do not impact the approvability of Veklury.

- *Other Good Clinical Practice (GCP) issues*

The clinical trial discussed in this review was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Counsel (ICH) Good Clinical Practice (GCP) guidelines.

- *Office of Scientific Investigations (OSI) audits*

For this application with a PK/safety study, no clinical inspections were warranted.

- *Office of Study Integrity and Surveillance (OSIS) audits*

For this application, OSIS determined that an inspection is not warranted at this time for the bioanalytical site (b) (4)) used for GS-US-540-5823. OSIS inspected the site in (b) (4), which falls within the surveillance interval. The final classification for the inspection was No Action Indicated (NAI).

OSIS inspections of the following Study GS-US-540-5823 sites (Carolinas Medical Center - Levine Children's Hospital, Charlotte, NC [Site #11115] and Texas Children's Hospital, Houston, TX [Site #07633]) did not identify any objectionable conditions were observed. The final inspection classification is No Action Indicated (NAI) for both sites. Please refer to the OSIS Consult Review for further details.

- *Office of Surveillance and Epidemiology (OSE)*

Based on the review of EUA data and postmarketing data, no additional labeling is warranted at this time. Routine pharmacovigilance will be in place to detect postmarketing signals. Please refer to the OSE Consult Review for further details.

- *Division of Medication Error Prevention and Analysis (DMEPA)*

For this application, DMEPA determined there will be a period of time when there will be inconsistencies between the proposed prescribing information and the approved Veklury for injection container label and carton labeling. Because these inconsistencies may lead to medication errors, especially in the pediatric population, the Agency recommended a Dear Health Care Provider (DHCP) letter be provided. Please refer to the DMEPA Consult Review for further details.

12. Labeling

Prescribing Information

The summary that follows reflects the major changes to the prescribing information (PI) that have been proposed by the Agency and accepted by the Applicant.

- INDICATIONS AND USAGE section:

The indication for Veklury was expanded to encompass pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg.

The revised indication is treatment of adults and pediatric patients (28 days and older and weighing at least 3 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.

- DOSAGE AND ADMINISTRATION section

The review team recommends the following dosages for pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg: single loading dose of RDV 5 mg/kg on Day 1 via IV infusion followed by once-daily maintenance doses of RDV 2.5 mg/kg from Day 2 via IV infusion. The treatment duration depends upon the patient population, is unchanged from the currently approved label, and is as follows:

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

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

- ADVERSE REACTIONS section:

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

Adverse reactions leading to RDV discontinuation will be displayed.

Laboratory data from Study GS-US-540-5823 will also be displayed.

- USE IN SPECIFIC POPULATIONS section

The data that support expanding the indication to encompass pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg was described (see above Sections 5, 7, 8 and 10).

- CLINICAL PHARMACOLOGY section:

The population pharmacokinetic data and clinical trial pharmacokinetic data that support expanding the indication to encompass pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg was described (see above Section 5).

- CLINICAL STUDIES section:

The ordinal scale assessment on Day 10 was not prespecified as the primary efficacy endpoint in the protocol or the SAP for Study GS-US-540-5823. The protocol and SAP also did not prespecify Day 10 as the timepoint for any of the efficacy assessments. Despite these study design limitations, the Applicant proposed the Day 10 timepoint for inclusion in labeling because Day 10 is the final assessment day when this data was collected in all subjects, and subjects could receive RDV for up to 10 days. The Applicant proposed Day 10 as the summary descriptive efficacy measure for labeling because the Applicant assessed this timepoint provides information about clinical status at the end of the dosing period and the Applicant assessed this information would be meaningful to health care providers.

Revisions were made to clarify that the primary objectives of Study GS-US-540-5823 were to obtain pharmacokinetic and safety data in pediatric subjects; describe the schedule of study assessments to provide context to the descriptive outcome analyses; clarify that subjects were unvaccinated; add the proportion of subjects who were discharged by Day 30.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Reference ID: 4971782

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

Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

To date, the Agency has determined that the following PMR should be issued:

- PMR to evaluate substitutions meeting the following criteria for their impact on remdesivir susceptibility of virus in cell culture, or, if virus is unable to be recovered, in a replicon assay or biochemical assay of RdRp activity:

  Substitutions identified in replication complex subunits as treatment-emergent at a frequency of ≥15% of the virus population or are polymorphisms associated with viral RNA rebound in more than one subject, including different amino acid substitutions at the same position:
  nsp9: N95D
  nsp10: D64Y, T101I
  nsp12: V495F, A656P, G670V, A656P+G670V
  nsp13: R248I, S259L, V266F
  nsp14: N129D

  Study Completion: 02/2023
  Final Report Submission: 03/2023

14. Recommended Comments to the Applicant

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

Appendix 1 – 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): GS-US-540-5823

Was a list of clinical investigators provided:	Yes X	No __ (Request list from Applicant)
Total number of investigators identified: 126 Overall: 19 Principal Investigators, 107 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): 0		
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: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes	No __ (Request explanation from Applicant)

Reference ID: 4971782

Is a description of the steps taken to minimize potential bias provided: N/A	Yes	No __ (Request explanation 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 trials, 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. There are no investigators with a financial interest.

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

Reference ID: 4971782

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
04/21/2022 07:17:52 AM

KIRK M CHAN-TACK
04/21/2022 07:57:05 AM

MARIO SAMPSON
04/21/2022 09:42:05 AM

JUSTIN C EARP
04/21/2022 10:49:07 AM

VIKRAM ARYA
04/21/2022 10:55:10 AM

KIMBERLY A STRUBLE
04/21/2022 10:57:31 AM

YODIT BELEW
04/21/2022 11:42:32 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s011

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-11
   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	11/30/2021	11/30/2021	12/08/2021	05/30/2022	02/25/2022

3. **Provides For:**
   Provides for the expansion of the patient population for Veklury to include pediatric patients aged ≥ 28 days weighing ≥ 3 kg and provides interim safety, tolerability, pharmacokinetics (PK), and efficacy data from Cohorts 1 through 4 and Cohort 8 in the ongoing Phase 2/3 Study GS-US-540-5823, titled, *"A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With COVID-19."*

4. **Review #**: 1

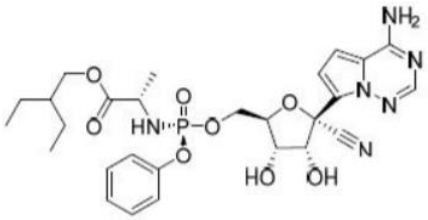
5. **Clinical Review Division**: OID/DAV

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:
The Environmental Assessment (EA) was provided in the Section 1.12.14.

11. Disciplines/Consults: None

12. Executive Summary:

This Prior Approval Efficacy supplement provides for the expansion of the patient population for Veklury to include pediatric patients aged ≥ 28 days weighing ≥ 3 kg and provides interim safety, tolerability, pharmacokinetics (PK), and efficacy data from Cohorts 1 through 4 and Cohort 8 in the ongoing Phase 2/3 Study GS-US-540-5823, titled, *"A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With COVID-19."*

No updates to the CMC-related Module 3 are provided. No information was submitted to the Module 3 for Product Quality reviewer's evaluation.

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-11 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: 2/25/2022 10:33:01AM
GUID: 5407887b000a1c7a2c99827ec2cd922d

David Lewis

Digitally signed by David Lewis
Date: 2/25/2022 10:35:28AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s011

VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW

NDA: **214787 SE-011 SDN 208 (0116) DATE REVIEWED**: 11/30/2021 to 3/25/2022
Virology Reviewer: William L. Ince, Ph.D. and Eric Donaldson, Ph.D.

CDER Receipt Date:	Assigned Date:	Review Complete Date	PDUFA Date
11/30/2021	12/1/2021	3/25/2022	5/30/2022

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

Amendments: None
Additional Submissions Reviewed:

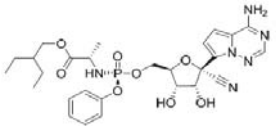
SDN	eCTD (SN)	Received	Assigned	Description	Appendix
208	0116	11/30/2021	12/1/2021	Supplement 11	*NA*
209	7623723	11/24/2021	12/6/2021	NGS data	*NA*
225	0128	12/23/2021	12/23/2021	Response to Virology IR – Mock reformatted dataset	*NA*
251	0148	1/31/2022	1/31/2022	Response to Virology IR – Reformatted dataset	*NA*
259	0154	2/15/2022	2/15/2022	Labeling	*NA*
266	0159	3/4/2022	3/4/2022	Response to Virology IR – PMR	*C*
268	0160	3/7/2022	3/08/2022	Labeling	*NA*
274	0161	3/15/2022	3/16/2022	Response to Virology IR – Assay information	*D*
276	0162	3/17/2022	3/18/2022	Response to Virology IR – PMR	*E*
278	0164	3/18/2022	3/18/2022	Labeling	*NA*
283	0166	3/25/2022	3/25/2022	Response to Virology IR – PMR	*F*
290	0169	3/31/2022	3/31/2022	Response to Virology IR – PMR / Labeling	*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
Current indication: Treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg with coronavirus disease 2019 (COVID-19).

Dosage Form/Route of administration: 100 mg powder for aqueous reconstitution/intravenous
Supporting documents: Pre-IND 125566 submissions; IND147753; IND14771

Abbreviations: ACE2, Angiotensis-1 Converting Enzyme-2; AST, aspartate aminotransferase; ATP, adenosine triphosphate; CI, confidence interval; CoV, coronavirus; COVID-19, coronavirus infectious disease originating in 2019; CPE, cytopathic effect; EC_{50} value; effective concentration 50%; ELISA, enzyme-linked immunosorbent assay; EUA, emergency use authorization; GISAID, Global Initiative on Sharing All Influenza Data; IC_{50} value, inhibitory concentration 50%; IV, intravenous; MOI, multiplicity of infection; NDA, new drug application; NGS, next-generation sequencing; NHBE, normal human bronchial epithelial; nsp, nonstructural protein; NTP, nucleoside triphosphate; PAS, Prior Approval Supplement; PBS, phosphate buffered saline; PFU, plaque forming units; RdRp, RNA dependent RNA polymerase; RDV, remdesivir; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; $TCID_{50}$, tissue culture infectious dose 50%; TP, triphosphate; USPI, United States Package Insert.

Reference ID: 4962753 7623753

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW
NDA: **214787 SE-011 SDN 208 (0116) DATE REVIEWED**: 11/30/2021 to 3/25/2022
Virology Reviewer: William L. Ince, Ph.D. and Eric Donaldson, Ph.D.

SUMMARY

The purpose of Supplement 11 of New Drug Application 214787 is to extend the current indication for remdesivir (VEKLURY®) to *pediatric patients 28 days and older and weighing at least 3 kg for the treatment of coronavirus disease 2019 (COVID-19)*. Remdesivir is currently indicated for adults and pediatric patients ≥12 years of age and weighing ≥40 kg for the treatment of coronavirus disease 2019 (COVID-19) who require hospitalization [approved 10/22/2020 (Clinical Virology Review N214787.000, E. Donaldson, Ph.D., DARRTS Reference ID: 4672246)] and who are non-hospitalized and at high risk of progression to severe COVID-19, including hospitalization or death [approved 1/21/2022 (N214787.SE-010.190, W. Ince, Ph.D., DARRTS reference ID: 4672246)].

Clinical Virology
Interim clinical virology data from the single-arm trial GS-US-540-5823 submitted to support this supplement included longitudinal quantitative viral RNA shedding and baseline and post-baseline sequence data from respiratory samples. A total of 54 subjects were enrolled, and 53 subjects were positive for SARS-CoV-2 at baseline and included in the Full Analysis Set and virologic analyses.

Viral RNA Shedding
Nasopharyngeal/oropharyngeal, nasal/oropharyngeal, and/or endotracheal samples were collected at baseline (Day 1) and Days 3, 5, 7, and 10. Viral RNA quantified by RT-PCR exhibited a general declined in all sample types for most subjects over the observation period; however, <50% of subjects were confirmed viral RNA-negative (based on two consecutive negative RT-PCR results) through Day 10. While a placebo comparator arm was not included in this trial, the results are consistent with the lack of a significant impact of RDV treatment on viral RNA in nasopharyngeal swabs that was observed in adult, placebo-controlled trials [see Clinical Virology Review for NDA 214787, Supplement 9 by E. Donaldson Ph.D., DARRTS Reference ID: 4917124 (N214787.S-009.MI.219) and Clinical Virology Review for NDA 214787, Supplement 10 Clinical Virology Review by W. Ince Ph.D., DARRTS Reference ID: 4672246; (N214787.SE-010.190)].

Viral Nucleotide Sequence Analyses
SARS-CoV-2 whole-genome sequence analysis was attempted for all subjects in the Full Analysis Set who had respiratory samples with viral RNA ≥LLOQ of the viral RNA load assay. Of the 53 subjects in the FAS, sequencing was attempted for baseline and/or post-baseline samples for 39 subjects with evaluable samples. Sequence data at any time point were obtained for 34 subjects. Baseline sequence data were obtained for 30 subjects, post-baseline sequence data were obtained for 27 subjects, and sequence data were successfully obtained at baseline and post-baseline for 23 subjects.

The SARS-CoV-2 variant was determined for 34 subjects. The most common variant represented was B.1.2 (5 subjects), followed by B.1.1.7 (Alpha; 4 subjects) and B.1.429 (Epsilon; 3 subjects). All other variants were identified in ≤2 subjects. SARS-CoV-2 Variants of Concern including Delta and Omicron were not represented in this trial, which completed enrollment of the cohorts included in the interim analysis prior to widespread circulation of Delta and Omicron variants. Cell culture antiviral activity evaluations indicate that remdesivir has similar activity across all major variants, including Delta and Omicron. For additional details, refer to the Clinical Virology Review for NDA 214787, Supplement 9 by E. Donaldson Ph.D., Reference ID in DARRTS: 4917124 (N214787.S-009.MI.219); and Clinical Virology Review for NDA 214787, Supplement 13 by W. Ince Ph.D., Reference ID in DARRTS: 4957456 (N214787.S-013.265). Data were inadequate to draw a conclusion regarding the association between the SARS-CoV-2 genotype and a treatment effect or clinical outcome.

SARS-CoV-2 replication complex genes nsp8, nsp9, nsp10, nsp12, nsp13, and nsp14 were evaluated for baseline and treatment-emergent substitutions potentially associated with reduced susceptibility to RDV.

Reference ID: 4974753

Substitutions meeting the following criteria were identified as requiring evaluation for their impact on RDV susceptibility (see PMR 1):

i. Identified as treatment-emergent at a frequency of ≥15% of the virus population, or
ii. Baseline substitutions associated with viral RNA rebound in more than one subject, including different amino acid substitutions at the same position; rebound was defined as an increase RNA from the previous time point to a level greater than the median viral RNA level for the time point and sample type.

INTRODUCTION AND BACKGROUND

Remdesivir (VEKLURY®) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor currently indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) in patients requiring hospitalization (approved 10/22/2022; [N214787.000, E. Donaldson, Ph.D.) and in non-hospitalized patients who are at high risk of progression to severe COVID-19, including hospitalization or death (N214787.SE-010.190, W. Ince, Ph.D.).

In NDA 214787 Supplement 11, the Applicant proposes to extend the current indication to *pediatric patients 28 days and older and weighing at least 3 kg for the treatment of coronavirus disease 2019 (COVID-19)*.

The sNDA is supported by interim results from a single trial, GS-US-540-5823 (NCT04431453): *Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN).*
Virology data from trial GS-US-540-5823 submitted with this supplement include:

- Longitudinal quantitative respiratory sample viral RNA data
- Baseline and post-baseline viral RNA sequence analyses.

To date, in addition to IV remdesivir (VEKLURY®), 7 other direct-acting antivirals have been authorized or approved for the treatment or prevention of SARS-CoV-2 infection. Five IV monoclonal antibody products have received Emergency Use Authorization; however, authorization for some antibodies has been revoked due to a lack of sufficient activity against SARS-CoV-2 variants that have become dominant in the U.S. Previously authorized antibody products include casirivimab + imdevimab (authorized 11/21/2020 for treatment of COVID-19 in high risk patients; deauthorized 1/24/2022) and bamlanivimab + etesevimab (authorized 2/9/2021 for treatment of COVID-19 in high risk patients; deauthorized 1/24/2022). Currently authorized antibody products include bebtelovimab (authorized 2/11/2022 for treatment of COVID-19 in high risk patients), sotrovimab (authorized 5/26/2021 for treatment of COVID-19 in high risk patients; use is currently restricted in regions where BA.2 is predominant due to significantly reduced activity against this variant), and tixagevimab+cligavimab (authorized 12/8/2021 for pre-exposure prophylaxis in immunocompromised patients or patients for whom vaccination is not recommended). 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).

Non-Clinical Virology

There were no non-clinical virology data submitted to support Supplement S-11. 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), Clinical Virology Review for NDA 214787, Supplement 9 by E. Donaldson Ph.D., Reference ID in DARRTS: 4917124 (N214787.S-009.MI.219); and Clinical Virology Review for NDA 214787, Supplement 13 by W. Ince Ph.D., Reference ID in DARRTS: 4957456 (N214787.S-013.265)].

Reference ID: 4962753

Clinical Trials in Adult Subjects
RDV has been evaluated in two open label trials and in one randomized, placebo-controlled trials in adult subjects hospitalized due to COVID-19 and in one trial in non-hospitalized subjects at risk of severe disease:

- GS-US-540-5773 (NCT04292899; open label): *Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)* [reviewed in N214787.000 and N214787.S-009.MI.219 (virology data) by E. Donaldson, Ph.D.]

- GS-US-540-5774 (NCT04292730; open label) *Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment* [reviewed in N214787.000 and N214787.S-009.MI.219 (virology data) by E. Donaldson, Ph.D.]

- GS-US-540-5776 (ACTT-1) (NCT04280705) *A Multicenter, Adaptive, Randomized, Blinded, Placebo-Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults* [reviewed in N214787.000 and N214787.S-009.MI.219 (virology data) by E. Donaldson, Ph.D.]

- GS-US-540-9012 (NCT04501952): *Study to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of Coronavirus Disease 2019 (COVID-19) in an Outpatient Setting* [reviewed in N214787.SE-010.190 by W. Ince, Ph.D.]

In placebo-controlled trials GS-US-540-5776 and GS-US-540-9012, RDV treatment was associated with a statistically significant clinical benefit relative to placebo in each trial; however, no significant impact on viral RNA levels in upper respiratory samples was observed in either trial (N214787.S-009.MI.219 by E. Donaldson Ph.D. ; N214787.SE-010.190 by W. Ince, Ph.D.). Clinical resistance evaluations based on sequence data submitted to the FDA have been reviewed for trial GS-US-540-9012; treatment-emergent substitutions were identified and will be evaluated for their impact on RDV susceptibility as a Post Marketing Requirement (N214787.SE-010.190 by W. Ince, Ph.D.). Treatment-emergent substitutions have been observed in other clinical settings, including nsp12 substitution D484Y, which was reported in a patient failing remdesivir treatment (Martinot et al., 2021). E802D was treatment-emergent in an immunocompromised patient treated with remdesivir and was associated with viral recrudescence (Gandhi et al., 2022); E802D has also been selected for in cell culture resistance selection studies (Szemiel et al, 2021).

CLINICAL VIROLOGY REVIEW OF EFFICACY
GS-US-540-5823: Interim Clinical Study Report (ICSR).
Title: GS-US-540-5823 (NCT04431453): *Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN)*

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

Secondary endpoints:
- Oxygen usage and ventilation modality and settings

Reference ID: 4962753

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

Exploratory endpoints:
- Correlation between duration of SARS-CoV-2 [RNA] shedding and timing and amplitude of SARS-CoV-2-specific IgG, IgM, and IgA
- Viral sequencing of the SARS CoV-2 polymerase gene

Inclusion criteria relevant to Virology:
- Aged < 18 years of age who meet one of the following weight criteria (where permitted according to local law and approved nationally and by relevant institutional review board or independent ethics committee).
    - Cohort 1: ≥ 12 years to < 18 years of age and weight at screening ≥ 40 kg
    - Cohorts 2-4: ≥ 28 days to < 18 years of age and weight at screening ≥ 3 kg and < 40 kg
    - Cohort 5: ≥ 14 days to <28 days of age, gestational age > 37 weeks and weight at screening ≥ 2.5 kg
    - Cohort 6: 0 days to < 14 days of age, gestational age > 37 weeks and birth weight of ≥ 2.5 kg
    - Cohort 7: 0 days to < 56 days of age, gestational age ≤ 37 weeks and birth weight of ≥ 1.5 kg
- SARS-CoV-2 infection confirmed by RT-PCR
- Hospitalized and requiring medical care for COVID-19

Exclusion criteria relevant to Virology:
- Concurrent treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing

Design: GS-US-540-5823 is a single-arm, open-label study to evaluate the safety, tolerability, PK, and efficacy in subjects from birth to < 18 years of age with laboratory-confirmed COVID-19. Subjects were to be enrolled in 8 cohorts representing a range of age and weight bands (Table 1). Cohorts 1-4 and 8 were enrolled first. Enrollment in cohorts 5-7 was dependent on PK and safety assessments of cohorts 1-4.

Reference ID: 4962753

Table 1: GS-US-540-5823 Age and Dosing Cohorts

Cohort	Description	Dose
Pediatric participants ≥ 28 days to < 18 years old		
1	≥ 12 years to < 18 years and weight ≥ 40 kg	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days
2	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days
3	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg	
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg	
Term neonatal participants 0 days to < 28 days old		
5	≥ 14 days to < 28 days of age, gestational age > 37 weeks, and weight at screening ≥ 2.5 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days
6	0 days to < 14 days of age, gestational age > 37 weeks, and birth weight ≥ 2.5 kg	RDV at a dose to be determined up to 10 days
Preterm neonates and infants 0 days to < 56 days old		
7	0 days to < 56 days of age, gestational age ≤ 37 weeks, and birth weight ≥ 1.5 kg	RDV at a dose to be determined up to 10 days
Exploratory cohort for pediatric participants < 12 years		
8	< 12 years and weight ≥ 40 kg	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days

Source: ICSR GS-US-540-5823 Table 2.

Virologic Assessments

Sample collection:

Nasopharyngeal and oropharyngeal samples (combined) and/or nasal and oropharyngeal samples (combined), and/or endotracheal aspirates (intubated subjects), and rectal or fecal swab samples were collected at baseline and on Days 3, 5, 7, and 10 (if feasible) or discharge if sooner. Endotracheal tube aspirates were also collected on the indicated Study Days above while a subject is intubated.

Viral RNA analysis

Viral RNA ("viral load") was determined by the 2019-nCoV Real-Time RT-PCR Viral Load assay (CDC 2019-nCoV). The lower limit of quantification (LLOQ) and limit of detection (LOD) for the assay on upper and lower respiratory specimens was determined to be 1018 copies/mL and 925 copies/mL when testing for SARS-CoV-2 N1 target, respectively (ICSR GS-US-540-5823 p. 45). The validation report for the 2019-nCoV Real-Time RT-PCR Viral Load assay at [redacted] (b) (4)) is provided in ICSR Appendix 16.1.10. Rectal and fecal viral RNA assessments were not included in the ICSR; the Applicant states that validation of the quantitative viral RNA assay for rectal or fecal swab was ongoing the time of the ICSR submission and that LOD/LLOQ data will be provided with the final study report. Quantitative SARS-CoV-2 viral RNA results that were below LLOQ but had a positive signal were reported as "<1018 cp/mL SARS-CoV-2 detected"; negative results were reported as "No SARS-CoV-2 detected." The data in these categories were imputed as follows:

- A value of 509 copies/mL (one-half of the LLOQ of 1018 copies/mL) was used to calculate descriptive statistics if the datum was reported as "<1018 cp/mL SARS-CoV-2 detected," from NP/OP swabs, nasal/OP swabs, and ET aspirates samples.
- A value of 462.5 copies/mL (one-half of the LOD of 925 copies/mL) was used to calculate descriptive statistics if the datum was reported as "No SARS-CoV-2 detected," from NP/OP swab, nasal/OP swabs, and ET aspirates samples.

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The Applicant defined subjects who were confirmed negative by RT-PCR as those with 2 consecutive negative RT-PCR results, or with a negative RT-PCR result for the last available sample for subjects who completed or discontinued from the study (Statistical Analysis Plan – Interim Analysis, p. 29)

Subjects with a negative result for viral RNA at baseline or who had received RDV prior to study enrollment were not included in the quantitative viral RNA analysis. After quantitative viral RNA testing was completed, selected remnant samples were sent to (b) (4) to evaluate the emergence of viral resistance by SARS-CoV-2 sequencing and/or phenotypic testing.

Resistance/viral sequence analysis
Resistance analysis was planned for all subjects in the Full Analysis Set (FAS) as outlined in the Virology Analysis Plan (PC-540-2014; reviewed in I147753.239 by E. Donaldson, Ph.D.). For subjects who received additional SARS-CoV-2 antivirals during the study (including chloroquine, hydroxychloroquine, bamlanivimab, casirivimab/imdevimab, molnupiravir, lopinavir-ritonavir, and ribavirin), any time points on or after receipt of these antivirals were excluded from the analysis. Subjects who had received RDV prior to the enrollment of this study were also excluded from the analysis (PC-540-2030 p. 8).

For each subject, baseline and postbaseline (during and/or after treatment) samples with SARS-CoV-2 viral RNA above the lower limit of quantification (LLOQ) were selected for sequencing. The sample type (nasopharyngeal and oropharyngeal samples (combined) OR nasal and oropharyngeal samples (combined) OR endotracheal tube aspirates (if the subject was intubated) with the highest viral RNA value at the latest timepoint for each subject was utilized. The last sample while the subject was still on study drug with SARS-CoV-2 viral RNA above the LLOQ was also selected for sequencing. The same sample type was selected for sequencing at the baseline and postbaseline timepoints (PC-540-2030 p. 8). The whole genome of SARS-CoV-2 was amplified using the ARTIC version 3 Amplicon Set and the nucleotide sequence was determined for nsp8, nsp10, nsp12, nsp13, and nsp14 SARS-CoV-2 genes by next generation sequencing at (b) (4) .

Phenotypic analysis
Phenotypic analysis was attempted on postbaseline clinical isolates with identified treatment-emergent amino acid substitutions compared with their baseline sample in the SARS-CoV-2 nsp12 gene. As a secondary analysis, phenotyping was planned on any postbaseline clinical isolates with identified treatment-emergent amino acid substitutions compared with their baseline sample in SARS-CoV-2 nsp8, nsp10, nsp13 and nsp14 for substitutions occurring in two or more RDV-treated subjects. Substitutions at known sites of resistance (F480 or V557) or common polymorphisms (occurring in ≥ 3 subjects) in nsp12 (but not in other genes) identified at baseline were to be evaluated for their effect on the susceptibility of SARS-CoV-2 to RDV.

The samples used for phenotyping were remnant samples aliquoted after quantitative viral RNA testing. The Applicant reported that samples had been freeze-thawed twice prior to phenotypic analysis, which may have negatively impacted recovery of virus. Sequencing of the passage 1 virus stock was to be conducted to confirm homogeneity to the original virus. Phenotyping was performed at (b) (4) using the 96-well format SARS-CoV-2 ViroSpot assay. In this assay, virus/drug mixtures are added to Vero E6 cells simultaneously (remdesivir is not pre-incubated with cells prior to infection to allow accumulation of the active triphosphate prior to infection) followed by incubated for a duration of 16-24 hours. Infection is quantified in each well using a peroxidase conjugated anti-nucleocapsid antibody followed by development with the TrueBlue substrate and automated detection of positive cells. EC_{50} and EC_{90} values in the ViroSpot assay are derived from the % well area covered (%WAC) by positive cells using linear extrapolation as described in Zielinska et al., 2005, which does not yield a concentration-response curve (VC-M205; PC-540-2030; see also Appendix D). When being used to screen clinical specimens for resistance, the

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need for virus to be expanded from respiratory specimens may obscure resistant variants that either preexist as mixtures with wild type in the respiratory specimen or are outcompeted by wild type in the expansion step, thus this assay should not be relied upon to detect or rule out resistant variants in clinical specimens. Furthermore, to date, the Applicant reports that attempts to evaluate selected clinical specimens using this assay have failed due to the inability to recover virus. Instead, sequence data will be used to identify substitutions for additional phenotypic analysis in cloned virus or replicon-based assays based on whether they are treatment-emergent above a certain frequency threshold or are polymorphisms associated with reduced response to treatment.

RESULTS

Baseline Characteristics

The interim analysis of trial ICSR GS-US-540-5823 includes subjects enrolled between July 21, 2020 and April 24, 2021. Subjects were enrolled and treated at a total of 19 study sites in Italy, Spain, the U.S., and the UK (ICSR Table 15.8.1.2). Of the 54 subjects screened in the study, 53 were enrolled into cohorts 1 (n=12), 2 (n=12), 3 (n=12), 4 (n=12), and 8 (n=5) and received at least 1 dose of study drug and were included in the Full Analysis Set for the interim analysis. (b) (4)

The overall median duration of symptoms at the time of first dose was 5 days. Among the 3 sample types reported, baseline viral RNA was highest in nasopharyngeal swab samples (median: 6.37 $\log_{10}$ copies/mL, n=24), followed by endotracheal (median: 5.50 $\log_{10}$ copies/mL, n=9), whereas nasal swabs had the lowest levels of viral RNA at baseline (median: 4.63 $\log_{10}$ copies/mL, n=18). Subjects 12-18 years of age weighing ≥40 kg had the lowest baseline nasopharyngeal viral RNA levels (median: 5.05 $\log_{10}$ copies/mL, n=5) while subjects < 12 Years and ≥ 40 kg had the highest (median: 6.89 $\log_{10}$ copies/mL, n=4); however, subsets were too small and confounded by differences in covariates (e.g. time from symptoms onset) to draw conclusions regarding baseline viral RNA levels.

Proportion positive for viral RNA at each Study Day

Longitudinal nasopharyngeal/oropharyngeal (NP/O), nasal/oropharyngeal (N/O), and endotracheal (ET) samples were collected and evaluated for viral RNA by quantitative RT-PCR for 24, 18, and 9 subjects, respectively. As noted above, the most common sample type was NP/O swab, which were also the most consistently positive sample type and exhibited the highest viral RNA levels at baseline (Table 2). Of note, the proportion of subjects negative for viral RNA at each time point did not increase above 50% up to Day 10; most subjects remained positive across sample types through the Day 10 (Table 3). The Applicant noted that the time to first RT-PCR negative result was generally not estimable (ICSR GS-US-540-5823 p. 72). Similar trends were observed across study cohorts (Table 4); however, there were too few subjects in each cohort to draw a meaningful conclusion.

Table 2: Baseline Characteristics Relevant to Virology by Cohort

	Cohort 1: 12 to < 18 Years and ≥ 40 kg	**Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg**	**Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg**	**Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg**	**Cohort 8: < 12 Years and ≥ 40 kg**	**Total**
Duration of hospitalization prior to first dose of RDV (days)						
N	12	12	12	12	5	53
Mean (SD)	8 (25.1)	2 (1.1)	2 (1.4)	13 (26.3)	5 (9.2)	6 (17.6)
Median	1	1	2	2	1	1

Q1, Q3	0, 3	1, 2	1, 3	1, 7	0, 1	1, 3
Min, max	0, 88	0, 4	0, 5	1, 82	0, 21	0, 88
Duration of symptoms prior to first dose of RDV (days)						
N	12	12	12	12	5	53
Mean (SD)	21 (49.4)	5 (2.7)	5 (3.0)	5 (3.3)	7 (3.0)	9 (23.8)
Median	7	5	3	5	5	5
Q1, Q3	3, 11	3, 7	3, 7	2, 8	5, 7	3, 7
Min, max	1, 177	2, 11	1, 11	0, 9	5, 12	0, 177
SARS-CoV-2 RNA viral shedding (log_{10} copies/mL) from nasal swabs						
N	5	5	4	3	1	18
Mean (SD)	5.35 (1.796)	4.87 (2.807)	3.18 (0.967)	5.41 (2.165)	6.20	4.79 (2.055)
Median	5.72	3.14	2.71	5.14	6.20	4.63
Q1, Q3	4.63, 6.44	2.67, 7.69	2.69, 3.67	3.40, 7.70	6.20, 6.20	2.71, 6.44
Min, max	2.67, 7.31	2.67, 8.17	2.67, 4.63	3.40, 7.70	6.20, 6.20	2.67, 8.17
SARS-CoV-2 RNA viral shedding (log_{10} copies/mL) from nasopharyngeal swabs						
N	5	3	5	7	4	24
Mean (SD)	5.93 (2.172)	5.02 (2.133)	5.67 (2.273)	5.55 (1.854)	6.12 (1.628)	5.68 (1.862)
Median	5.05	5.57	6.58	6.39	6.89	6.37
Q1, Q3	4.98, 6.35	2.67, 6.82	4.02, 6.84	3.85, 7.15	5.24, 7.01	3.93, 6.91
Min, max	3.81, 9.47	2.67, 6.82	2.67, 8.26	2.67, 7.69	3.69, 7.03	2.67, 9.47
SARS-CoV-2 RNA viral shedding (log_{10} copies/mL) from endotracheal tube aspirates						
N	1	3	2	3	0	9
Mean (SD)	5.36	5.07 (4.168)	6.09 (0.840)	6.68 (1.540)		5.87 (2.357)
Median	5.36	2.67	6.09	7.38		5.50
Q1, Q3	5.36, 5.36	2.67, 9.88	5.50, 6.68	4.91, 7.74		4.91, 7.38
Min, max	5.36, 5.36	2.67, 9.88	5.50, 6.68	4.91, 7.74		2.67, 9.88
Baseline SARS-CoV-2 IgG status [a]						
N	9	9	8 [b]	0	4	30
Positive	3	6	4	0	0	13
Negative	6	3	4	0	4	17

Source: Derived from ICSR GS-US-540-5823 Table 12, except where noted.
a. FDA reviewer analysis of ADLB; SARS-CoV-2 IgG Qualitative. Subjects were designated “Positive”, “Negative”, or “Borderline” (not shown).
b. One subject had a “borderline” result.

Table 3: Proportion RT-PCR Negative at Each Visit by Respiratory Sample Type in Trial GS-US-540-5823

Visit [a]	**NP/O % negative (negative/N)**	**N/O % negative (negative/N) [b]**	**ET % negative (negative/N)**
Baseline/Day 1 [c]	12.5 (3/24)	22.2 (4/18)	22.2 (2/9)
Day 3	16.7 (5/30)	20 (3/15)	28.6 (2/7)
Day 5	4.8 (1/21)	33.3 (5/15)	28.6 (2/7)
Day 7	9.1 (1/11)	41.7 (5/12)	33.3 (1/3)
Day 10	25 (2/8)	40 (4/10)	0 (0/2)

Confirmed negative Day 2 through Day 10 [d]	21.4% (6/28)	42.1% (8/19)	22.2% (2/9)

Source: FDA reviewer analysis of ADEFF; trial GS-US-540-5823.
NP/O: Nasopharyngeal/oropharyngeal
N/O: Nasal/oropharyngeal
ET: Endotracheal
a. AVISIT
b. Excludes inconclusive results obtained for N/O swabs from 2 subjects at baseline.
c. One subject had both NP/O and N/O sampled at baseline but not at other time points (Subject ID (b) (6)); both sample types were positive.
d. Defined as 2 consecutive negative results or a negative result at the last available sample for participants who completed or discontinued from the study. Some subjects were sampled post baseline who were not sampled at baseline.

Table 4: Proportion RT-PCR Negative at Each Visit in Each Cohort by Respiratory Sample Type in Trial GS-US-540-5823

Cohort	Visit [a]	NP/O % negative (negative/N)	N/O % negative (negative/N) [b]	ET % negative (negative/N)
COHORT 1: >=12 YEARS TO <18 YEARS AND WEIGHT >=40 KG	Baseline/Day 1	0 (0/5)	20 (1/5)	0 (0/1)
	Day 3	0 (0/6)	25 (1/4)	0 (0/0)
	Day 5	0 (0/4)	40 (2/5)	0 (0/2)
	Day 7	0 (0/3)	50 (2/4)	0 (0/1)
	Day 10	0 (0/1)	33.3 (2/6)	0 (0/0)
	Confirmed negative Day 2 through Day 10 [c]	0% (0/3)	33.3% (2/6)	0% (0/2)
COHORT 2: >=28 DAYS TO <18 YEARS AND WEIGHT >=20KG TO <40KG	Baseline/Day 1	33.3 (1/3)	40 (2/5)	66.7 (2/3)
	Day 3	42.9 (3/7)	50 (2/4)	33.3 (1/3)
	Day 5	0 (0/5)	33.3 (1/3)	50 (1/2)
	Day 7	33.3 (1/3)	50 (1/2)	100 (1/1)
	Day 10	33.3 (1/3)	100 (1/1)	0 (0/1)
	Confirmed negative Day 2 through Day 10 [c]	28.6% (2/7)	60.0% (3/5)	3.3% (1/3)
COHORT 3: >=28 DAYS TO <18 YEARS AND WEIGHT >=12KG TO <20KG	Baseline/Day 1	20 (1/5)	25 (1/4)	0 (0/2)
	Day 3	16.7 (1/6)	0 (0/4)	0 (0/1)
	Day 5	20 (1/5)	25 (1/4)	0 (0/0)
	Day 7	0 (0/1)	66.7 (2/3)	0 (0/0)
	Day 10	0 (0/0)	50 (1/2)	0 (0/0)
	Confirmed negative Day 2 through Day 10 [c]	28.6% (2/7)	50.0% (2/4)	0 (0/1)
COHORT 4: >=28 DAYS TO <18 YEARS AND WEIGHT >=3KG TO <12KG	Baseline/Day 1	14.3 (1/7)	0 (0/3)	0 (0/3)
	Day 3	14.3 (1/7)	0 (0/2)	33.3 (1/3)
	Day 5	0 (0/4)	50 (1/2)	33.3 (1/3)
	Day 7	0 (0/2)	0 (0/2)	0 (0/1)
	Day 10	33.3 (1/3)	0 (0/0)	0 (0/1)
	Confirmed negative Day 2 through Day 10 [c]	28.6% (2/7)	33.3% (1/3)	3.3% (1/3)
COHORT 8: <12 YEARS AND WEIGHT >=40KG	Baseline/Day 1	0 (0/4)	0 (0/1)	0 (0/0)
	Day 3	0 (0/4)	0 (0/1)	0 (0/0)
	Day 5	0 (0/3)	0 (0/1)	0 (0/0)
	Day 7	0 (0/2)	0 (0/1)	0 (0/0)
	Day 10	0 (0/1)	0 (0/1)	0 (0/0)
	Confirmed negative Day 2 through Day 10 [c]	8: 0% (0/4)	0% (0/1)	0 (0/0)

Source: FDA reviewer analysis of ADEFF; trial GS-US-540-5823.
NP/O: Nasopharyngeal/oropharyngeal.
N/O: Nasal/oropharyngeal.

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ET: Endotracheal.
a. AVISIT.
b. Excludes inconclusive results obtained for N/O swabs from 2 subjects at baseline.
c. Defined as 2 consecutive negative results or a negative result at the last available sample for participants who completed or discontinued from the study. Some subjects were sampled post baseline who were not sampled at baseline.

Viral RNA declined in each sample type, with endotracheal aspirate exhibiting the sharpest decline; however, the numbers of subjects represented by individual sample types were too small to draw a strong conclusion regarding the relative rate of viral RNA decline in each sample type (Figure 1). Viral RNA shedding patterns were similar between cohorts; however individual viral RNA kinetics were highly variable and did not uniformly decline over the observation period in all subjects, consistent with the lack of an impact of RDV treatment on upper respiratory viral RNA noted in previous, placebo-controlled clinical trials (N214787.S-009.MI.219, E. Donaldson, Ph.D.; N214787.SE-010.190, W. Ince, Ph.D.). The numbers of subjects were too small to derive a meaningful conclusion regarding associations of viral RNA shedding decline and age/weight cohort (Figure 2).

Figure 1: Absolute (A) and change from baseline (B) in viral RNA by sample type. B) subjects with baseline viral RNA <LLOQ were excluded. Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823. Study Day: AVISIT.

A B

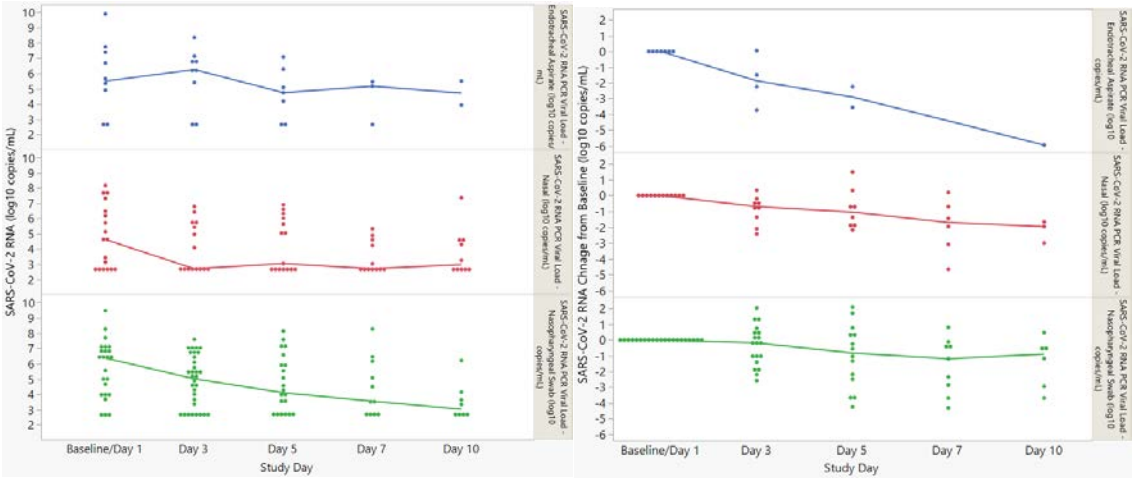
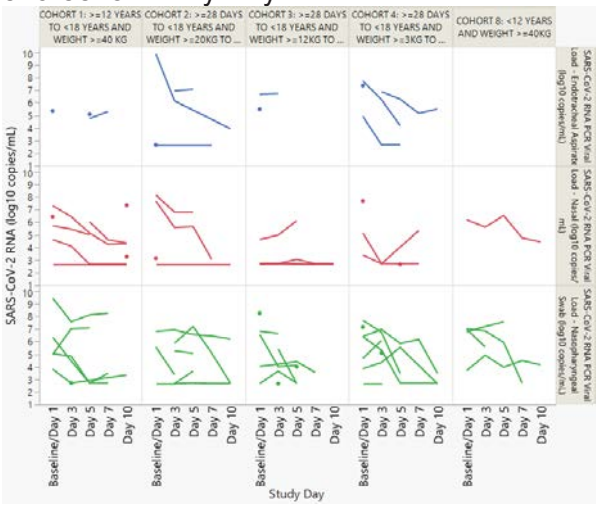


Figure 2: Viral RNA levels by sample type and cohort. Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823. Study Day: AVISIT.



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A subset of subjects weighing >12 Kg were evaluated for serum SARS-CoV-2 IgG at each time point. Overall, 43.3% of the 31 subjects evaluated at baseline were positive for SARS-CoV-2 IgG, and all but one subject (Cohort 1) seroconverted by Day 10 based on the Applicant's analysis (Table 5).

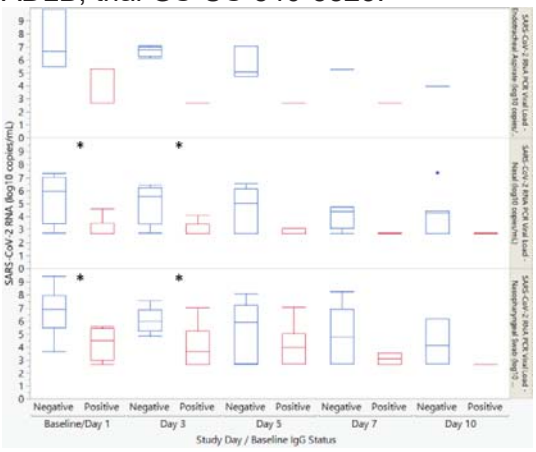
Table 5: Serum SARS-CoV-2 IgG Status at Each Time Point

		SARS-CoV-2 IgG status [a]			
Cohort [b]	**Study Day**	**Borderline**	**Negative (n)**	**Positive (n)**	**% Positive**
OVERALL	Baseline/Day 1	1	17	13	43.3
	Day 5	1	6	20	76.9
	Day 10	1	0	13	100
	Day 30	0	1	23	95.8
COHORT 1: >=12 YEARS TO <18 YEARS AND WEIGHT >=40 KG	Baseline/Day 1	0	6	3	33.3
	Day 5	1	2	6	75
	Day 10	1	0	5	100
	Day 30	0	1	6	85.7
COHORT 2: >=28 DAYS TO <18 YEARS AND WEIGHT >=20KG TO <40KG	Baseline/Day 1	0	3	6	66.7
	Day 5	0	4	5	55.6
	Day 10	0	0	3	100
	Day 30	0	0	6	100
COHORT 3: >=28 DAYS TO <18 YEARS AND WEIGHT >=12KG TO <20KG	Baseline/Day 1	1	4	4	50
	Day 5	0	0	6	100
	Day 10	0	0	2	100
	Day 30	0	0	7	100
COHORT 8: <12 YEARS AND WEIGHT >=40KG	Baseline/Day 1	0	4	0	0
	Day 5	0	0	3	100
	Day 10	0	0	3	100
	Day 30	0	0	4	100

Source: FDA reviewer analysis ADLB; trial GS-US-540-5823.
a. Qualitative status is derived from the immunological status ratio (ISR) calculated from the ratio of the optical density obtained with the test sample divided by the calculated cut-off value based on control IgG.
b. Subjects weighing ≤12 Kg were not included in serological analysis.

Of the subset of subjects evaluted for SARS-CoV-2 IgG, those who were positve for IgG at baseline had significantly lower viral RNA amounts at baseline and at subsequent time points (Figure 3), indicating a significant impact of prior infeciton or vaccination on SARS-CoV-2 viral RNA in each respiratory sample type.

Figure 3: Viral RNA level in each sample type by SARS-CoV-2 IgG status at baseline. * P>0.05 comparing Negative and Positive subjects at each time point, Mann-Whitney test. Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823.



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Sequence and Resistance Analyses

Of the 53 subjects in the FAS, sequence analysis attempts were reported for baseline and/or post-baseline samples for 39 subjects with evaluable samples. Sequence analyses performed by the Applicant focused on RNA replication complex genes nsp8, nsp9, nsp10, nsp12, nsp13, and nsp14. Sequence data at any time point were obtained for 34 subjects. Baseline sequencing was obtained for 30 subjects, post-baseline sequencing was obtained for 27 subjects, and sequence data were successfully obtained both at baseline and post-baseline for 23 subjects (PC-540-2030, Section 4).

Virus genotype based on baseline or post-baseline sequence data was determined for 34 subjects (Table 6). The most common variant represented was B.1.2 (first reported in the U.S. in October of 2020), followed by B.1.1.7 (Alpha; first reported in the UK in December of 2020) and B.1.429 (Epsilon; first reported in the U.S. in January of 2020). All other variants were identified in ≤2 subjects (Table 6). SARS-CoV-2 Variants of Concern including Delta and Omicron were not represented in this trial, which completed enrollment of the cohorts included in the interim analysis prior to widespread circulation of Delta and Omicron. There was no clear association between the SARS-CoV-2 variant and viral RNA shedding (Figure 4); however, the variant was only identified for subjects with evaluable RNA levels, thus the subset is not an unbiased sample. In addition, there were too few subjects in each variant subset to draw a meaningful conclusion regarding impacts of genotype on virus shedding.

Table 6: SARS-CoV-2 Variants among Subjects with Available Sequence Data in Trial GS-US-540-5823

Variant (WHO label)	Number of Subjects
B.1.2	5
B.1.1.7 (Alpha)	4
B.1.429 (Epsilon)	3
B.1.509	2
B.1.564	2
B.1.577	2
B.1.596	2
B.1	1
B.1.1	1
B.1.1.222	1
B.1.1.231	1
B.1.1.518	1
B.1.110.3	1
B.1.177	1
B.1.177.32	1
B.1.177.35	1
B.1.177.50	1
B.1.234	1
B.1.305	1
B.1.311	1
B.1.595	1

Source: FDA reviewer analysis of data derived from Study Report PC-540-2030.

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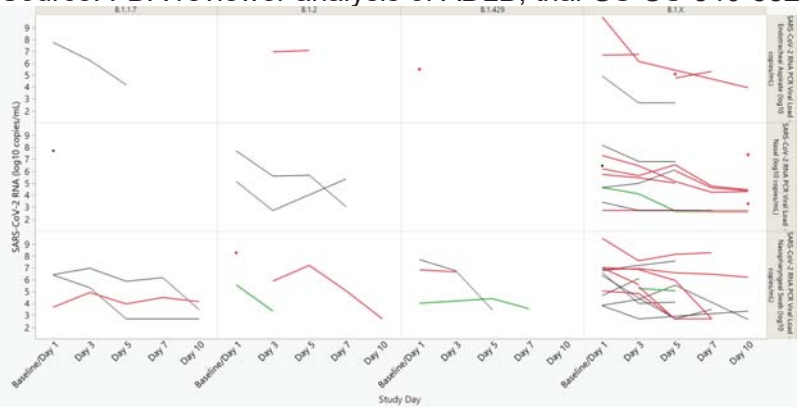
Figure 4: Viral RNA by SARS-CoV-2 variant and baseline IgG status in each sample type. Curves are color coded as based on baseline IgG status: red = negative, green = positive, black = not evaluated for IgG status. Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823.



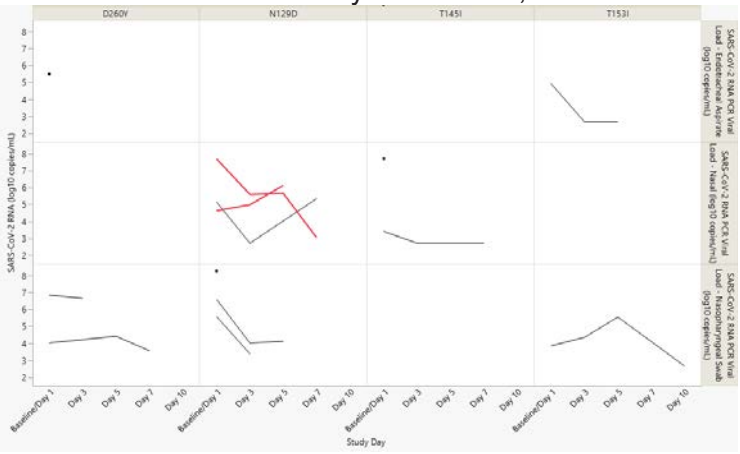
In an analysis of baseline polymorphisms, virus from all subjects contained the nsp12 P323L polymorphism, which has been demonstrated to have no impact on RDV susceptibility (N214787.S-009.MI.219, E. Donaldson, Ph.D.). In genes other than nsp12, there were 4 polymorphisms identified in more than one subject: nsp8 T145I (2 subjects), nsp13 T153I (2 subjects), nsp13 D260Y (3 subjects), and nsp14 N129D (6 subjects) (Table 7). Apparent viral RNA rebound above the median viral RNA level for the sample type and time point was noted for 2 of the 6 subjects with nsp14 N129D (Figure 5). Given the lack of an impact of RDV on viral RNA declines, the small sample size, and variability in viral RNA levels over time, the association of the baseline polymorphism and viral RNA levels is unclear.

Table 7: Baseline Polymorphisms Identified in More Than One Subject in Trial GS-US-540-5823

Baseline polymorphism	Variant	NSP gene	Number of subjects with polymorphism
T145I	B.1.1.7, B.1.311	8	2
T153I	B.1.595, B.1.577	13	2
D260Y	B.1.429	13	3
N129D	B.1.2, B.1.596	14	6

Source: FDA reviewer analysis of data derived from Study Report PC-540-2030.

Figure 5: Viral RNA shedding by sample type and baseline polymorphisms identified in multiple subjects. Polymorphisms: N129D (nsp14), D260Y (nsp13), T153I (nsp13), and T145I (nsp8). Viral RNA curves highlighted in red exhibited rebound above the median viral RNA level for the time point and sample type. Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823.



Reference ID: 4962753

Treatment-emergent resistance

The Applicant evaluated the presence of treatment-emergent substitutions in ≥15% of sequence reads in nsp8, nsp10, nsp12, nsp13, and nsp14 genes (nsp9 was not included in the Applicant's analysis) among the 23 subjects with both baseline and post-baseline sequence data available. The Applicant reported 3 subjects with treatment-emergent substitutions: nsp12 A656P and G670V at Day 3 in subject (b) (6), nsp10 D64Y and T101I at Day 3 in subject (b) (6), and nsp13 R248I and V266F at Day 10 in subject (b) (6), and nsp13 S259L was identified at Day 7 in subject (b) (6) (Study Report PC-540-2030 Tables 8 and 9). The Applicant evaluated nsp12 sequence data for the 4 additional subjects with post-baseline sequence data but for whom baseline sequence data were not successfully obtained and did not identify post-baseline substitutions other than P323L among these subjects. For the subject with the nsp12 substitutions A656P and G670V, the Applicant reported that phenotypic analysis was attempted on the clinical isolates collected at Baseline and Day 3, but no viable virus could be cultured at either timepoint.

In an independent analysis (FDA reviewer analysis) of deep sequencing data for nsp8, nsp9, nsp10, nsp12, nsp13, and nsp14 genes, in all 27 post-baseline samples, 10 putative treatment-emergent substitutions (in addition to the previously identified resistance-associated substitution nsp12 E802D) that were ≥15% of sequence reads were identified in nsp9, nsp10, nsp12, nsp13, or nsp14 genes in a total of 6 subjects (Table 8).

The Applicant reported nsp10 substitution T101I as treatment-emergent; however, this substitution was not detected in the FDA analysis. T101-frameshift was detected in 3 subjects but coverage was <220 at this position. In addition, the Applicant reported nsp13 substitution S259L as treatment-emergent; however, S259L appeared to be polymorphic as it was treatment-emergent in subject (b) (6) (D7:28.1%), subject (b) (6) (D10:2.9%), and subject (b) (6) (D3:1.3%), but was present at baseline in subject (b) (6) (D1:62.8%). There was no evidence of treatment-emergent substitutions at other known resistance-associated sites in nsp12, including: V166A/L (none detected), N198S (none detected), F480L (none detected), V557L (none detected), S759A (none detected), V792I (none detected), and C799F/R (none detected).

Table 8: Treatment-Emergent Substitutions Identified at ≥15% in Treated Subjects in Trial GS-US-540-5823

Protein	SUBS [a]	No. Subjects	RESIST CAT	Notes
nsp9	G17V	1	POLY	G17V was TE in subject (b) (6) (D3:23.3%); G17A/R appeared at D1 in 2 subjects
	N95D	1	P-RAS	N95D was TE in subject (b) (6) (D10:15.3%)
nsp10	D64Y	1	P-RAS	D64Y was TE in subject (D3:16.8%) (b) (6)
nsp12	V495F	1	P-RAS	V495F was TE in subjec (b) (6) (D3:15.01%)
	A656P	2	P-RAS	A656P was TE in subjec (b) (6) (D3: 31.4%) and subject (b) (6) (D10:1%)
	G670V	1	P-RAS	G670V was TE in subject (b) (6) (D3: 34.9%)
	E802D	4	K-RAS	E802D was detected at baseline in two subjects (b) (6), (b) (6)) at ~2% frequency and post-baseline in three subjects (b) (6)) at frequencies <2%
nsp13	R248I	1	P-RAS	R248I was TE in subject (b) (6) (D10:30.1%)
	V266F	1	P-RAS	V266F was TE in subject (b) (6) (D10:29.6%)
	S301F	1	P-RAS	S301F was TE in subject (b) (6) (D10:24.9%)
nsp14	T16I	2	P-RAS	T16I was TE in subject (b) (6) (D3:99.9%) and subject (b) (6) (D7: 1.9%)

Source: FDA reviewer analysis of raw sequence data (SDN 209).
a. Identified in ≥15% of reads with a minimum total coverage of 500x
nsp, nonstructural protein; SUBS, substitution identified; RESIST CAT, resistance category for classification; POLY, polymorphic; P-RAS, potential resistance-associated site; K-RAS, known resistance-associated site; TE, treatment-emergent; D, Day (D1=baseline, >D1 = on treatment); Action, regulatory action recommended by reviewer; Phenotype, recommend that the Applicant determine the activity of remdesivir in the presence of a SARS-CoV-2 protein containing the substitution; Requested, phenotypic assessment already requested. Underlined substitutions are those that were also detected by the Applicant.

Reference ID: 4964753

Additional substitutions were identified as treatment-emergent in nsp8, nsp9, nsp10, nsp12, nsp13, and nsp14 genes at <15% but >5% frequency among sequencing reads (Table 9). Substitutions in this subset were identified in more than one subject, including different amino acid substitutions identified in at the same position in more than one subject, or were associated with viral RNA rebound greater than the median viral RNA level for the time point and sample type (Table 10; Figure 6). There were 20 additional substitutions that met these criteria (Table 9).

Table 9: Treatment-Emergent Substitutions Identified at ≥5% in Treated Subjects in Trial GS-US-540-5823

Protein	SUBS [a]	No. Subjects	RNA Rebound? [b]	RESIST CAT	Explain
nsp8	E60K	1	Yes	P-RAS	E60K was TE in subject (b) (6) (D10: 8.59%)
nsp8	A102V	1	Yes	P-RAS	A102V was TE in subject (b) (6) (D5: 10.85%)
nsp9	L94S	1	Yes	P-RAS	L94S was TE in subject (b) (6) (D10: 12.43%)
nsp10	G2D	1	Yes	P-RAS	G2D was TE in subject (b) (6) (D10: 9.11%)
nsp12	G228C	1	Yes	P-RAS	G228C was TE in subject (b) (6) (D10: 13.8%)
nsp12	P243S	1	Yes	P-RAS	P243S was TE in subject (b) (6) (D10: 9.19%)
nsp12	R640C	1	Yes	P-RAS	R640C was TE in subject (b) (6) (D5: 5.71%)
nsp12	E665K	1	Yes	P-RAS	E665K was TE in subject (b) (6) (D10: 8.32%)
nsp13	N46Y	1	Yes	P-RAS	N46Y was TE in subject (b) (6) (D10: 8.38%)
nsp13	T255I [b]	1	No	P-RAS	T255I was TE in subject (b) (6) (D3: 6.29%)
nsp13	E261D	1	Yes	P-RAS	E261D was TE in subject (b) (6) (D3: 5.02%)
nsp13	A296V	1	Yes	P-RAS	A296V was TE in subject (b) (6) (D10: 6.61%)
nsp13	A313S	1	No	P-RAS	A313S was TE in subject (b) (6) (D3: 6.93%)
nsp13	T380I	1	Yes	P-RAS	T380I was TE in subject (b) (6) (D10: 6.08%)
nsp13	R409P	1	Yes	P-RAS	R409P was TE in subject (b) (6) (D10: 13.62%)
nsp13	L590P	1	Yes	P-RAS	L590P was TE in subject (b) (6) (D10: 12.63%)
nsp14	P24L/S	2	Yes	P-RAS	P24S was TE in subject (b) (6) (D10: 6.58%) and P24L was TE in (b) (6) (D10: 1.77%)
nsp14	I87T	1	No	P-RAS	I87T was TE in subject (b) (6) (D3: 10.15%)
nsp14	H95Y	2	Yes	P-RAS	H95Y was TE in subject (b) (6) (D10: 8.71%) and (b) (6) (D5: 1.05%)
nsp14	T293I	1	Yes	P-RAS	T293I was TE in subject (b) (6) (D10: 6.37%)
nsp14	S470F	1	Yes	P-RAS	S470F was TE in subject (b) (6) (D10: 6.2%)
nsp14	D515H	1	Yes	P-RAS	D515H was TE in subject (b) (6) (D10:5.18%)

Source: FDA reviewer analysis of raw sequence data (SDN 209).
a. Identified in ≥5% of reads with a minimum total coverage of 100x
nsp, nonstructural protein; SUBS, substitution identified; RESIST CAT, resistance category for classification; POLY, polymorphic; P-RAS, potential resistance-associated site; K-RAS, known resistance-associated site; TE, treatment-emergent; D, Day (D1=baseline, >D1 = on treatment); Action, regulatory action recommended by reviewer; Phenotype, recommend that the Applicant determine the activity of remdesivir in the presence of a SARS-CoV-2 protein containing the substitution.
a. Identified in a subject exhibiting viral RNA rebound above the median viral RNA level for the time point and sample type.
b. Baseline sequence not obtained.

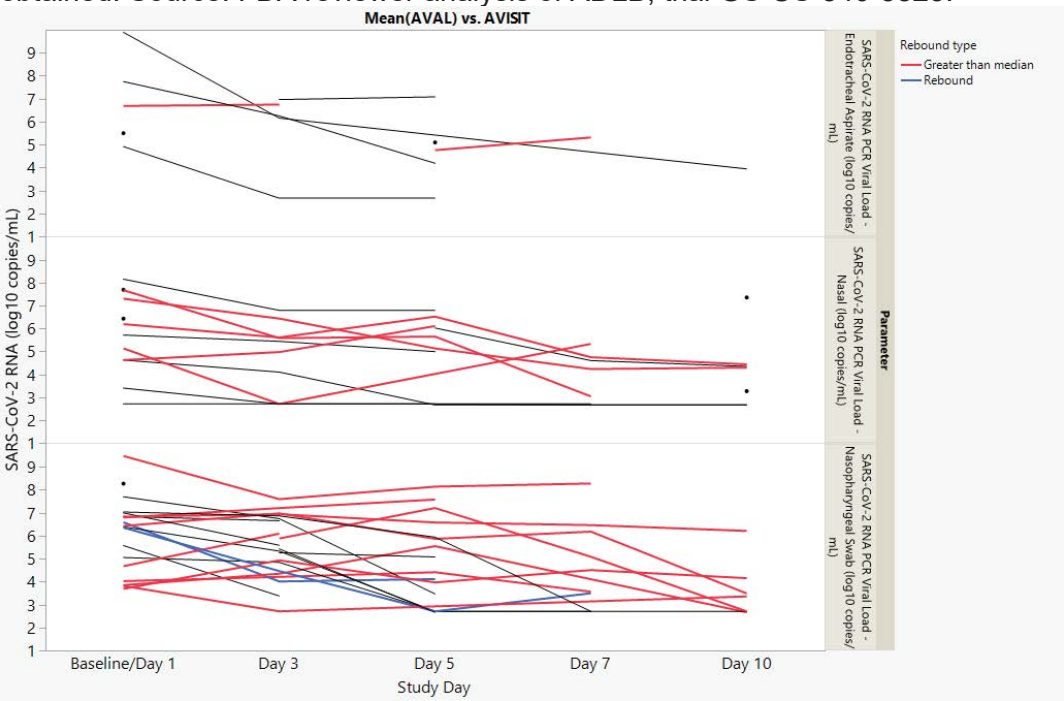
Table 10: Median viral RNA Levels by Time Point and Sample Type in Trial GS-US-540-5823

	Median SARS-CoV-2 RNA (log_{10} copies/mL)		
	Endotracheal aspirate	Nasal swab	Nasopharyngeal swab
Visit	Median	Median	Median
Baseline/Day 1	5.5	4.6	6.4
Day 3	6.2	2.7	5.0
Day 5	4.8	3.1	4.1
Day 7	5.2	2.7	3.6
Day 10	4.7	3.0	3.0

Source: FDA reviewer analysis; ADLB.

Reference ID: 4964753

Figure 6: Viral RNA rebound by sample type. Red highlighted curves indicate subjects with a post-baseline viral RNA increase from the previous time point to a level that that is greater than the median viral RNA level for the rebound time point and sample type. Includes subjects for whom sequence data were successfully obtained. Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823.



Substitutions identified by either FDA or Applicant sequence analyses were indicated for independent phenotypic analysis as a Post Marketing Requirement (PMR) (Table 11) if they met the following criteria:

i. Identified as treatment-emergent at a frequency of ≥15% of the virus population, or
ii. Baseline polymorphisms associated with viral RNA rebound in more than one subject, including different amino acid substitutions at the same position; rebound was defined as an increase in RNA from the previous time point greater than the median viral RNA level for the time point and sample type.

Other treatment-emergent substitutions identified in the FDA or Applicant analyses that did not meet the above criteria will continue to be monitored and may be indicated for phenotypic analysis in a future PMR if they appear to be associated with resistance to RDV.

Table 11: Substitutions Indicated for Phenotypic Analysis

Gene	Substitution	Criteria met for inclusion
nsp9	N95D	TE in subject (b) (6) at 15.3% on D10
nsp10	D64Y	TE in subject (b) (6) at 16.8% on D3
	T101I	Identified in Applicant's analysis in subject (b) (6) at >15% on D3
nsp12	V495F	TE in subject (b) (6) at 15.01% on D3
	A656P	TE in subject (b) (6) at 31.4% on D3 and subject (b) (6) at 1% on D10
	G670V	TE in subject (b) (6) at 34.9% on D3
nsp13	R248I	TE in subject (b) (6) at 30.1% on D10
	S259L	Identified in Applicant's analysis in subject (b) (6) at >15% on D7
	V266F	TE in subject (b) (6) at 29.6% on D10

Reference ID: 4962753

nsp14	N129D	Observed in 6 subjects at baseline; 4 subjects exhibited viral RNA rebound; two of these subjects exhibited viral RNA rebound greater than the median level for the sample and time point.

TE: Treatment-emergent.
* No baseline sequence available; post-baseline substitutions relative to reference were inferred to be treatment-emergent in these cases based on the substitution being confirmed treatment-emergent in another subject and not being observed as a common polymorphism.

LABELING

Applicant proposed edits for S-11 are in red.
FDA edits are in green.
Note: Original labeling language below (black font) includes updated labeling from Supplements S-009 (N214787.S-009.MI.219), S-010 (N214787.SE-010.190), and S-013 (N214787.S-013.265).

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.

Cell Culture 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.

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Based on cell culture susceptibility testing by virus yield reduction assay and/or N protein ELISA assay, remdesivir retained similar antiviral activity (<2.5-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), Gamma (P.1), Epsilon (B.1.429), Kappa (B.1.617.1), Lambda (C.37), Iota (B.1.526), and Zeta (P.2) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates. For the clinical isolates of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants, remdesivir maintained antiviral activity (<0.6-fold change).

Clinical Antiviral Activity

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

(b) (4) *Cell Culture 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.

Treatment-Emergent Resistance

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.

(b) (4)

(b) (4)

[redacted]

POST-MARKETING REQUIREMENT (PMR)

Number	PMR Description	Timetable
1	Evaluate substitutions meeting the following criteria for their impact on remdesivir susceptibility of virus in cell culture, or, if virus is unable to be recovered, in a replicon assay or biochemical assay of RdRp activity: Substitutions identified in replication complex subunits as treatment-emergent at a frequency of ≥15% of the virus population or are polymorphisms associated with viral RNA rebound in more than one subject, including different amino acid substitutions at the same position: nsp9: N95D; nsp10: D64Y, T101I; nsp12: V495F, A656P, G670V, A656P+G670V; nsp13: R248I, S259L, V266F; nsp14: N129D.	Final Protocol Submission: NA Study Completion: 2/2023 Final Report Submission: 3/2023

CONCLUSION:

NDA 214787 supplement 11 is approvable from a Virology perspective. Data submitted to support supplement 11 included interim clinical and virologic data, including NGS data, from trial GS-US-540-5823, a single-arm, open-label study to evaluate the safety, tolerability, PK, and efficacy in subjects from birth to <18 years of age with laboratory-confirmed COVID-19. Viral RNA was evaluated in nasopharyngeal/oropharyngeal, nasal/oropharyngeal, or endotracheal swabs. Nasopharyngeal/oropharyngeal swab samples exhibited the highest median baseline viral RNA levels compared to nasal swabs. Baseline SARS-CoV-2 IgG positivity was associated with lower baseline viral RNA levels and reduced viral RNA shedding over the 10-day observations period. SARS-CoV-2 genotypes represented in the study did not include Delta or Omicron variants, consistent with the time-period of enrollment for the clinical trial. Deep sequencing of respiratory samples was attempted for all subjects in the Full Analysis Set who did not receive remdesivir prior to enrollment. Treatment-emergent substitutions were identified that are indicated for phenotypic evaluation as part of a Post-Marketing Requirement.

ADMINISTRATIVE SIGNATURES

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

Eric Donaldson, Ph.D.
Clinical Virology Reviewer

CONCURRENCES

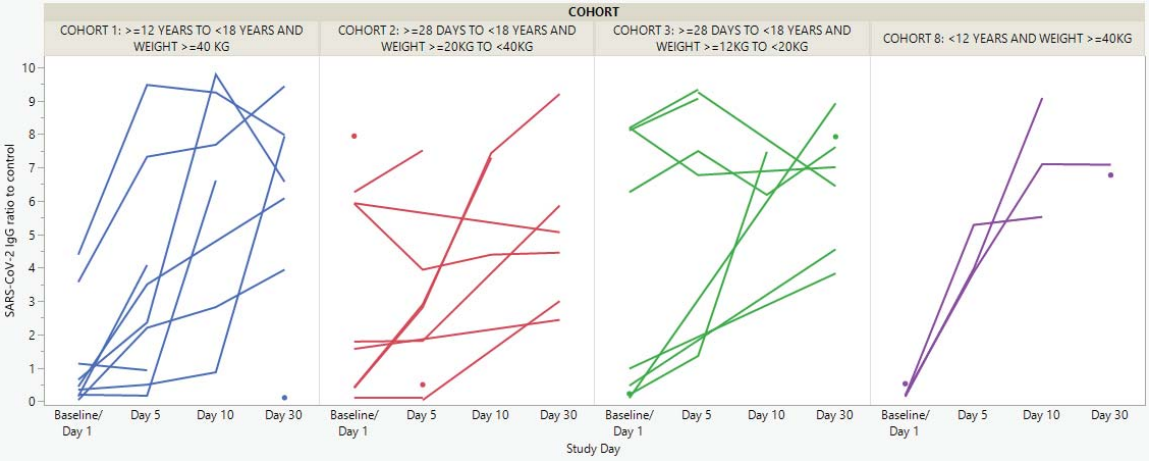
Date: _____

HFD-530/Clin Virol TL/J O'Rear

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

Reference ID: 4962553

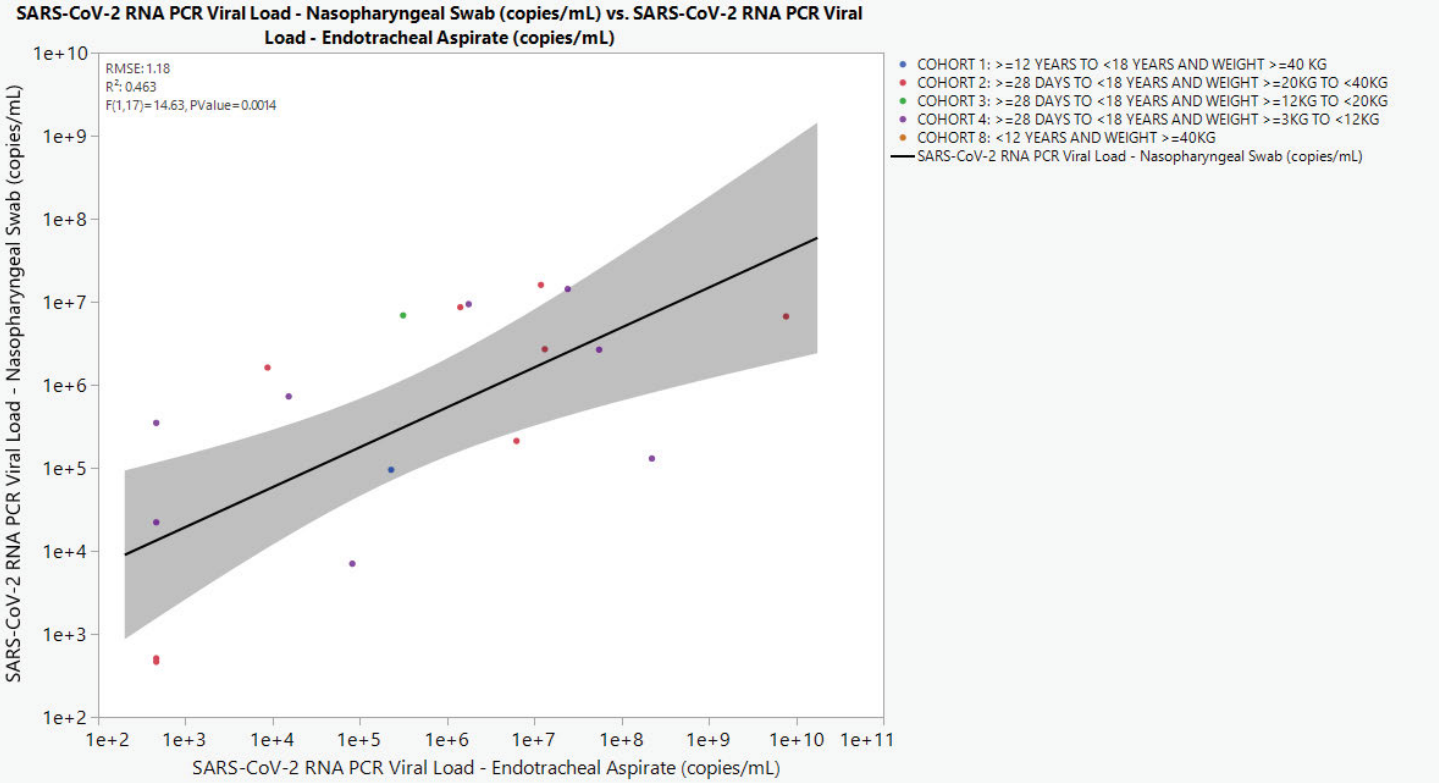
APPENDIX A: SARS-CoV-2 IgG in serum at each time point in evaluated subjects.



Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823.

Reference ID: 4962753

APPENDIX B: Viral RNA in nasopharyngeal/oropharyngeal vs endotracheal aspirates.



Source: FDA reviewer analysis of ADLB; trial GS-US-540-5823.

Reference ID: 4962753

APPENDIX C: Response to IR sent 2/25/2022 regarding PMR 1. Received 3/4/2022; SDN 266:

Original IR language is in **bold**
Applicant response language is in Times New Roman.

Original PMR 1 Information Request sent 2/25/2022:
At this time, we have the following PMR for your review. Additional PMR/PMC proposals may be forthcoming as the review progresses. Please review the following PMR description and propose a timeline.

Number	PMR Description	Timetable
1	**Evaluate substitutions meeting the following criteria for their impact on remdesivir susceptibility of virus in cell culture, or, if virus is unable to be recovered, in a biochemical assay of RdRp activity:** **Criterion A: Substitutions identified as treatment-emergent at a frequency of ≥15% of the virus population or are treatment-emergent in more than one subject or are associated with viral RNA rebound in more than one subject, including different amino acid substitutions at the same position:** **nsp9: G17V, N95D;** **nsp10: D64Y;** **nsp12: V495F, A656P, G670V;** **nsp13: R248I, V266F, S301F;** **nsp14: T16I, P24L, P24S, H95Y, N129D.** **Should any substitution identified under Criterion A be found to reduce susceptibility to remdesivir greater than concurrently assessed nsp12 N198S, evaluate substitutions that meet Criterion B: Substitutions identified as treatment-emergent at a frequency of ≥5% of the virus population and associated with viral RNA rebound:** **nsp8: E60K, A102V;** **nsp9: L94S;** **nsp10: G2D;** **nsp12: G228C, P243S, R640C, E665K;** **nsp13: N46Y, E261D, A296V, T380I, R409P, L590P;** **nsp14: T293I, S470F D515H.**	**Final Protocol Submission: MM/YYYY** **Study Completion: MM/YYYY** **Final Report Submission: MM/YYYY**

Please provide a response by COB (ET), March 4, 2022.

12 Pages have been Withheld in Full as B4 (CCI/TS) and B6 (PPI) immediately following this page

Reference ID: 4962753

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/

WILLIAM L INCE
04/01/2022 02:03:44 PM

ERIC F DONALDSON
04/01/2022 02:07:07 PM

JULIAN J O REAR
04/01/2022 02:32:14 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s011

OTHER REVIEW(S)

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:	March 22, 2022
Reviewer:	Kate McCartan, MD Division of Pharmacovigilance II
Team Leader:	Rachna Kapoor, PharmD, 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-11
Applicant:	Gilead Sciences, Inc.
OSE RCM #:	2021-2392

Reference ID: 4956496

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 (ACMT) – FDA ACMT COVID-19 Toxicology Investigators Consortium (ToxIC) (FACT) Pharmacovigilance Project Sub-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).

The Division of Antivirals (DAV) consulted DPV II to provide a safety summary of adverse event reports submitted for remdesivir through February 14, 2022. Additionally, DAV requested that this summary include an overview of adverse event reports for patients who received remdesivir as an outpatient and an overview of adverse event reports for pediatric patients. 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-11.

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.[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.[3] 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 November 30, 2021, the Applicant submitted sNDA 214787/S-11 which expands the approved indication for Veklury (remdesivir) to include the treatment of COVID-19 in pediatric patients aged ≥ 28 days weighing ≥ 3 kg.

On January 21, 2022, sNDA 214787/S-10 was approved which expanded the indication for Veklury (remdesivir) to include the treatment of COVID-19 in non-hospitalized adults and

Reference ID: 4956496

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] At the time of this approval, the EUA letter was reissued to expand authorization of remdesivir use to treatment of non-hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg.[2]

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.[4] 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.[5] 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.[6] 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 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, another 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 another NISS was opened, tracked under NISS #1004496, and this NISS was 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.[7] Bradycardia is a labeled event in the context of infusion-related

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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 FACT Pharmacovigilance Project Sub-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.

On January 10, 2022, DPV II completed a high-level overview of *all adverse events* with remdesivir use through December 13, 2021.[8] This memorandum was completed in response to a consult from DAV in association with sNDA 214787/S-10. As a result of the safety summary no new safety signals were identified that warranted regulatory action at that time.

1.3 RELEVANT PRODUCT LABELING[1]

The relevant sections from the remdesivir label are detailed below.

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.

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.

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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

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. In addition, we screened these adverse event cases to identify those reporting remdesivir use for the treatment of COVID-19 in the outpatient setting[a] as well as to identify those reporting remdesivir use for the treatment of COVID-19 in pediatric patients (i.e., patients aged 0 to ≤ 17 years). 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**.

[a] Cases were screened for remdesivir use for the treatment of COVID-19 in the outpatient setting starting January 21, 2022, the date of approval of sNDA 214787/S-10 which expanded the indication of Veklury (remdesivir) to treatment of non-hospitalized patients.

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Table 1. FAERS Search Strategy*	
Date of search	Recurring daily searches†
Time period of search	December 1, 2019‡ - February 14, 2022
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 February 15, 2022. Searches recurring daily on Tuesday-Friday with a 1-day prior completion date and on Monday with a 3-day prior completion date.
‡ The first cases of patients infected with the SARS-CoV-2 virus were reported in December 2019.
§ 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 – February 14, 2022

In addition, we reviewed weekly PubMed and EMBASE Early Alerts for COVID-19 and safety-related articles (March 15, 2020 – February 9, 2022) for cases of adverse events with all COVID-19 treatments, including remdesivir.

2.4 OTHER SAFETY DATA

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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 FACT sub-registry from November 23, 2020[b] through February 14, 2022. 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 February 14, 2022, we identified 6,132 unique cases of adverse events with remdesivir use for the treatment of COVID-19 in FAERS. Of the 6,132 total cases, 110 occurred in pediatric patients. From January 21, 2022 through February 14, 2022, two cases reported remdesivir use in the outpatient setting.

3.2 LITERATURE CASE SELECTION

From January 1, 2020 through February 14, 2022, we identified 274 case reports of adverse events with remdesivir use for the treatment of COVID-19 in the medical literature. Of the 274 total cases, 19 occurred in pediatric patients. From January 21, 2022 through February 14, 2022, no cases reported remdesivir use in the outpatient setting.

3.3 FACT PHARMACOVIGILANCE PROJECT SUB-REGISTRY CASE SELECTION

From November 23, 2020 through February 14, 2022, we identified 422 cases of adverse events with remdesivir use for the treatment of COVID-19 in the FACT Pharmacovigilance Project Sub-registry. Of the 422 total cases, one occurred in a pediatric patient. From January 21, 2022 through February 14, 2022, no cases reported remdesivir use in the outpatient setting.

3.4 FINAL CASE SERIES

3.4.1 All Patients

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.

[b] The first case in the FACT sub-registry was received on November 23, 2020.

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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 February 14, 2022 (n=6,828)	
Source*	
FAERS	6,132 (3,200 EUA)
Literature	274
FACT Pharmacovigilance Project Sub-registry	422 (21 EUA)
Sex	(n=6,706)
Male	4,176
Female	2,528
Transgender	2
Age	(n=6,398)
Range	4 days – 100 years
Median	64
Mean	61
Fatal Outcome	1,937

* 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.

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 (n=2,861)*	
<u>Hepatobiliary Disorders</u>	(n=126)
Hepatic failure	40
Hyperbilirubinemia/cholestasis	85
Sclerosing cholangitis	1
<u>Blood and Lymphatic System Disorders</u>	(n=271)‖
Thrombocytopenia/anemia/leukopenia	204
Hemorrhage (non-neuro)/coagulopathy	81
Thrombocytosis	18
Methemoglobinemia	1
Hemolytic anemia	4
<u>Renal and Urinary Disorders</u>	(n=1,106)‖
AKI/renal impairment/renal failure	1,098
ATN	19
Bladder calculus	1
Hematuria	9
Renal tubular acidosis	1
<u>Neurologic Disorders</u>	(n=108)‖
Ischemic stroke	53
Empty sella syndrome	1
Hemorrhagic stroke/intracranial hemorrhage	15
Dystonia	1

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Table 4. Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events (n=2,861)*	
Guillain-Barre syndrome	11
Neuroleptic malignant syndrome/Malignant hyperthermia	4
PRES	5
Tremor	16
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=159)‖
Hyperkalemia	30
Hypernatremia	20
Hypokalemia	11
Hypophosphatemia	3
Hyperphosphatemia	3
Hypermagnesemia	5
Hyperglycemia	63
Hypoglycemia	14
SIADH	3
Hyponatremia	14
Diabetes insipidus	2
Hypomagnesemia	1
Hypocalcemia	2
Hyperparathyroidism	1
Hyperamylasemia	3
Hypertriglyceridemia	7
Psychiatric Disorders	(n=85)‖
Anxiety/agitation	34
Hallucinations/delirium	36
Confusion/mental status changes	21
Suicidal ideation	1
Completed suicide	3
Abnormal dreams	1
Catatonia	1
Psychosis	3
Cardiac Disorders**	(n=1,187)‖
VF/VT/SVT	50
Atrial fibrillation/atrial flutter	85
Tachycardia	55
Cardiac arrest/PEA	249
Hypotension	169
Bradycardia	722

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Table 4. Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events (n=2,861)*	
Myocardial infarction	47
QT prolongation††	45
TdP‡‡	6
Hypertension	26
Arrhythmia	11
AV block (1st and 2nd degree)	21
AV block complete	2
RBBB/LBBB	4
Cardiac failure	14
Musculoskeletal and Connective Tissue Disorders	(n=17)
Rhabdomyolysis	17
Investigations	(n=22)‖
Increased CPK	13
Increased drug level¶¶	10
*Decreased drug level***	2
Drug interaction†††	4
Gastrointestinal Disorders	(n=81)
Pancreatitis	40
Intestinal/gastric perforation	36
Intestinal ischemia	5
Vascular Disorders	(n=207) ‖
Pulmonary embolism	98
Deep vein thrombosis	52
Unspecified thrombosis	53
Renal infarction	20
Splenic infarction	5
Ear and Labyrinth Disorders	(n=8)‖
Hearing loss/deafness	4
Tinnitus	6
Pregnancy, Puerperium and Perinatal conditions	(n=7)
Fetal bradycardia	4
Fetal tachycardia	1
Congenital malformations in infant	1
Fetal demise	1

* The table lists AEs reported with remdesivir use; however, causality criteria have not been applied.
† Cases received through February 14, 2022.
‖ A case may have more than one AE.
** Cardiac AEs that were **not** reported in the context of infusion-related reactions
††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, two patients were on dexmedetomidine, one patient was on diltiazem, two patients were on amiodarone, one patient was on donepezil, one patient was on methadone, one patient was on azithromycin and quetiapine, one patient was on levofloxacin, one patient was on quetiapine, and twenty-two 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.
¶¶ Seven 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 and decreased tacrolimus level.

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Table 4. Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events (n=2,861)*

††† 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: AE = adverse event, 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.
- There was a fatal outcome in 32% 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, multiple organ dysfunction, and various infections (e.g., Aspergillus infection, Cytomegalovirus infection), all of which can occur with COVID-19 independent of remdesivir use.
- The most commonly reported unlabeled adverse event was acute kidney injury/renal impairment/renal failure (n=1,098) followed by bradycardia occurring outside of infusion-related reactions (n=722).

3.4.2 Outpatients

From January 21, 2022[c] through February 14, 2022, we identified two cases which reported outpatient treatment with remdesivir. See **Appendix D** for a line listing of these cases.

- One case reported an infusion-related reaction with an increase in blood pressure in a male patient of an unknown age. It was not clear if this elevation was during or after the infusion, but the blood pressure was taken by a home infusion nurse. Notably, there was concern in this case that the tubing used was defective and led to the medication being administered at a faster rate than expected (i.e., 90% had run in 5 minutes).
- A second case reported an infusion site reaction in a 56-year-old female occurring the day after completion of the three-day series of infusions. The patient described erythema, pruritus and swelling of the arm in which she had received two of the three infusions and a small pruritic area on the other arm in which she received the remaining infusion. Three days later, she also reported pruritus, erythema and swelling of the face. The day after that, she reported worsening of the initial reaction, with spreading erythema. This patient planned for evaluation in an urgent care. On follow-up with the patient, she stated that she was diagnosed at the urgent care with an "allergic reaction to remdesivir" and was prescribed prednisone. She reported the prednisone helped, but the redness persisted for weeks before it completely resolved.

[c] Date of approval of sNDA 214787/S-10 which expanded the indication of Veklury (remdesivir) to treatment of non-hospitalized patients.

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3.4.3 Pediatric Patients

Table 5 provides the total number of cases identified from FAERS, the medical literature, and the FACT Pharmacovigilance Project Sub-registry reporting adverse events with the use of remdesivir for the treatment of COVID-19 in pediatric patients and describes characteristics of these cases.

Table 5. All Pediatric 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 February 14, 2022 (n=130)	
Source*	
FAERS	110 (49 EUA)
Literature	19
FACT Pharmacovigilance Project Sub-registry	1
Sex	(n=123)
Male	59
Female	64
Age	(n=129)
Range	4 days – 17 years
Median	12
Mean	10
Fatal Outcome	17
* 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.	

Table 6 summarizes the unlabeled adverse events of interest reported in cases with remdesivir use for the treatment of COVID-19 in pediatric patients.

Table 6. Pediatric Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events of Interest (n=51)* †	
Hepatobiliary Disorders	(n=1)
Hyperbilirubinemia/cholestasis	1
Blood and Lymphatic System Disorders	(n=3)
Thrombocytopenia/anemia/leukopenia	1
Hemorrhage (non-neuro)/coagulopathy	2
Renal and Urinary Disorders	(n=12) †
AKI/renal impairment/renal failure	11
Hematuria	1
Renal tubular acidosis	1
Metabolism and Nutrition Disorders	(n=7)
Hypernatremia	1
Hypokalemia	1
Hyperglycemia	1
SIADH	2
Hypertriglyceridemia	1

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Table 6. Pediatric Cases with Remdesivir Use for the Treatment of COVID-19 Reporting Unlabeled Adverse Events of Interest (n=51)* †	
Hyperamylasemia	1
Cardiac Disorders‡	(n=33) †
Tachycardia	1
Cardiac arrest/PEA	2
Hypotension	5
Bradycardia	20
QT prolongation§	3
Hypertension	3
AV block (1st and 2nd degree)	1
Cardiac failure	1
Gastrointestinal Disorders	(n=1)
Intestinal/gastric perforation	1
Vascular Disorders	(n=5)
Pulmonary embolism	2
Unspecified thrombosis	3

* 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 infusion-related reactions
§One patient was on hydroxychloroquine, one patient was on dexmedetomidine, and one patient was not on any reported QT prolonging drugs.
Abbreviations: AKI = acute kidney injury, AV = atrioventricular, PEA = pulseless electrical activity, SIADH = syndrome of inappropriate antidiuretic hormone

Key Points:

- Slightly more of the cases occurred in females than in males. The median age in the cases was 12 years, but cases were reported throughout the entire pediatric age range, from 4 days to 17 years.
- Of the 129 pediatric cases which reported an age, approximately half reported adverse events occurring with patients aged less than 12 years.
- The most commonly reported unlabeled adverse event was bradycardia (n=20) followed by acute kidney injury/renal impairment/renal failure (n=11).
- Of the 17 cases with a fatal outcome
    - 14 cases either reported the cause of death as COVID-19 or described worsening COVID-19 or complications secondary to COVID-19 (e.g., respiratory failure, multiple organ failure) at the time of death.
    - 1 case reported meningoencephalitis from Mycobacterium infection and brain herniation as the cause of death.
    - 1 case reported pulmonary embolism and cardiac arrest as the cause of death. This patient was on concomitant baricitinib.
    - 1 case reported no details beyond patient death, occurring after 2 doses of remdesivir.

4 REVIEWER'S COMMENTS

All Patients:

Adverse event reporting trends and the cases reporting unlabeled adverse events of interest including acute kidney injury (AKI), bradycardia, hepatotoxicity, INR/PT increased, and QT

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prolongation, have remained similar to those noted in the January 10, 2022 DPV II memorandum summarizing all adverse events with remdesivir use and which included data through December 13, 2021.[8]

Outpatients:

The small number of cases reporting outpatient use of remdesivir limits the safety assessment in this treatment setting. We do note, however, that one of the two outpatient cases described an infusion-related reaction with a labeled sign or symptom (i.e., hypertension) and occurred during the infusion or the labeled one-hour post-infusion observation period.[1] In the second case, the patient reported initial injection site erythema, which is labeled, followed by facial symptoms three days later and worsening of the initial rash four days later. It is unclear if the facial symptoms were a non-immediate hypersensitivity reaction or were additional manifestations of the initial reaction. This patient was ultimately diagnosed with an allergic reaction to the remdesivir and required treatment with steroids. DPV II will continue to monitor for adverse events reported with outpatient use of remdesivir as part of our routine surveillance of treatments used for COVID-19.

Pediatric Patients:

Overall, adverse events reported with the use of remdesivir for the treatment of COVID-19 in pediatric patients were similar to those identified with the use of remdesivir for the treatment of COVID-19 in all patients. The two most commonly reported adverse events in pediatric patients were also the two most commonly reported adverse events in all patients, which are, acute kidney injury and bradycardia:

- **Acute kidney injury (AKI):** Cases reporting AKI with remdesivir use were previously actively monitored for six months post-approval, ultimately returning to routine pharmacovigilance as the cases were found to have limited information and the majority had confounding factors. The eleven cases describing AKI in pediatric patients had similar limitations. Ten of the eleven cases did not report specific timing of the AKI in relation to the remdesivir treatment and in the remaining case, AKI occurred after discontinuation of remdesivir, making remdesivir less likely to be the cause. Six of the eleven cases also reported confounding factors (e.g., other nephrotoxic treatments, shock or hypotension, clinical deterioration). DPV II will continue to monitor AKI, including in pediatric patients, 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.[7] DPV II reviewed cases received through May 31, 2021 from FAERS, the medical literature and the FACT Pharmacovigilance Project Sub-registry as part of this assessment. This assessment included five pediatric cases. From June 1, 2021 through February 14, 2022, an additional 15 cases have been identified which reported bradycardia in pediatric patients being treated with remdesivir. Of these 15 cases, none reported symptomatic bradycardia, and none reported 2nd or 3rd degree atrioventricular block. No cases reported treatments including pharmacologic or device management, however, four cases reported remdesivir being discontinued early due to the bradycardia. The findings from these additional fifteen pediatric cases are consistent with the findings in the ISA. DPV II will continue to monitor bradycardia, including in pediatric patients, as part of our routine surveillance of treatments used for COVID-19.

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

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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.

Reference ID: 4956496

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

Reference ID: 4956496

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.

Reference ID: 4956496

6.4 APPENDIX D. FAERS LINE LISTING OF CASES REPORTING ADVERSE EVENTS WITH REMDESIVIR OUTPATIENT TREATMENT (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	1/30/2022	20404689	1	N/A	Direct	56	Female	USA	
2	2/2/2022	20417925	2	US-GILEAD-2022-0567483	Non-expedited	Unknown	Male	USA	

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: USA = United States

Reference ID: 4956496

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/s/

KATE L MCCARTAN
03/22/2022 02:53:04 PM

RACHNA KAPOOR
03/22/2022 04:18:58 PM

IDA-LINA DIAK
03/22/2022 09:41:16 PM

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

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

Memorandum

Date: 2/28/2022

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-11

In response to DAVP's consult request dated February 24, 2022, OPDP has reviewed the proposed dear healthcare provider letter for VEKLURY (remdesivir) for injection, for intravenous use.

DHCP Letter: OPDP's comments on the proposed labeling are based on the draft fact sheet received by electronic mail from DAVP on February 25, 2022, and are provided below.

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

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

NIMA OSSAREH
02/28/2022 11:24:20 AM

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

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

Memorandum

Date: 2/23/2022

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-11

In response to DAVP's consult request dated December 10, 2021, OPDP has reviewed the proposed patient fact sheet and HCP fact sheet for VEKLURY (remdesivir) for injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft fact sheet received by electronic mail from DAVP on February 16, 2022, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the fact sheet 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.

37 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reference ID: 4942083

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/s/

NIMA OSSAREH
02/23/2022 11:21:05 AM

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

PATIENT LABELING REVIEW

Date:	February 22, 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)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route:	• VEKLURY (remdesivir) for injection, for intravenous use • VEKLURY (remdesivir) injection, for intravenous use
Application Type/Number:	NDA 214787
Supplement Number:	S-11
Applicant:	Gilead Sciences, Inc

Reference ID: 4974652

1 INTRODUCTION

On November 30, 2021, Gilead Sciences, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their New Drug Application (NDA) 214787/S-11 for VEKLURY (remdesivir) for injection and VEKLURY (remdesivir) injection. With this efficacy supplement the Applicant proposes the expansion of the patient population for Veklury to include pediatric patients aged ≥ 28 days weighing ≥ 3 kg and provides interim safety, tolerability, pharmacokinetics (PK), and efficacy data from Cohorts 1 through 4 and Cohort 8 in the ongoing Phase 2/3 Study GS-US-540-5823, titled, "*A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With COVID-19.*"

On December 10, 2021, the Division of Antivirals (DAV) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for VEKLURY (remdesivir).

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI for VEKLURY (remdesivir).

2 MATERIAL REVIEWED

- Draft VEKLURY (remdesivir) PPI received on November 30, 2021, and received by DMPP on February 16, 2022.
- Draft VEKLURY (remdesivir) Prescribing Information (PI) received on November 30, 2021, and received by DMPP on February 16, 2022.
- Approved VEKLURY (remdesivir) PPI labeling on January 21, 2022.

3 CONCLUSIONS

We find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

Reference ID: 4974652

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/s/

SUSAN W REDWOOD
02/22/2022 02:51:28 PM

SHARON R MILLS
02/22/2022 02:56:44 PM

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:	February 2, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214787/S-011
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:	November 30, 2021
OSE RCM #:	2021-2377
DMEPA Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

Reference ID: 4934193

1 REASON FOR REVIEW

Gilead submitted an efficacy supplement for Veklury (remdesivir) for injection, 100 mg and Veklury (remdesivir) injection, 100 mg/20 mL to update the prescribing information to include the expansion of the patient population to include pediatric patients 28 days of age and weighing 3 kg to less than 40 kg. Subsequently, the Division of Antivirals (DAV) requested that we review the proposed prescribing information (PI) and patient prescribing information (PPI) 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 RECOMENDATIONS

We note that the proposed Veklury PI and PPI is being revised to update labeling to include recommended dosing for pediatric patients 28 days of age and weighing 3 kg to less than 40 kg.

Veklury is currently approved in adult and pediatric patients aged 12 years or older weighing ≥ 40 kg. There are two approved formulations:

1) Veklury (remdesivir) lyophilized powder for injection, 100 mg and

2) Veklury (remdesivir) injection, 100 mg/2 mL.

The Veklury (remdesivir) lyophilized powder for injection, 100 mg will be the only approved dosage form for pediatric patients less than 12 years of age and the recommended dose will be a loading dose of 5 mg/kg on Day 1 followed by once-daily maintenance doses of 2.5 mg/kg from day 2. We did not identify any areas of vulnerability to medication error with the proposed PPI.

Reference ID: 4934193

3.1 Assessment of Prescribing in Formation *(PI)*

Our evaluation of the PI identified areas of vulnerability that may lead to medication errors. We collaborated with the review team to revise the PI to address the following identified medication error concerns:

1. Improve clarity related to the approved dosage form (remdesivir lyophilized powder for injection, 100 mg) for pediatric patients less than 12 years of age.

2. Improve clarity and streamline the dose preparation and administration instructions related to infusion time and rate.

3.2 Assessment of Approved Container Labels and Carton Labeling

We reviewed the currently approved container labels and carton labeling for Veklury. Our evaluation of the container labels and carton labeling identified areas of vulnerability that could lead to medication error. Table 2 below includes the identified medication error issues with the currently marketed Veklury (remdesivir) lyophilized powder for injection container label and carton labeling, DMEPA's rationale for concern and the proposed recommendation to minimize the risk for medication error. In addition, we recommend that the division consider asking Gilead to inform the healthcare community about label and labeling revisions through a Dear Health Care Provider (DHCP) letter.

Table 2: Identified Issues and Recommendations for Gilead Sciences, Inc. (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Veklury for Injection (lyophilized powder)			
Container Label			
(b) (4)			

Reference ID: 4934193

Carton Labeling
(b) (4) 

4 CONCLUSION AND RECOMMENDATION TO THE DIVISION OF ANTIVIRALS (DAV)

Our evaluation of the approved Veklury for injection container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for Gilead. We ask that the Division convey Table 2 in its entirety to Gilead so that recommendations are implemented prior to approval of this supplement.

In addition, as we noted in Table 2 above, the inconsistency between the proposed PI and the approved Veklury for injection container label and carton labeling may lead to medication errors. Thus, we recommend that the Division ask Gilead to inform the healthcare community through a Dear Health Care Provider (DHCP) letter about this inconsistency.

Reference ID: 4934193

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 1 presents relevant product information for Veklury received on November 30, 2021 from Gilead Sciences, Inc.

Table 1. Relevant Product Information for Veklury	
Initial Approval Date	N/A
Active Ingredient	remdesivir
Indication	Indicated for treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg with coronavirus disease 2019 (COVID-19).
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.

Reference ID: 4934193

	Diluted Solution: Store Veklury diluted solution for infusion 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]).
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 January 31, 2022, 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 and Patient Prescribing Information (Image not shown) received on November 30, 2021, available from \\CDSESUB1\evsprod\NDA214787\0116\m1\us\114-labeling\draft\labeling

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

Reference ID: 4934193

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/s/

MELINA N FANARI
02/02/2022 12:29:57 PM

SEVAN H KOLEJIAN
02/02/2022 12:50:04 PM

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

PATIENT LABELING REVIEW

Date:	February 22, 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)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Patient Package Insert (PPI)
Drug Name (established name), Dosage Form and Route:	• VEKLURY (remdesivir) for injection, for intravenous use • VEKLURY (remdesivir) injection, for intravenous use
Application Type/Number:	NDA 214787
Supplement Number:	S-11
Applicant:	Gilead Sciences, Inc

Reference ID: 4941602

1 INTRODUCTION

On November 30, 2021, Gilead Sciences, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their New Drug Application (NDA) 214787/S-11 for VEKLURY (remdesivir) for injection and VEKLURY (remdesivir) injection. With this efficacy supplement the Applicant proposes the expansion of the patient population for Veklury to include pediatric patients aged ≥ 28 days weighing ≥ 3 kg and provides interim safety, tolerability, pharmacokinetics (PK), and efficacy data from Cohorts 1 through 4 and Cohort 8 in the ongoing Phase 2/3 Study GS-US-540-5823, titled, "*A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With COVID-19.*"

On December 10, 2021, the Division of Antivirals (DAV) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for VEKLURY (remdesivir).

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI for VEKLURY (remdesivir).

2 MATERIAL REVIEWED

- Draft VEKLURY (remdesivir) PPI received on November 30, 2021, and received by DMPP on February 16, 2022.
- Draft VEKLURY (remdesivir) Prescribing Information (PI) received on November 30, 2021, and received by DMPP on February 16, 2022.
- Approved VEKLURY (remdesivir) PPI labeling on January 21, 2022.

3 CONCLUSIONS

We find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

Reference ID: 4941602

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/s/

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SHARON R MILLS
02/22/2022 02:56:44 PM

M E M O R A N D U M

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

DATE: February 15, 2022

TO: Debra Birnkrant, M.D.
Director
Division of Antivirals (DAV)
Office of Infectious Diseases (OID)
Office of New Drugs (OND)

FROM: Monica Javidnia, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Routine inspection of Carolinas Medical Center - Levine Children's Hospital, Charlotte, NC and Texas Children's Hospital, Houston, TX

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of study GS-US-540-5823 (NDA 214787/S-011) conducted at Carolinas Medical Center - Levine Children's Hospital, Charlotte, NC (Site #11115) and Texas Children's Hospital, Houston, TX (Site #07633).

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out at either site. The final inspection classification is No Action Indicated (NAI) for both sites.

After reviewing the inspectional findings, I conclude the data from the audited studies are reliable.

1.1. Surveillance Recommendation

Based on the inspectional findings, studies of similar design conducted at Carolinas Medical Center - Levine Children's Hospital and Texas Children's Hospital during the current

surveillance interval should be considered reliable without an inspection.

2. Inspected Studies:

NDA 214787/S-011

Study Number: GS-US-540-5823
Study Title: (CARAVAN), A Phase 2/3 Single-Arm, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With COVID-19
Dates of conduct: 07/21/2020 – 05/24/2021*

*The trial is ongoing; the end date refers to the last visit of the last participant included in the interim report dated 10/04/2021. The interim report included data from Cohorts 1-4 and 8. Records for one additional participant # (b) (6) from Cohort 5 were evaluated during the inspection at Clinical Site #11115.

Clinical Site #11115:
Site Name: Carolinas Medical Center - Levine Children's Hospital**
Clinical Investigator Name: Amina Ahmed, M.D.

**Levine Children's Hospital is on the Carolinas Medical Center campus and operated by Atrium Health.

Clinical Site #07633:
Site Name: Texas Children's Hospital
Clinical Investigator Name: Flor de Maria Munoz-Rivas, M.D.

3. Inspectional Findings

3.1 Carolinas Medical Center - Levine Children's Hospital, Charlotte, NC (Site #11115)

ORA investigator Brandy D. Brown inspected Carolinas Medical Center - Levine Children's Hospital, Charlotte, NC from January 18-21, 2022.

This was the first OSIS inspection of Carolinas Medical Center - Levine Children's Hospital under the BA/BE program.

Reference ID: 4938553

The blood transfusion facility was inspected in February 2018 (FEI #1072484) in accordance with CP 7342.001 - Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors. Form FDA 483 was not issued. One item was discussed during the inspection close out regarding two expired reagents. The firm stated these were primarily used for research, were not currently in use, and were removed as a corrective action. The final classification was NAI.

The current inspection included auditing the following items:

-Subject records, documentation, and electronic data capture
-Training of study personnel
-Protocol deviations
-Adverse events
-Informed consent process
-Institutional review board approvals and correspondence
-Delegation of authority
-Organization chart
-Test article shipment records
-Test article accountability and disposition
-Collection and processing of samples
-Freezer sample storage logs
-Study record retention
-Reports to sponsor
-Study monitoring records

At the conclusion of the inspection, investigator Brown did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

3.2 Texas Children's Hospital, Houston, TX (Site #07633)

ORA investigator Anya D. Lockett-Evans inspected Texas Children's Hospital, Houston, TX from January 18-24, 2022.

This was the first OSIS inspection of Texas Children's Hospital under the BA/BE program.

The site's blood bank had previously been inspected in August 2018 (FEI # 1671800) in accordance with CP 7342.001. Form FDA 483 was not issued. One item was discussed during the inspection close out meeting. Specifically, the daily temperature logs had numerous cross-outs and write-overs. The firm stated the procedure is to draw a single line through an entry and initial and date corrections. The firm stated they would remind the employees of the procedure. The final classification was NAI.

Reference ID: 4938553

The current inspection included auditing the following items:

-Case report forms (CRFs) for dosing and randomization accuracy
-Source data documentation
-Adverse events and serious adverse event reporting
-Informed consent
-Protocol adherence and deviations
-Accuracy of electronic data capturing
-Compliance with SOPs
-Corrective action plan created due to a deviation that occurred during the audited study
-Drug accountability
-Training
-Institutional review board documentation
-Financial disclosures
-Monitoring
-Safety reporting

At the conclusion of the inspection, investigator Lockett-Evans did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

Monica Javidnia, Ph.D.
Staff Fellow

Final Classification:

NAI - Carolinas Medical Center - Levine Children's Hospital (Atrium Health Levine Children's Hospital)
Charlotte, NC
FEI#: 1072484

NAI - Texas Children's Hospital
Houston, TX
FEI#: 3004640893

cc:
OTS/OSIS/Kassim/Folian/Pham/Fenty-Stewart/Johnson
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Lewin/Javidnia
ORA/OMPTO/OBIMO/Brown/ORABIMOE.Correspondence@fda.hhs.gov
ORA/OMPTO/OBIMO/Lockett-Evans/
ORABIMOW.Correspondence@fda.hhs.gov

Draft: MJ 02/14/2022; 2/15/2022
Edit: AL 02/14/2022; JC 2/14/2022

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Carolinas Medical Center - Levine Children's Hospital, Charlotte, NC, USA

http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f884a347ae

Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Texas Children's Hospital, Houston, TX, USA

http://ecmsweb.fda.gov/webtop/drl/objectId/0b0026f884a347d2

OSIS File #: BE 9263

eNSPECT/FACTS: 191008

Operation ID 215465: Carolinas Medical Center – Levine Children’s Hospital
Operation ID 215493: Texas Children’s Hospital

Reference ID: 4938553

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/s/

MONICA JAVIDNIA
02/15/2022 04:02:55 PM

AMANDA E LEWIN
02/15/2022 04:08:22 PM

SEONGEUN CHO
02/15/2022 04:13:01 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 14, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214787/S-011
Product Name and Strength:	Veklury (remdesivir)) for Injection, 100 mg per vial; Veklury (remdesivir) Injection, 100 mg/20 mL (5 mg/mL)
Applicant/Sponsor Name:	Gilead Sciences, Inc.
OSE RCM #:	2021-2377-1
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph.
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label and carton labeling received on February 8, 2022 for Veklury (remdesivir) for injection. The Division of Antivirals (DAV) requested that we review the revised container label and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Fanari, M. Label and Labeling Review for Veklury (remdesivir) for injection (NDA 214787/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Feb 2. RCM No.: 2021-2377.

Reference ID: 4937737

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 8, 2022

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/s/

MELINA N FANARI
02/14/2022 02:48:57 PM

SEVAN H KOLEJIAN
02/14/2022 02:58:22 PM

M E M O R A N D U M

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

DATE: 1/19/2022

TO: Division of Antivirals (DAV)
Office of Infectious Diseases (OID)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214787/S-011

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4).

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

JAMES J LUMALCURI
01/19/2022 09:17:46 AM