Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology Review

Application Type	Supplemental New Drug Application (sNDA), S-26
Application Number(s)	214787
Priority or Standard	Priority
Submit Date(s)	August 28, 2023
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Division/Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)	Division of Antivirals Yodit Belew, MD, Associate Director for Therapeutic Review 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 and Pharmacometrics Reviewer Justin Earp, PhD, Pharmacometrics Team Leader Kunyi Wu, PharmD, Clinical Pharmacology Team Leader
Review Completion Date	February 23, 2024
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	The recommended dosage depends upon the patient population (bold font denotes changes from the currently approved label): • The recommended dosage for adults and pediatric patients weighing at least 40 kg is a single loading dose of RDV 200 mg on Day 1 via intravenous infusion followed

	by once-daily maintenance doses of RDV 100 mg from Day 2 via intravenous infusion. • The recommended dosage for pediatric patients 28 days of age and older and weighing at least 3 kg to less than 40 kg is a single loading dose of RDV 5 mg/kg on Day 1 via intravenous infusion followed by once-daily maintenance doses of RDV 2.5 mg/kg from Day 2 via intravenous infusion • **The recommended dosage for pediatric patients weighing at least 1.5 kg to less than 3 kg is a single loading dose of RDV 2.5 mg/kg on Day 1 via intravenous infusion followed by once-daily maintenance doses of RDV 1.25 mg/kg from Day 2 via intravenous 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 weighing at least 1.5 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
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (birth to less than 18 years of age weighing at least 1.5 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

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 (28 days 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.

These assessments and regulatory actions were based on the following:
- The efficacy of RDV was assessed in three Phase 3 clinical trials in hospitalized patients (reviewed under the original NDA; action date October 22, 2020) 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 (reviewed under sNDA-10; action date January 21, 2022).
- Based on the totality of the data, including extrapolation of efficacy from the aforementioned four Phase 3 clinical trials in adults, and the pharmacokinetic (PK)/pharmacodynamic (PD) and safety data from Cohorts 1-4, and 8 from one Phase 2/3 clinical trial in hospitalized pediatric subjects, the indication was extended to include the pediatric population 28 days and older and weighing at least 3 kg to less than 40 kg (reviewed under sNDA-11; action date April 25, 2022).

RDV is a nucleotide prodrug that is intracellularly metabolized into its active form GS-443902, which is an analog of adenosine triphosphate that inhibits viral 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). COVID-19 is a significant and ongoing public health concern, one that affects a large population, including pediatric patients, in the United States and worldwide. RDV is currently the only approved antiviral for COVID-19 in pediatric patients; the current label encompasses pediatric patients 28 days and older and weighing at least 3 kg.

In this supplemental new drug application (sNDA), the Applicant's proposed indication is treatment of adults and pediatric patients weighing at least 1.5 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.

The Applicant's proposed expansion of the population to include pediatric patients weighing at least 1.5 kg to less than 3 kg is based on the results from Cohorts 5-7 of GS-US-540-5823, a Phase 2/3, single-arm, open-label study to investigate the safety, tolerability, 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, in this sNDA, similar to sNDA-11 (action date April 25, 2022), 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 PK/PD and safety data from pediatric patients.

In pediatric patients weighing ≥1.5 kg to < 3kg, exposures were higher for RDV and its metabolites compared to adults; however, the increases were not considered clinically significant. As limited PK data were available in the youngest cohorts (subjects weighing ≥1.5 kg to <3kg), additional analyses were conducted using a simulated population. Results from the simulated population led to the recommended dosing regimen as they more closely align with adult exposures compared to the doses studied.

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 weighing at least 1.5 kg to less than 3 kg.

The revised indication is treatment of adults and pediatric patients (birth to less than 18 years of age weighing at least 1.5 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. In pediatric patients weighing at least 1.5 kg to less than 3 kg, the recommended dosage is RDV 2.5 mg/kg on Day 1 via intravenous infusion followed by once-daily maintenance doses of RDV 1.25 mg/kg from Day 2 via intravenous infusion The treatment duration depends upon the patient population, is unchanged from the currently approved label, and is summarized below: Hospitalized patients: 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. Non-hospitalized patients: 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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. • According to the Centers for Disease Control and Prevention (CDC), as of June 28, 2023, there have been 14,370 hospitalizations and 2223 deaths confirmed in pediatric patients in the US.	COVID-19 is a significant and ongoing public health concern, one that affects a large population, including pediatric patients, in the United States and worldwide. When infected with SARS-CoV-2, patients can experience symptoms that are severe, debilitating, and can be fatal.
Current Treatment Options	• RDV is currently the only approved antiviral for COVID-19 in pediatric patients. The current RDV approval encompasses pediatric patients 28 days and older and weighing at least 3 kg. • The following products are authorized for emergency use for the treatment	An unmet medical need exists for effective antiviral regimens for pediatric patients with COVID-19, including younger ages/lower weights.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

of COVID-19 in the following hospitalized pediatric patients:

Hospitalized Pediatric Patient Population	EUA
Pediatric patients 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO	Baricitinib*
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	Tocilizumab‡
Patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings	COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies

*On May 10, 2022, baricitinib was approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

‡On December 21, 2022, tocilizumab was approved for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

- The following products are authorized for emergency use for the treatment of mild-to-moderate COVID-19 in the following nonhospitalized pediatric patients:

Nonhospitalized Pediatric Patient Population	EUA
Certain adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death	Paxlovid*
Patients with immunosuppressive disease or receiving immunosuppressive treatment, in inpatient or outpatient settings	COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies

*On May 25, 2023, Paxlovid was approved for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

- Due to the mortality and severe morbidity associated with COVID-19, there is an urgent need to develop effective treatments.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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. • In sNDA-11 (action date April 25, 2022), despite the inherent limitations of its small sample size (n=53) and single-arm, open-label design, GS-US-540-5823 provided supportive evidence for the efficacy of RDV in pediatric patients (≥ 28 days of age and weighing ≥ 3 kg) 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. • In the current sNDA (GS-US-540-5823 Cohorts 5-7, n=5), clinical outcomes provided supportive evidence for the efficacy of RDV in pediatric patients (weighing ≥ 1.5 kg to < 3 kg) hospitalized with COVID-19. One subject (in Cohort 5) was discharged alive by Day 10. Three subjects (one each in Cohorts 5 to 7) were discharged alive by Day 30. No subjects in Cohorts 5-7 died during the study.	Based on the totality of the data, including extrapolation of efficacy from four Phase 3 clinical trials as described 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 weighing at least 1.5 kg to less than 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. RDV fills an important unmet medical need for pediatric patients with COVID-19, including those weighing at least 1.5 kg to less than 3 kg.
Risk	• No major safety issues were encountered during this review. • No adverse drug reactions (ADRs) occurred across Cohorts 5-7 in GS-US-540-5823.	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. 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.[1]

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.[2,3] In the US, according to the Centers for Disease Control and Prevention (CDC), there have been 14,370 hospitalizations and 2223 deaths confirmed in pediatric patients as of June 28, 2023.[4]

RDV is a direct acting antiviral drug that inhibits viral RNA synthesis. 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.[5] 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 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

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[1] COVID-NET: COVID-19-Associated Hospitalization Surveillance Network, CDC. https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html. Accessed on August 28, 2023.
[2] 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.
[3] CDC – Information for Pediatric Healthcare Providers – https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html. Accessed on August 28, 2023.
[4] CDC – Hospitalization and Deaths in the U.S. -- https://covid.cdc.gov/covid-data-tracker/.
[5] Center for Drug Evaluation and Research. Approval Package and Reviews for NDA 214787; action date, October 22, 2020 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000TOC.cfm).
[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.

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.

On April 25, 2022, the indication was expanded to include 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 inclusion of this pediatric sub-population (aged ≥28 days and weighing ≥ 3 kg to <40 kg) was based on[8]:

- Extrapolation of efficacy from adequate and well-controlled studies in adults (three phase 3 randomized clinical trials [RCTs] in hospitalized adults of varying disease severity).
- Extrapolation of efficacy from an adequate and well-controlled phase 3 RCT 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.
- PK data from pediatric patients enrolled in Phase 2/3 study GS-US-540-5823, which was compared to the adult PK data.
- Safety and pharmacodynamic data from pediatric patients.

There are currently no approved therapies for treatment of COVID-19 in pediatric patients weighing at least 1.5 kg to less than 3 kg. RDV would provide an approved antiviral drug to address this unmet medical need.

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[7] Center for Drug Evaluation and Research. Approval Package and Reviews for NDA 214787/Supplement-10; action date, January 21, 2022 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214787Orig1s010.pdf).
[8] Center for Drug Evaluation and Research. Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology, and Division Director Review for NDA 214787/Supplement-11; action date, April 25, 2022 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214787Orig1s011JointReview.pdf).

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 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

Executive Summary

GS-US-540-5823 (Study 5823) evaluated the pharmacokinetics (PK), safety, and efficacy of RDV in hospitalized pediatric subjects. We previously reviewed the PK data for Cohorts 1-4 and 8 for pediatric subjects ≥28 days of age and weighing ≥3 kg (NDA 214787, Integrated review dated 4/21/2022). RDV was approved for patients at least 28 days old and weighing ≥3 kg - <40 kg prior to submission of the current supplement, where the approved dosing is 5 mg/kg on day 1 then 2.5 mg/kg daily from day 2.

This submission contains PK data for Cohorts 5-7, i.e., preterm neonates (neonate defined as <28 days postnatal age [PNA], preterm defined as gestational age ≤37 weeks) and infants (PNA ≥ 28 days) and term neonates weighing ≥1.5 kg (NDA 214787, CSR submitted 8/28/2023). In the initial proposed labeling, dosing for neonates (and certain infants depending on age and weight) weighing ≥1.5 kg is 2.5 mg/kg on day 1 then 1.25 mg/kg daily from day 2 (Table 1).

Table 1. Proposed RDV dosing for pediatric patients in labeling

Pediatric Patient Population	Loading Dose Via Intravenous Infusion	Maintenance Dose Via Intravenous Infusion
(b) (4)	VEKLURY 2.5 mg/kg on Day 1	VEKLURY 1.25 mg/kg once daily from Day 2
Less than 28 days old and at least 1.5 kg		
At least 28 days old and 1.5 kg to less than 3 kg		
At least 28 days old and 3 kg to less than 40 kg	VEKLURY 5 mg/kg on Day 1	VEKLURY 2.5 mg/kg once daily from Day 2

Source: Proposed labeling, p4.

The bioanalytical site (b) (4) for measurement of RDV and metabolite samples was not inspected due to a recent favorable inspection (NDA 214787, OSIS review dated 12/14/2023). The bioanalytical site (b) (4) for measurement of SBECD samples was inspected and no objectional conditions were observed (NDA 214787, OSIS review dated 12/5/2023).

The Clinical Pharmacology review focused on a comparison of exposures in neonates and infants to adults.

Proposed dosing for term neonates weighing ≥1.5 kg and term infants (i.e., PNA >28 days) weighing 1.5 - <3 kg is 2.5/1.25 mg/kg. One term neonate ((b) (6)) received the proposed 2.5/1.25 mg/kg dose and there was no enrollment of term infants (Table 2). Due to the limited data for enrolled subjects, the focus for approval was on virtual population simulation results. Using virtual population simulations, term neonates weighing ≥1.5 kg and term infants weighing 1.5 - <3 kg who were administered the proposed dose were predicted to have RDV and metabolite exposures that were comparable to adults administered the approved adult dosage (RDV and metabolites exposure comparison in neonates and infants vs adults).

There were three samples from neonates with detectable plasma concentrations of the renally eliminated excipient SBECD present in the RDV formulation; these concentrations were within the range of healthy adults with normal renal function administered a single RDV dose of 100 mg.

The Clinical Pharmacology review team supports approval of RDV 2.5 mg/kg IV daily for term neonates weighing ≥1.5 kg and term infants weighing 1.5 - <3 kg.

RDV and metabolites exposure comparison in neonates and infants vs adults

Below is a brief summary table describing the pediatric cohorts.

Cohort	Sample size Planned	Description
		>28 days to <18 years old
1	12	≥ 12 years to < 18 years and weight ≥ 40 kg
2	12	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg
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
		Term neonates (PNA 0 to <28 days)
5	4	≥ 14 days to < 28 days of age, gestational age > 37 weeks and weight at Screening ≥ 2.5 kg
6		0 days to < 14 days of age, gestational age > 37 weeks and birth weight ≥ 2.5 kg
		Preterm neonates and infants
7	1	0 days to < 56 days of age, gestational age ≤ 37 weeks and birth weight ≥ 1.5 kg
8	5	**< 12 years and weight ≥ 40 kg**

Observed plasma concentrations of RDV and its metabolites in enrolled subjects (Cohorts 5-7)

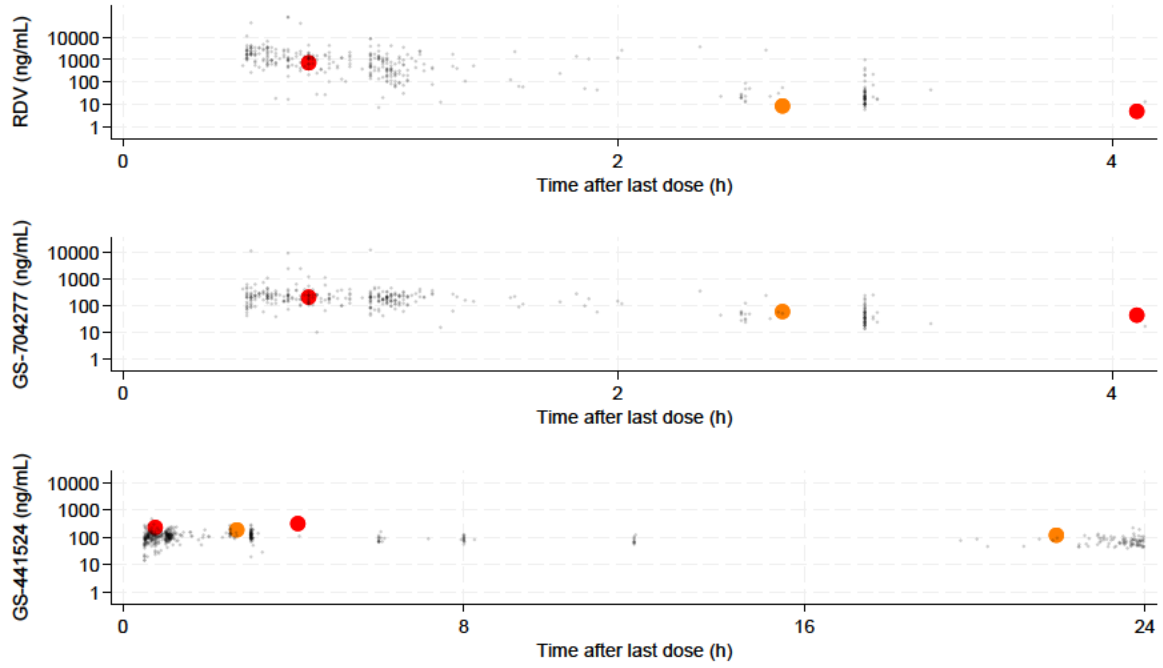
Four term neonates and one premature infant were enrolled, with two subjects weighing <3 kg and the other three weighing 3.5 kg (Table 2).

Table 2. Dosing for subjects in cohorts 5-7 in study 5823

ID (b) (6)	Dose (mg/kg)	GA (weeks)	PNA (days)	Weight (kg)
	5/2.5	39	15	2.8
	2.5/1.25	32	30	2.2
	5/2.5	37	16	3.5
	5/2.5	38	16	3.5
	2.5/1.25	37	12	3.5

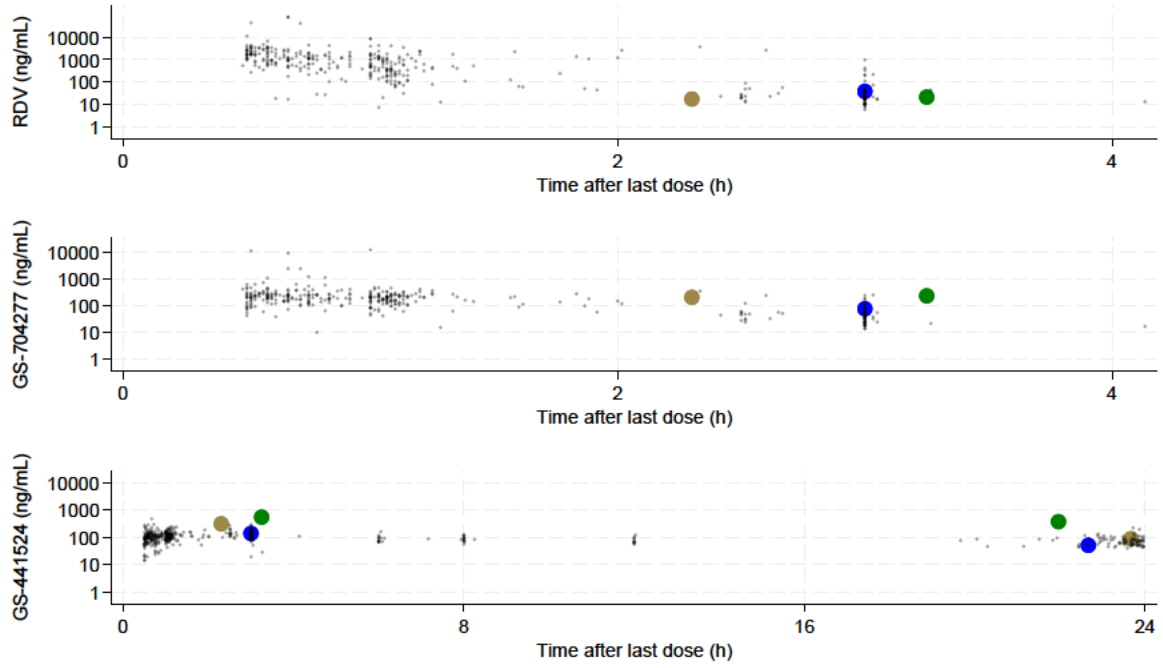
Observed RDV and metabolite plasma concentrations in Cohorts 5-7 of study 5823 were generally in the range of adults (study 9012) (Figure 1, Figure 2).

Figure 1. Observed RDV and metabolite plasma concentrations in Cohorts 5-7 of study 5823 and weighing <3 kg compared to adults in study 9012.



Source: plotted by reviewer from popPK dataset. Large dots = Cohorts 5-7 of study 5823 (different color for each subject); small dots = Non-hospitalized adults from study 9012.

Figure 2. Observed RDV and metabolite plasma concentrations in Cohorts 5-7 of study 5823 and weighing ≥3 kg compared to adults in study 9012.



Source: plotted by reviewer from popPK dataset. Large dots = Cohorts 5-7 of study 5823 (different color for each subject); small dots = Non-hospitalized adults from study 9012.

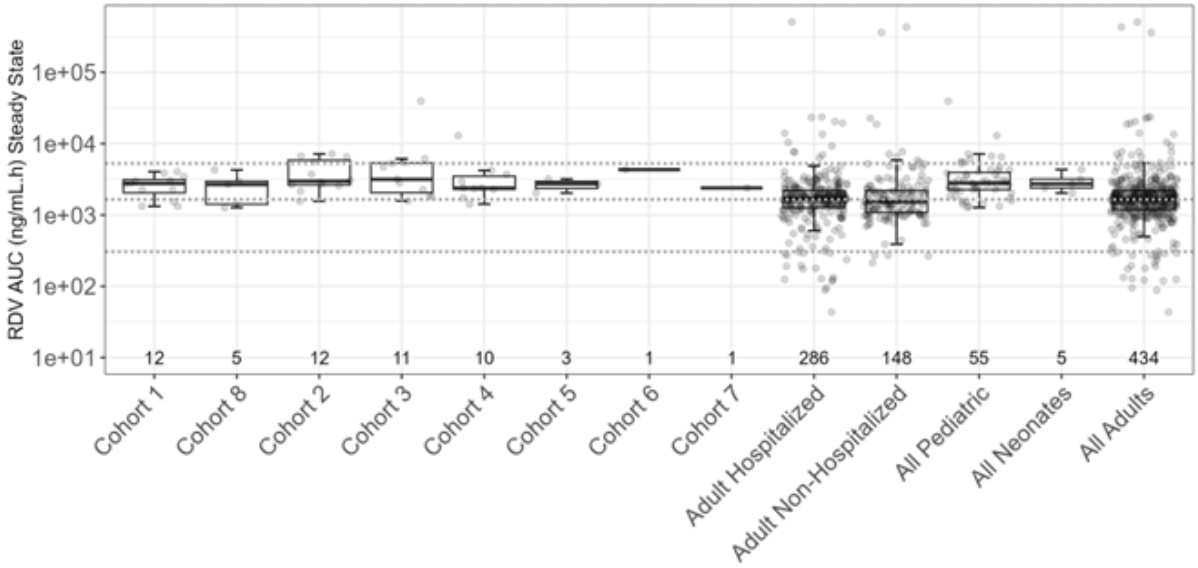
Estimated PK parameters of RDV and its metabolites based on PopPK models

The Applicant's popPK models are acceptable (RDV and Metabolite Population PK models). PopPK analysis was used to estimate PK parameters (Cmax, AUC, Ctau [for GS-441524]).

For pediatric vs adult exposure comparisons, the Applicant's analysis used an adult reference consisting of studies 5844 and 9012. Because only study 9012 is in the current label and used as the reference for the RDV and metabolite exposure comparison for the previous pediatric supplement, we requested the Applicant to repeat their analysis using study 9012 as the reference.

Cmax and AUC of RDV and GS-704277 in Cohorts 5-7 of Study 5823 were comparable to adults in Study 9012 and pediatric subjects in Study 5823 Cohorts 1-4 and 8 (Figure 3; see PopPK report p260-263 for all figures). GS-441524 PK parameters in Cohorts 5-7 of Study 5823 were higher but within the range of those in adults in Study 9012 and pediatric subjects in Study 5823 Cohorts 1-4 and 8 (Figure 4; see PopPK report p265-266 for Cmax and Ctau).

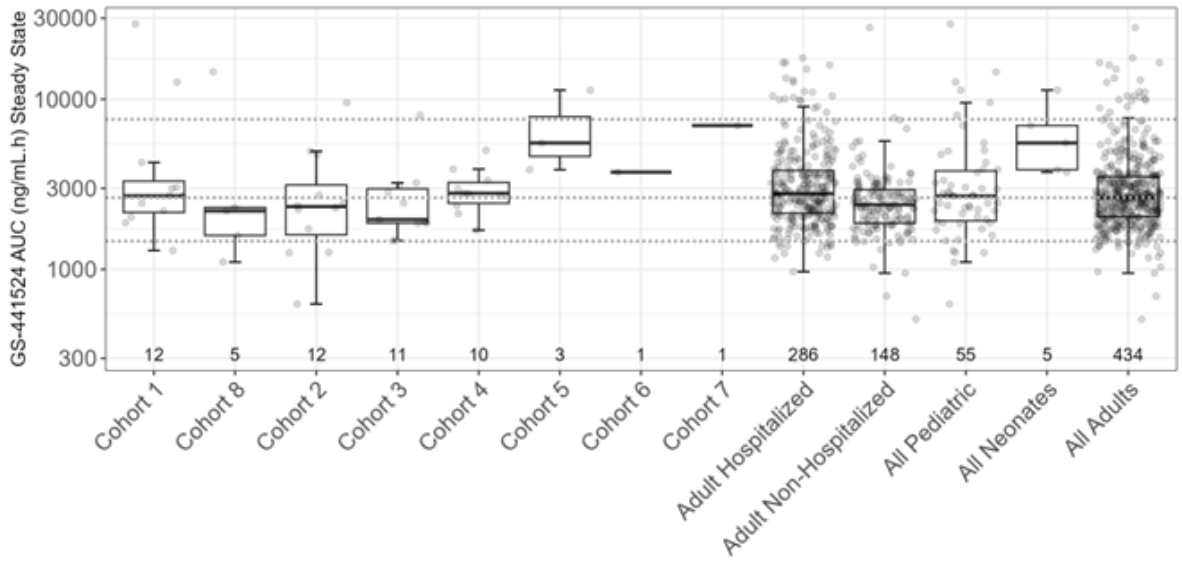
Figure 3. Boxplot of Observed Post Hoc RDV AUC in Pediatric Cohorts and Phase 3 Adults.



AUC = area under the concentration-time curve; RDV = remdesivir.
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5× the interquartile range.
Dashed lines represent the 5th, 50th, and 95th percentiles in Phase 3 adult subjects (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012).

Source: PopPK report, p260.

Figure 4. Boxplot of Observed Post Hoc GS-441524 AUC in Pediatric Cohorts and Phase 3 Adults.



AUC = area under the concentration-time curve.
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5× the interquartile range.
Dashed lines represent the 5th, 50th, and 95th percentiles in Phase 3 adult subjects (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012).

Source: PopPK report, p264.

Virtual population simulations

Due to the limited sample size and sparse PK sampling (at most two samples per subject per analyte) from subjects in Cohorts 5-7 of Study 5823, virtual population simulations were conducted by the Applicant to evaluate dosing for neonates and infants weighing ≥1.5 kg. The term "virtual population" refers to a patient dataset that does not consist of data collected from enrolled subjects. The datasets consisted of 600 virtual subjects per simulation, where the relevant covariates for each subject were age and weight. Age and weight for virtual subjects were generated from growth charts (Table 3). The population PK model has parameters for inter-individual variability on parameters affecting exposure such as clearance and volume of distribution (Table 11). In the simulations, model parameters for each virtual subject are sampled from the distribution of each population parameter. Using each subject's age, weight, dosing, and model parameters, concentration-time profiles were simulated for each virtual subject. PK parameters such as Cmax and AUC were calculated from the concentration-time profiles. Simulations were done based on the study 5823 age/weight enrollment criteria for each cohort, as well as for an adult reference (Table 3).

For pediatric vs. adult exposure comparisons, the Applicant's analysis used an adult reference consisting of studies 5844 and 9012. Because only Study 9012 is refereced in labeling, we requested the Applicant repeat their analysis using Study 9012 as the reference. In addition, Phase 3 adult severe renal impairment study (Study 5912) evaluated the approved adult RDV

dosing regimen. As stated in approved labeling, higher exposures were observed in Study 5912 than in the general adult population, but no dose adjustment is recommended based on renal function.Thus, the Agency requested the Applicant also perform the pediatric vs. adult exposure comparison using Study 5912.

Term neonates weighing ≥2.5 kg

In virtual Cohorts 5-6, RDV and metabolite exposures after a dose of 2.5/1.25 mg/kg better overlapped with observed exposures in adults (Study 9012) than a dose of 5/2.5 mg/kg (Table 4, Figure 5, Figure 6, Figure 7; see NDA 214787, SDN 544, response to IR for boxplots of Cmax and Ctau). This conclusion was unchanged when the pediatric vs adult analysis was separately done for subjects weighing 2.5 -<3 kg vs ≥3 kg (NDA 214787 SDN 552, response to IR).

While the 2.5/1.25 mg/kg dosing results in a better overlap of RDV and metabolite exposures between neonates and adults, the exposures were nonetheless up to ~2-fold higher for the virtual neonates (Cohorts 5-6) compared to adults in Study 9012 (Table 4). This is not a concern as exposures in these cohorts overlap with adults in Study 5912 (Figure 8, Figure 9).

Table 3. Specifications for Virtual Population Simulations

Group[a]	Weight Criteria	Age Criteria	RDV Dose	Database
Virtual Adults	≥ 40 kg	≥ 18 years	200/100 mg	NHANES
Virtual Cohort 5	≥ 2.5 kg	14 to < 28 days (> 37 weeks GA)	5/2.5 mg/kg, 2.5/1.25 mg/kg	WHO
Virtual Cohort 6	≥ 2.5 kg	0 to < 14 days (> 37 weeks GA)	2.5/1.25 mg/kg	WHO
Virtual Cohort 7	≥ 1.5 kg	0 to < 56 days (≤ 37 weeks GA)	2.5/1.25 mg/kg	Fenton
Virtual Neonates[b]	≥ 1.5 kg	0 to < 28 days (> 37 weeks GA), 0 to < 56 days (≤ 37 weeks GA)	2.5/1.25 mg/kg	WHO, Fenton

GA = gestational age; NHANES = National Health and Nutrition Examination Survey; RDV = remdesivir; WHO = World Health Organization

a All virtual populations were 50% hospitalized and 50% nonhospitalized.

b The population for virtual neonates is a composite of Cohorts 5 to 7, with 50% full-term and 50% preterm.

Source: Clinical Pharmacology Summary, p36.

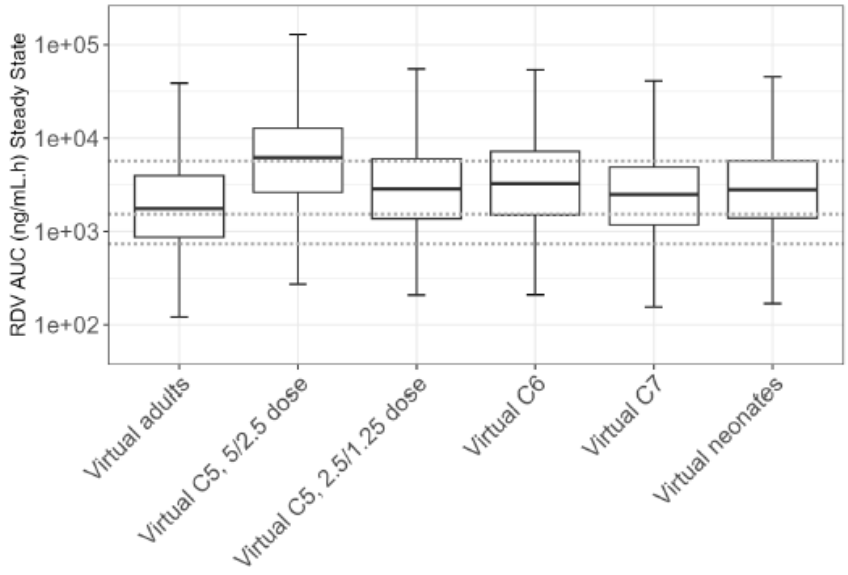
Table 4. RDV and metabolite geometric mean ratios (virtual neonates/adults in study 9012) and 90% confidence intervals of steady-state PK parameters

Analyte PK Parameter	Virtual Cohort 5 (5/2.5 mg/kg) N = 600	Virtual Cohort 5 (2.5/1.25 mg/kg) N = 600	Virtual Cohort 6 (2.5/1.25 mg/kg) N = 600	Virtual Cohort 7 (2.5/1.25 mg/kg) N = 600	Virtual Neonates (2.5/1.25 mg/kg) N = 600
GMR (90% CI) of Virtual Pediatric Group (Test) Versus Phase 3 Adults (Reference)					
RDV					
C_{max}	2.1 (1.88, 2.34)	1.1 (0.987, 1.23)	1.17 (1.05, 1.31)	0.94 (0.842, 1.05)	1.03 (0.925, 1.15)
AUC_{tau}	3.52 (3.02, 4.1)	1.66 (1.43, 1.93)	1.96 (1.68, 2.28)	1.42 (1.22, 1.65)	1.63 (1.4, 1.89)
GS-704277					
C_{max}	1.69 (1.52, 1.88)	0.863 (0.779, 0.955)	0.915 (0.825, 1.02)	0.81 (0.732, 0.898)	0.865 (0.779, 0.96)
AUC_{tau}	3.8 (3.32, 4.35)	1.81 (1.58, 2.07)	2.32 (2.02, 2.65)	1.68 (1.47, 1.93)	1.75 (1.53, 2)
GS-441524					
C_{max}	1.68 (1.58, 1.8)	0.85 (0.798, 0.906)	0.869 (0.816, 0.927)	0.786 (0.737, 0.839)	0.934 (0.876, 0.996)
AUC_{tau}	1.94 (1.8, 2.08)	0.975 (0.909, 1.05)	1.03 (0.959, 1.11)	0.87 (0.809, 0.935)	1.07 (0.995, 1.15)
C_{tau}	1.76 (1.61, 1.92)	0.866 (0.795, 0.943)	0.896 (0.823, 0.977)	0.788 (0.721, 0.86)	0.934 (0.856, 1.02)

CI = confidence interval; COVID-19 = coronavirus disease 2019; GA = gestational age; GMR = geometric mean ratio; PK = pharmacokinetic(s); RDV = remdesivir
Virtual Cohort 5 (age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state) or RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Neonates is a composite of Cohorts 5 to 7 (50% with age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg; 50% with age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).

Source: NDA 214787, SDN 544, response to IR, p7.

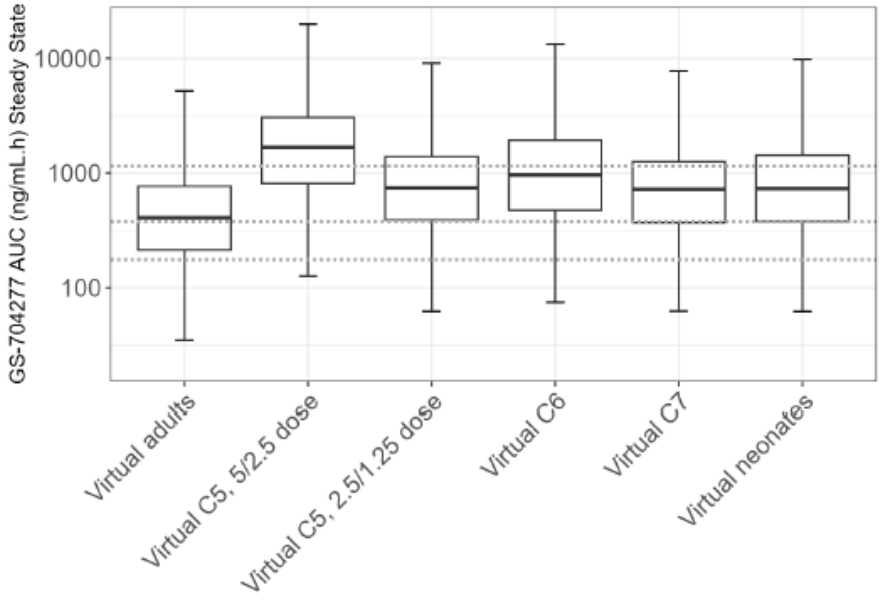
Figure 5. Boxplots of Steady-State RDV AUCtau in Virtual Neonate Cohorts and Adults in Study 9012.



C = Cohort; COVID-19 = coronavirus disease 2019; GA = gestational age; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (GS-US-540-9012).
Virtual adults (N = 600; age ≥ 18 years, weight ≥ 40 kg) received RDV 200 mg on first day (loading dose) followed by 100 mg daily for 5 days (steady state).
Virtual Cohort 5 (N = 600; age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 10 days (steady state) or RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (N = 600; age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (N = 600; age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Neonates is a composite of Cohorts 5 to 7 (N = 600; 50% with age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg; 50% with age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).

Source: NDA 214787, SDN 544, response to IR, p9.

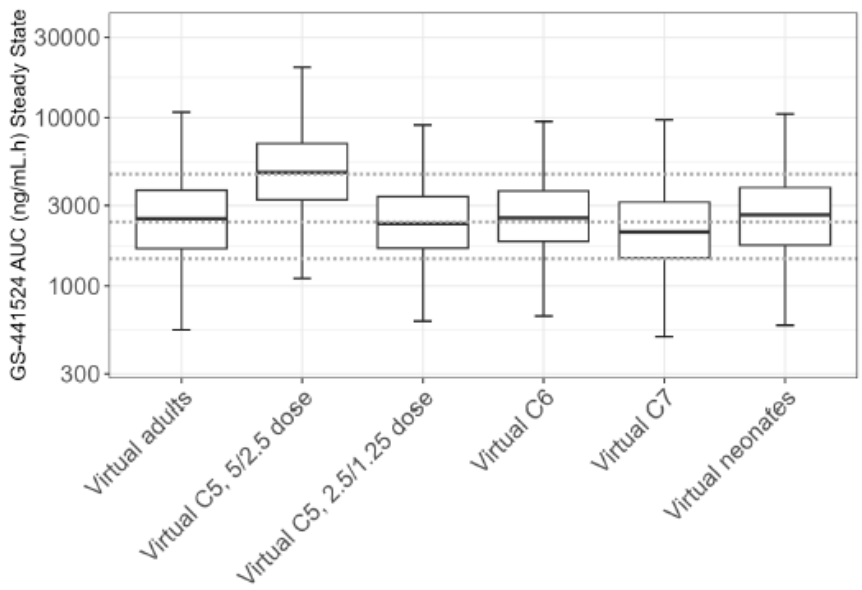
Figure 6. Boxplots of Steady-State GS-704277 AUCtau in Virtual Neonate Cohorts and Adults in Study 9012.



C = Cohort; COVID-19 = coronavirus disease 2019; GA = gestational age; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (GS-US-540-9012).
Virtual adults (N = 600; age ≥ 18 years, weight ≥ 40 kg) received RDV 200 mg on first day (loading dose) followed by 100 mg daily for 5 days (steady state).
Virtual Cohort 5 (N = 600; age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state) or RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (N = 600; age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (N = 600; age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Neonates is a composite of Cohorts 5 to 7 (N = 600; 50% with age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg; 50% with age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).

Source: NDA 214787, SDN 544, response to IR, p11.

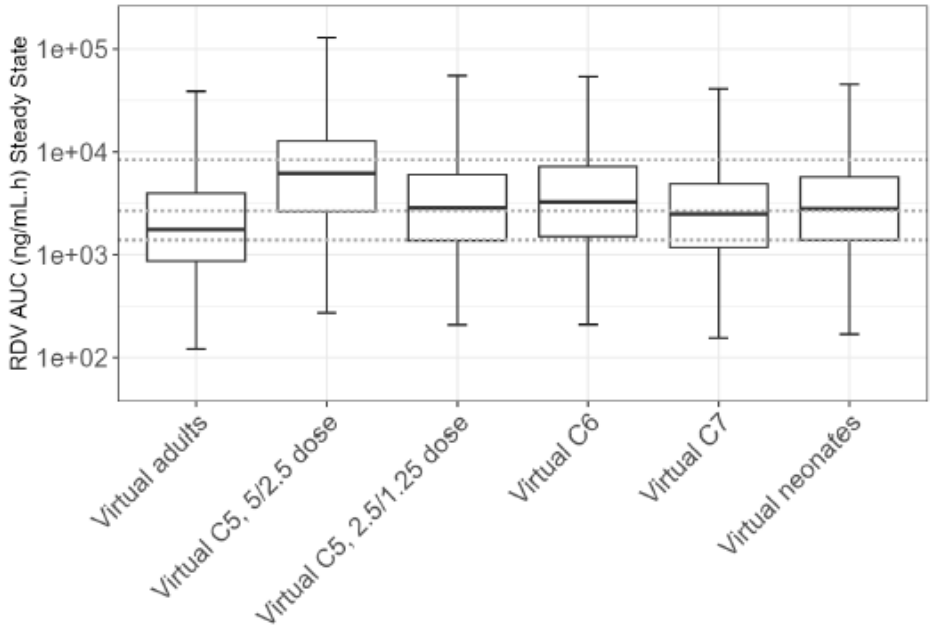
Figure 7. Boxplots of Steady-State GS-441524 AUCtau in Virtual Neonate Cohorts and Adults in Study 9012.



C = Cohort; COVID-19 = coronavirus disease 2019; GA = gestational age; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (GS-US-540-9012).
Virtual adults (N = 600; age ≥ 18 years, weight ≥ 40 kg) received RDV 200 mg on first day (loading dose) followed by 100 mg daily for 5 days (steady state).
Virtual Cohort 5 (N = 600; age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state) or RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (N = 600; age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (N = 600; age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Neonates is a composite of Cohorts 5 to 7 (N = 600; 50% with age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg; 50% with age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).

Source: NDA 214787, SDN 544, response to IR, p13.

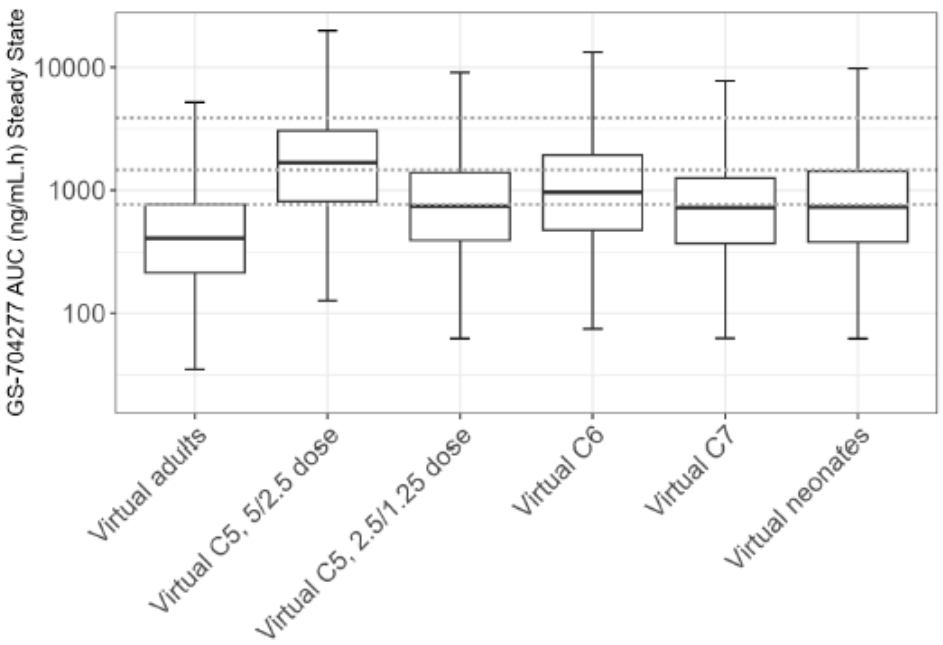
Figure 8. Boxplots of Steady-State RDV AUCtau in Virtual Neonate Cohorts and Adults in Study 5912.



C = Cohort; COVID-19 = coronavirus disease 2019; GA = gestational age; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (GS-US-540-5912; CTRA-2022-1068 RDV COV RI PopPK).
Virtual adults (N = 600; age ≥ 18 years, weight ≥ 40 kg) received RDV 200 mg on first day (loading dose) followed by 100 mg daily for 5 days (steady state).
Virtual Cohort 5 (N = 600; age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 10 days (steady state) or RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (N = 600; age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (N = 600; age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Neonates is a composite of Cohorts 5 to 7 (N = 600; 50% with age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg; 50% with age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).

Source: NDA 214787, SDN 544, response to IR, p23.

Figure 9. Boxplots of Steady-State GS-704277 AUCtau in Virtual Neonate Cohorts and Adults in Study 5912.



C = Cohort; COVID-19 = coronavirus disease 2019; GA = gestational age; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (GS-US-540-5912; CTRA-2022-1068 RDV COV RI PopPK).
Virtual adults (N = 600; age ≥ 18 years, weight ≥ 40 kg) received RDV 200 mg on first day (loading dose) followed by 100 mg daily for 5 days (steady state).
Virtual Cohort 5 (N = 600; age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state) or RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (N = 600; age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (N = 600; age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Neonates is a composite of Cohorts 5 to 7 (N = 600; 50% with age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg; 50% with age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).

Source: NDA 214787, SDN 544, response to IR, p25.

Term neonates weighing 1.5 - <2.5 kg

Only six of 300 subjects in the "Virtual Neonates" cohort weighed in the range of 1.5 - <2.5 kg (Table 5). According to WHO growth charts, the fifth percentile of weight at birth is ~2.6 kg for term girls and boys. Thus few term neonates are expected to weigh <2.5 kg.

Exposures were up to ~2-fold higher for term neonates weighing <2.5 kg who received 2.5/1.25 mg/kg vs adults in Study 9012 (Table 6). As previously discussed, 2-fold higher exposures compared to adults (from Study 9012) are not considered clinically significant.

Table 5. Weight distribution in term subjects in the "Virtual Neonates" cohort

Weight	Virtual Cohort 5 (term) (N=600)	Virtual Cohort 6 (term) (N=600)	Virtual Cohort 7 (preterm) (N=600)	Virtual Neonates (term) (N=300)
3 kg cutoff				
< 3 kg	42 (7.0%)	118 (19.7%)	378 (63.0%)	48 (16.0%)
≥ 3 kg	558 (93.0%)	482 (80.3%)	222 (37.0%)	252 (84.0%)
2.5 kg cutoff				
1.5 to < 2.5 kg	0 (0%)	0 (0%)	248 (41.3%)	6 (2.0%)
≥ 2.5 kg	600 (100%)	600 (100%)	352 (58.7%)	294 (98.0%)

Virtual Cohort 5 (age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg)
Virtual Cohort 6 (age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg)
Virtual Cohort 7 (age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg)
Virtual Term Neonates (age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg)

Source: NDA 214787, SDN 556, response to IR, p6.

Table 6. RDV and metabolite geometric mean ratios (virtual neonates/adults in study 9012) and 90% confidence intervals of steady-state PK parameters

Analyte PK Parameter	Virtual Cohort 7 (preterm) < 2.5 kg (N=248)	Virtual Cohort 7 (preterm) ≥ 2.5 kg (N=352)	Virtual Neonates (term) < 2.5 kg (N=6)	Virtual Neonates (term) ≥ 2.5 kg (N=294)
GMR (90% CI) of Virtual Pediatric Group (Test) Versus Phase 3 Adults (Reference)				
RDV				
AUC_{tau}	1.33 (1.11, 1.59)	1.48 (1.26, 1.75)	2.25 (0.971, 5.22)	1.85 (1.56, 2.19)
C_{max}	0.905 (0.791, 1.04)	0.966 (0.857, 1.09)	1.22 (0.631, 2.34)	1.10 (0.973, 1.25)
GS-704277				
AUC_{tau}	1.49 (1.28, 1.75)	1.83 (1.57, 2.12)	2.30 (0.978, 5.42)	2.05 (1.76, 2.38)
C_{max}	0.761 (0.671, 0.862)	0.847 (0.757, 0.948	1.03 (0.541, 1.98)	0.907 (0.803, 1.02)
GS-441524				
AUC_{tau}	0.82 (0.752, 0.893)	0.907 (0.838, 0.982)	1.17 (0.754, 1.8)	0.965 (0.892, 1.04)
C_{max}	0.761 (0.703, 0.824)	0.804 (0.748, 0.864)	1.01 (0.676, 1.51)	0.847 (0.788, 0.911)
C_{tau}	0.747 (0.671, 0.832)	0.818 (0.742, 0.901)	1.28 (0.895, 1.84)	0.867 (0.786, 0.955)

CI = confidence interval; COVID-19 = coronavirus disease 2019; GA = gestational age; GMR = geometric mean ratio; NA=not applicable; PK = pharmacokinetic(s); RDV = remdesivir
Virtual Cohort 5 (N=600; age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (N=600; age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (N=600; age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Term Neonates (N=300; age 0 to < 28 days, GA > 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Source: NDA 214787, SDN 556, response to IR, p7.

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SBECD exposure comparison in neonates and infants vs adults

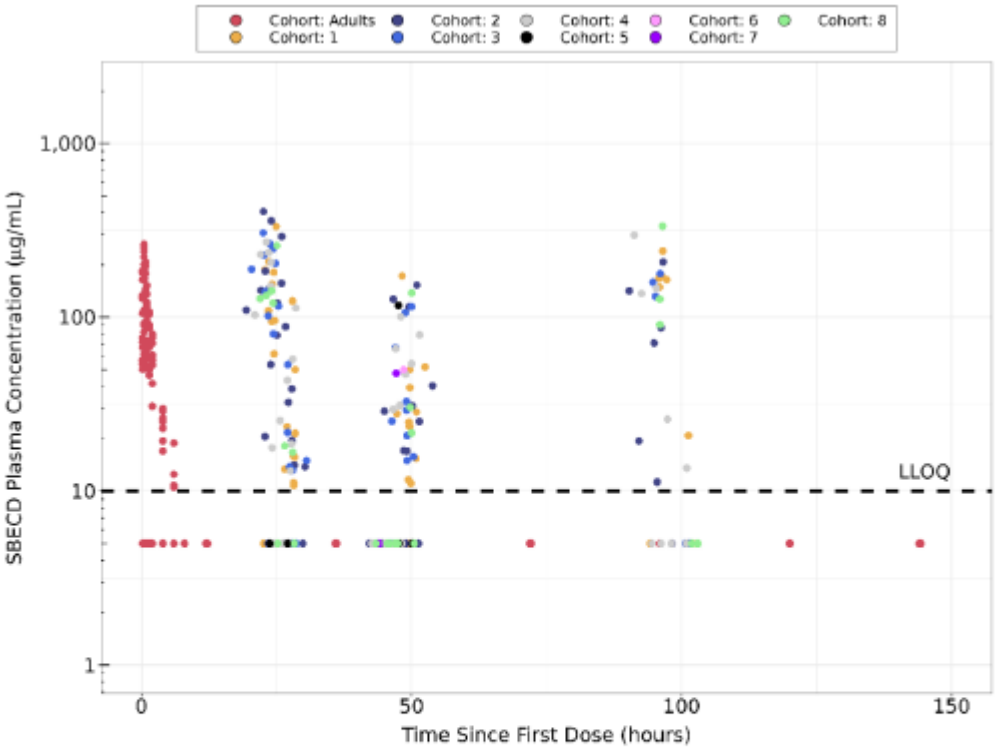
SBECD is a renally eliminated excipient present in the RDV formulation. At the time of the previous pediatric supplement for subjects ≥3 kg (S-11), SBECD PK data were not available.

SBECD PK data from the renal impairment adult studies GS-US-540-9015 and GS-US-540-5912 were previously discussed under S-19. In adults administered the approved RDV dosing regimen, Day 10 AUC_{tau} accumulation ratios for renal impairment categories (mild, moderate, severe, kidney failure) vs normal renal function were 1.7, 4.6, 8.3, and 21.4, respectively (NDA 214787, Integrated review dated 7/7/2023; DARRTS Reference ID: 5203171). In Phase 3 Study 5912, RDV without dose adjustment was found to be safe for patients with any degree of renal impairment. In labeling, no dose adjustment is recommended for any degree of renal impairment.

This submission contains PK data for all pediatric cohorts in Study 5823. Compared to healthy adults with normal renal function in Study 9015 administered a single RDV dose of 100 mg, plasma concentrations of SBECD in all pediatric subjects in Study 5823 were largely within the range of those in adults (Figure 10), and the three detectable concentrations from neonates were within the range of adults (Figure 11).

Per EMA, the maximum recommended safe dose of SBECD is 250 mg/kg/day. The ratio of SBECD (mg) to RDV (mg) in the RDV formulation is 30:1. Enrolled neonates receiving RDV 5 mg/kg on day 1 received SBECD 150 mg/kg/day. Per proposed labeling, maximum RDV dosing for neonates is 2.5 mg/kg, which amounts to 75 mg/kg/day SBECD (Section 10).

Figure 10. Plasma SBECD Concentrations in Pediatric Participants Hospitalized With COVID-19 (GS-US-540-5823) and Phase 1 Adults With Normal Renal Function (GS-US-540-9015).

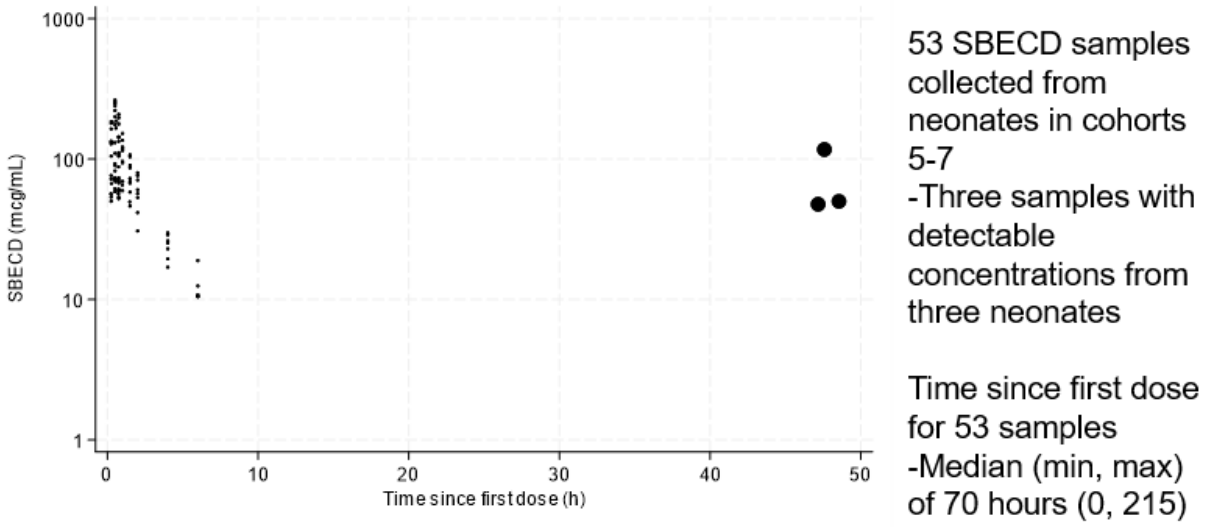


source code:SBECD_DATA_VIS_v20230525.Rmd
source graphic: adultspeds_RENIMP-norm-LOGLIN-CONTT-color-272-v20230716.pdf

COVID-19 = coronavirus disease 2019; eGFR = estimated glomerular filtration rate; LLOQ = lower limit of quantitation; RDV = remdesivir; SBECD = sulfobutylether β-cyclodextrin sodium
Pediatric participants from GS-US-540-5823 consisted of Cohorts 1 and 8 who received RDV 200 mg on first day (loading dose) followed by 100 mg daily for up to 10 days (steady state); Cohorts 2 to 5 who received RDV 5 mg/kg on the first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state); and Cohorts 6 and 7 who received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days.
Adult population consisted of participants with eGFR $\geq$ 90 mL/min/1.73 m^2 on Day 1 from Study GS-US-540-9015 who were simulated to receive RDV 200 mg on the first day (loading dose) followed by 100 mg daily for up to 10 days (steady state).
One pediatric participant in Cohort 1 was excluded as an outlier due high SBECD exposures, which were contributed by a second source of SBECD (prior and concomitant use of intravenous voriconazole)
Source: QP-2023-1077 SBECD PopPK, Figure 4, GS-US-540-5823 Final CSR Table 15.10.2.1.1 and Listing 16.2.4.3

Source: Clinical pharmacology summary, p31.

Figure 11. Plasma SBECD Concentrations in Neonates Hospitalized With COVID-19 (GS-US-540-5823) and Phase 1 Adults With Normal Renal Function (GS-US-540-9015).



Source: plotted by reviewer from popPK dataset. Large black dots = neonates from study 5823. Small black dots = healthy volunteers with normal renal function in study 9015.

GS-US-540-5823 summary

Methods

Study 5823 enrolled hospitalized pediatric subjects with SARS-CoV-2 infection (Table 7). The interim CSR was submitted in sNDA-11 and contained data for Cohorts 1-4 and 8 (≥28 days and ≥3 kg). The final CSR submitted in this application contains data for Cohorts 5-7.

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).

Table 7. Treatment and PK assessments in pediatric study 5823

Cohort	Description	Dose	PK Assessments
Pediatric subjects ≥28 days to <18 years old			
1	≥12 to <18 years and weight ≥40 kg	IV infusion of RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days	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)
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 for up to 10 days	
3	≥28 days to <18 years and weight ≥12 kg to <20 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily for up to 10 days	

Cohort	Description	Dose	PK Assessments
4	≥28 days to <18 years and weight ≥3 kg to <12 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily for up to 10 days	
Term neonatal subjects 0 to <28 days old			
5	≥14 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 for up to 10 days	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
6	0 to <14 days of age, gestational age >37 weeks and birth weight ≥2.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily for up to 10 days	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
Preterm neonatal subjects 0 to <56 days			
7	0 to <56 days of age, gestational age ≤37 weeks and birth weight ≥1.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily for up to 10 days	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
Exploratory cohort for pediatric subjects <12 years			
8	<12 years and weight ≥40 kg	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily for up to 10 days	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)

Source: popPK report, p13.

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.

Concentrations of SBECD (calibration curve: 10-1000 mcg/mL) were measured in human plasma using validated LC/MS-MS method V4702001P2 (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.

There were no reported uses of prohibited concomitant medications in cohorts 5-7 (CSR, p42).

One subject in cohort 5 had an important protocol deviation of severe adverse event not reported to the Applicant within 24 hours (CSR Appendix 16.2.2, p23), which does not affect the PK results.

RDV and Metabolite Population PK models

Review Summary
The Applicant's population PK (popPK) analysis is acceptable for the purpose of deriving RDV and metabolite exposure metrics (Cmax, AUC, Ctau) for labeling. The Applicant's final model parameters were verified by the reviewer.

Introduction
In prior submissions, RDV popPK modeling objectives were to characterize the PK of RDV and metabolites in the general adult population and subsequently in the pediatric population ≥28 days of age and ≥3 kg (S-11). The objectives of the current popPK analysis were to characterize the disposition of RDV, GS-704277, and GS-441524 among neonates <28 days of age and <3 kg.

Model development

The popPK models for the previous pediatric supplement (S-11) contained the same studies (Table 7, Table 8), structural models, methods for excluding samples, and method for BLQ sample handling (M6) as in the current analysis. We previously reviewed these models and found them to be acceptable (NDA 214787, Integrated review dated 4/21/22). The previous analysis included 10892 samples from 611 subjects and the current analysis contains 11518 samples from 615 subjects. New data from the current supplement consists of 22 samples with detectable concentrations from five neonates (Table 9, Table 10).

Table 8. Treatment and PK assessments in adult studies included in the popPK analysis

Study	Study Design/Population	Sampling (Intensive /Sparse)	Dosing	PK Sampling
GS-US-399-1812	A randomized, blinded, placebo-controlled, Phase 1 study to evaluate the safety and tolerability of single ascending IV doses of RDV compared with placebo and to evaluate the PK of RDV and its metabolites following single ascending IV doses of RDV in healthy subjects	Intensive	Cohorts 1 to 6: 3 to 225 mg (n = 8) or placebo (n = 2) on Day 1 Cohorts 7 to 9: 75 to 150 mg (n = 10) or placebo (n = 2) on Day 1 Cohorts 1 to 8: SD of study drug administered IV over a 2-hour period Cohort 9: SD of study drug administered IV over a 30-minute period	Predose; 0.5, 1, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours postdose; and Follow-Up
GS-US-399-1954	A randomized, blinded, placebo-controlled, Phase 1 study designed to evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo and to evaluate the PK of RDV and its metabolites following multiple IV doses of RDV in healthy adult subjects	Intensive	RDV 150 mg or matching placebo Each cohort comprised 2 groups of 6 subjects each (4 received RDV and 2 received placebo) Subjects received IV study drug administered over a 1-hour period once daily for 7 days in Cohort 1 and over 14 days in Cohort 2	Day 1: Predose and 0.5, 1, 1.17, 1.33, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose Day 4: Predose Day 7: Predose; 0.5, 1, 1.17, 1.33, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours postdose; Early Termination; and Follow-Up Cohort 2 had additional sampling at the following time points: Day 11: Predose Day 14: Predose; 0.5, 1, 1.17, 1.33, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours postdose; and Follow-Up

GS-US-399-5505	A Phase 1, blinded, randomized, placebo-controlled, multiple-dose study evaluating the safety, tolerability, and PK of intravenous RDV in healthy subjects	Intensive	Loading dose of 200 mg IV RDV on Day 1, followed by daily maintenance doses of 100 mg IV RDV for the following durations: Cohort 1: 4 days of treatment Cohort 2: 9 days of treatment Cohort 3: Up to 13 days of treatment (not initiated)	Day 1 (all cohorts): Predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours postdose Last RDV dosing day (Days 5, 10, and up to 14 for Cohorts 1, 2, and 3, respectively): Predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours postdose *Unscheduled blood sample if infusion was restarted
GS-US-540-9012	A Phase 3 randomized, double-blind, placebo-controlled study to evaluate	Sparse and Intense	Randomization was stratified by subjects who reside in a skilled nursing facility, by subject's age (<60 vs ≥60 years), and by region (US vs ex-US):	Sparse PK: Day 2: End of infusion and optional 2 hours postdose

Study	Study Design/Population	Sampling (Intensive /Sparse)	Dosing	PK Sampling
	the efficacy and safety of RDV in the treatment of COVID-19 in an outpatient setting		Group A: Single dose of IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3 (RDV group) Group B: IV PTM RDV on Days 1 to 3 (PTM group)	Day 3: Predose (within 30 minutes of dosing) and end of infusion Intensive PK: Days 1 and 3: 0 hours (predose) and 0.5, 0.75, 3, 6, 8, 12 (optional), and 24 hours postdose
CO-US-540-5844 (REMDACTA)	A Phase 3 randomized, double-blind, multicenter study to evaluate the efficacy and safety of RDV plus TCZ compared with RDV plus placebo in hospitalized subjects with severe COVID-19 pneumonia	Sparse	RDV+TCZ arm: A loading dose of 200 mg IV RDV followed by 1 infusion of TCZ 8 mg/kg (maximum dose of 800 mg) on Day 1. Subjects were subsequently administered a 100-mg once-daily IV maintenance dose of RDV from Days 2 to 10. RDV was discontinued at the time of hospital discharge even if 10 days of RDV dosing have not been completed. RDV+placebo arm: A loading dose of 200 mg IV RDV followed by 1 placebo infusion on Day 1. Subjects were subsequently administered a 100-mg once-daily IV maintenance dose of RDV from Days 2 to 10.	Days 4 and 7: Predose and 30 to 60 minutes postdose

COVID-19 = coronavirus disease 2019; IV = intravenous(ly); n = number of subjects in the subgroup; PK = pharmacokinetic(s); PTM = placebo-to-match; RDV = remdesivir; SD =single dose; TCZ = tocilizumab; US = United States.

Source: popPK report, p11.

Table 9. Samples with detectable concentrations of RDV and metabolites from neonates weighing <3 kg

ID	Analyte	Dose (mg/kg)	Time since first dose (h)	Time since last dose (h)	Plasma concentration (ng/mL)	GA (weeks)	PNA (days)	Weight (kg)
(b) (6)	RDV	5/2.5	24	0.8	720	39	15	2.8
	RDV	5/2.5	27	4.1	5	39	15	2.8
	RDV	2.5/1.25	47	2.7	8	32	30	2.2
	GS-704277	5/2.5	24	0.8	210	39	15	2.8
	GS-704277	5/2.5	27	4.1	45	39	15	2.8
	GS-704277	2.5/1.25	47	2.7	61	32	30	2.2
	GS-441524	5/2.5	24	0.8	228	39	15	2.8
	GS-441524	5/2.5	27	4.1	317	39	15	2.8
	GS-441524	2.5/1.25	44	21.9	119	32	30	2.2
	GS-441524	2.5/1.25	47	2.7	186	32	30	2.2

Source: Reviewer analysis of popPK datasets for RDV, GS-704277, and GS-441524.

Table 10. Samples with detectable concentrations of RDV and metabolites from neonates weighing ≥3 kg

ID	Analyte	Dose (mg/kg)	Time since first dose (h)	Time since last dose (h)	Plasma concentration (ng/mL)	GA (weeks)	PNA (days)	Weight (kg)
(b) (6)	RDV	5/2.5	50	2.3	17	37	16	3.5
	RDV	5/2.5	48	3.3	21	38	16	3.5
	RDV	2.5/1.25	49	3.0	38	37	12	3.5
	GS-704277	5/2.5	50	2.3	207	37	16	3.5
	GS-704277	5/2.5	48	3.3	234	38	16	3.5
	GS-704277	2.5/1.25	49	3.0	77	37	12	3.5
	GS-441524	5/2.5	48	23.7	88	37	16	3.5
	GS-441524	5/2.5	50	2.3	311	37	16	3.5
	GS-441524	5/2.5	44	22.0	372	38	16	3.5
	GS-441524	5/2.5	48	3.3	546	38	16	3.5
	GS-441524	2.5/1.25	45	22.7	51	37	12	3.5
	GS-441524	2.5/1.25	49	3.0	138	37	12	3.5

Source: Reviewer analysis of popPK datasets for RDV, GS-704277, and GS-441524.

RDV is primarily cleared by carboxylesterase (CES) 1 metabolism and GS-704277 is primarily cleared by HINT1 metabolism. A maturation function for CL of RDV and GS-704277 as a function of age was included in the prior and current analysis (Figure 12). The equation was based on human tissue samples with ages ranging from neonates to adults. CES1 protein abundance was analyzed as a function of age. Seventeen infants and four neonates were included in the analysis (Boberg 2017).

GS-441524 is primarily renally cleared. CL of GS-441524 was modeled using a maturation function for CL as a function of age (Rhodin 2009).

Figure 12. Maturation function for CL of RDV and GS-704277.

$$CL_i = TVCL \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(\frac{Adult_{max} - F_{birth}}{Age_{50}{}^{N} + Age^{N}}\right) \cdot Age^{N} + F_{birth}$$

which is a function of Age and WT with fixed parameters $Adult_{max} = 1$, $F_{birth} = 0.205$, $Age_{50} = 0.542$ years, and $N = 0.977$ as detailed below:

$$CL_i = TVCL \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(\frac{1 - 0.205}{0.542^{0.977} + Age^{0.977}}\right) \cdot Age^{0.977} + 0.205.$$

Source: popPK report, p24.

Figure 13. Maturation function for CL GS-441524.

$$CL_i = TVCL \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \frac{(Age \cdot WeeksPerYear + PMA)^{N}}{Age_{50}^{N} + (Age \cdot WeeksPerYear + PMA)^{N}}$$

which is a function of Age and WT with fixed parameters $Age_{50} = 47.7$ weeks, $PMA = 40$ (PMA = post-menstrual age reported in weeks), $WeeksPerYear = 52$, and hill coefficient $N = 3.38$ as detailed below:

$$CL_i = TVCL \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \frac{(age \cdot 52 + 40)^{3.38}}{47.7^{3.38} + (age \cdot 52 + 40)^{3.38}}$$

Source: popPK report, p25.

Model parameters had acceptable precision and interindividual variability parameters had acceptable shrinkages (Table 11, Table 12). The models demonstrated acceptable performance in goodness-of-fit and visual predictive check plots (Figure 14, Figure 15, Figure 16, Figure 17, Figure 18, Figure 19).

Table 11. Final population PK model parameters

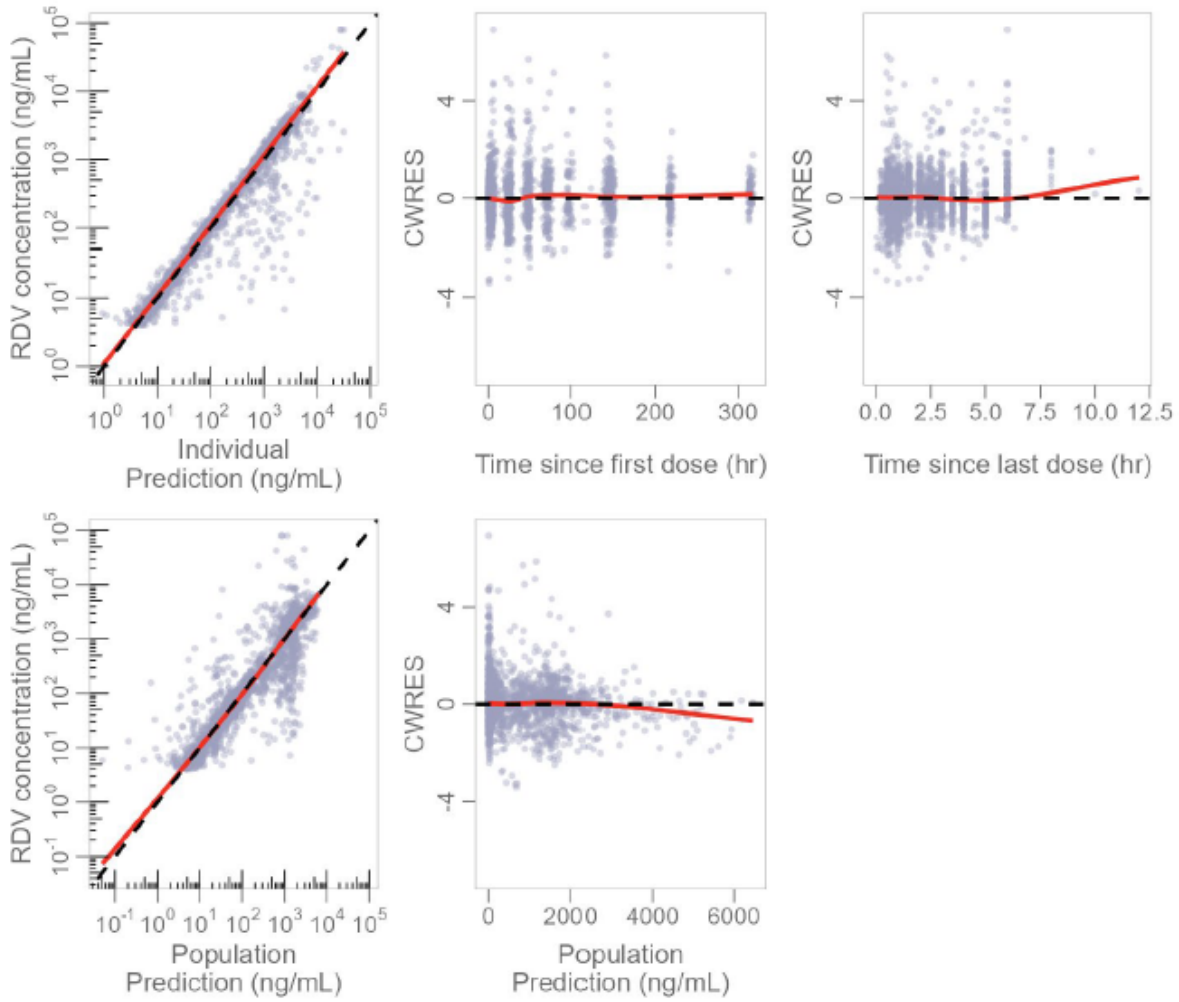
Parameter - Model	Parameter Description	Population Estimate	%RSE
θ_1 - remdesivir	CL - remdesivir (L/h)	50.4	2.56
θ_2 - remdesivir	Central volume - remdesivir (L)	7.01	0.443
θ_3 - remdesivir	Peripheral volume - remdesivir (L)	6.42	0.259
θ_4 - remdesivir	Intercompartmental clearance - remdesivir (L/h)	5.16	3.67
θ_1 - GS-704277	CL - GS-704277 (L/h)	292	5.08
θ_2 - GS-704277	Central volume - GS-704277 (L)	285	6
θ_3 - GS-704277	Peripheral volume - GS-704277 (L)	143	34.8
θ_4 - GS-704277	Intercompartmental clearance - GS-704277 (L/h)	11.3	12.5
θ_7 - GS-704277	Effect of baseline ferritin for pediatric subjects on clearance	-0.151	61
θ_8 - GS-704277	Effect of hospitalization for subjects on clearance	-0.318	19.7
θ_9 - GS-704277	Effect of age for subjects 60 years or older on central volume	-0.24	29.4
θ_1 - GS-441524	Clearance - GS-441524 (L/h)	26.2	2.99
θ_2 - GS-441524	Central volume - GS-441524 (L)	139	5.65
θ_3 - GS-441524	First peripheral volume - GS-441524 (L)	373	4.03
θ_4 - GS-441524	Intercompartmental clearance to first periph. cmt. GS-441524 (L/h)	537	4.89
θ_5 - GS-441524	Second peripheral volume - GS-441524 (L)	292	5.87

Parameter - Model	Parameter Description	Population Estimate	%RSE
θ_6 - GS-441524	Intercompartmental clearance to second periph. cmt. GS-441524 (L/h)	45.6	6.61
θ_9 - GS-441524	Effect of age for subjects 60 years or older on clearance	-0.35	10.4
ω^2_{11} - remdesivir	IIV of CL - remdesivir, Phases 1 and 2/3 (%CV)	42.8%	16.7
ω^2_{22} - remdesivir	IIV of V1 - remdesivir, Phases 1 and 2/3 (%CV)	39.6%	38.3
ω^2_{33} - remdesivir	IIV of CL - remdesivir, Phase 3 (%CV)	152%	5
ω^2_{44} - remdesivir	IIV of V1 - remdesivir, Phase 3 (%CV)	314%	61.9
ω^2_{11} - GS-704277	IIV of CL-GS-704277, Phases 1 and 2/3 (%CV)	45.4%	9.57
ω^2_{22} - GS-704277	IIV of V1 -GS-704277, Phases 1 and 2/3 (%CV)	56%	12.5
ω^2_{33} - GS-704277	IIV of CL-GS-704277, Phase 3 (%CV)	122%	13.7
ω^2_{44} - GS-704277	IIV of V1 -GS-704277, Phase 3 (%CV)	149%	11.8
ω^2_{11} - GS-441524	IIV of CL-GS-441524, Phases 1 and 2/3 (%CV)	51.5%	12
ω^2_{22} - GS-441524	IIV of V1 -GS-441524, Phases 1 and 2/3 (%CV)	90.9%	9.2
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524, Phases 1 and 2/3 (%CV)	54.8%	10.1
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524, Phases 1 and 2/3 (%CV)	62.4%	21.1
ω^2_{55} - GS-441524	IIV of CL-GS-441524, Phase 3 (%CV)	66.3%	8.77
ω^2_{66} - GS-441524	IIV of V1 -GS-441524, Phase 3 (%CV)	159%	11.1
ω^2_{77} - GS-441524	IIV of Vp1-GS-441524, Phase 3 (%CV)	182%	11.2
ω^2_{88} - GS-441524	IIV of Vp2-GS-441524, Phase 3 (%CV)	244%	10.2
σ_1 - remdesivir	Variance of residual error - remdesivir, Phases 1 and 2/3	0.593	10.5
σ_2 - remdesivir	Variance of residual error - remdesivir, Phase 3	1.75	0.0262
σ_1 - GS-704277	Variance of residual error - GS-704277, Phases 1 and 2/3	0.158	42.9
σ_2 - GS-704277	Variance of residual error - GS-704277, Phase 3	1.21	47.1
σ_1 - GS-441524	Variance of residual error - GS-441524, Phases 1 and 2/3	0.225	22.7
σ_2 - GS-441524	Variance of residual error - GS-441524, Phase 3	0.907	27.8
sqrt(θ_5) - remdesivir	Proportional residual error - remdesivir (%CV)	40.6%	0.142
θ_6 - remdesivir	Additive residual error - remdesivir (ng/mL)	1.8	0.428
sqrt(θ_8) - GS-704277	Proportional residual error - GS-704277 (%CV)	65%	24
θ_6 - GS-704277	Additive residual error - GS-704277 (ng/mL)	1	-
sqrt(θ_7) - GS-441524	Proportional residual error - GS-441524 (%CV)	22.3%	13.1
θ_8 - GS-441524	Additive residual error - GS-441524 (ng/mL)	1	-

%CV = percentage of the coefficient of variation; %RSE = percentage of the relative standard error; θ = absolute value of the estimate; σ = variance of residual error; ω = interindividual variability; CL = clearance; IIV = interindividual variability; OFV = objective function value; periph. cmt. = peripheral compartment; PK = pharmacokinetic(s); RDV = remdesivir; V1 = central volume of distribution; Vp1 = first peripheral volume of distribution; Vp2 = second peripheral volume of distribution.
OFV – remdesivir = 25333.8809, OFV – GS-704277 = 23830.4336, and OFV – GS-441524 = 28357.3737.
Condition number – Remdesivir = 6.891e7, Condition number – GS-704277 = 750.7, and Condition number – GS-441524 = 106.3.
Additive residual error was fixed to 1 ng/mL for the GS-704277 and GS-441524 models.

Source: PopPK report, p36.

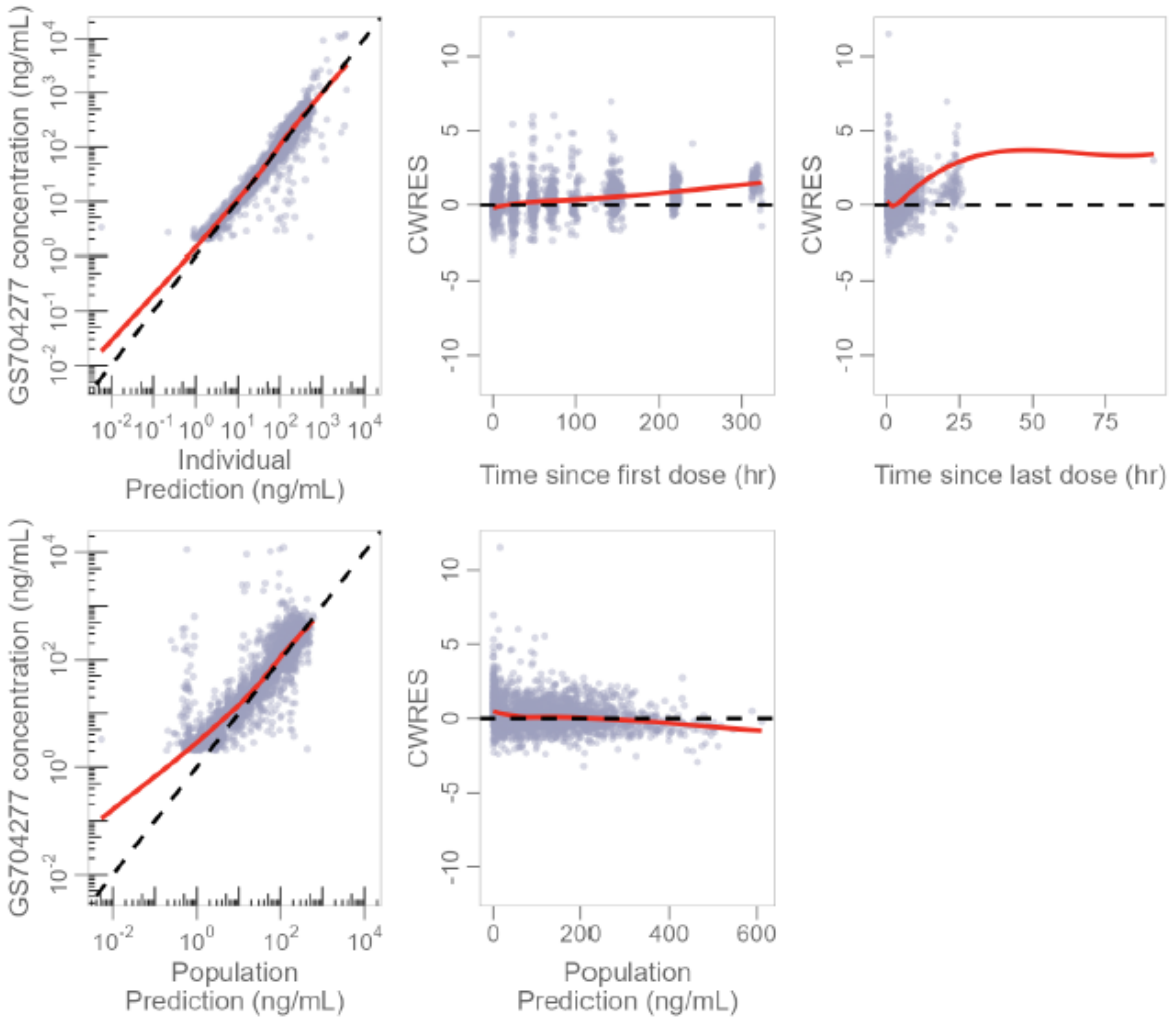
Figure 14. RDV final model GOF plots.



CWRES = conditional weighted residuals; PopPK = population pharmacokinetic; RDV = remdesivir.

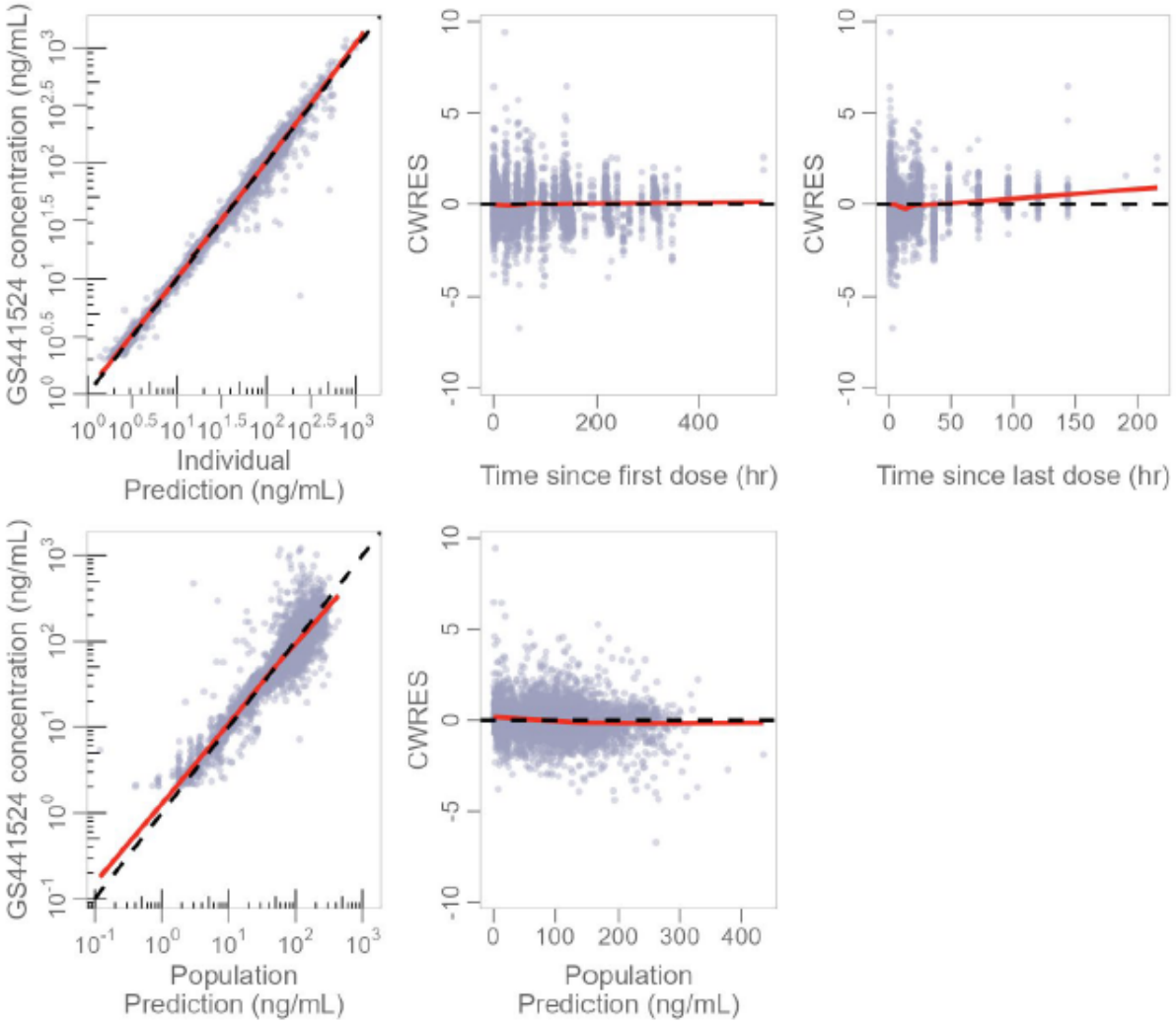
Source: PopPK report, p39.

Figure 15. **GS-704277 final model GOF plots.**



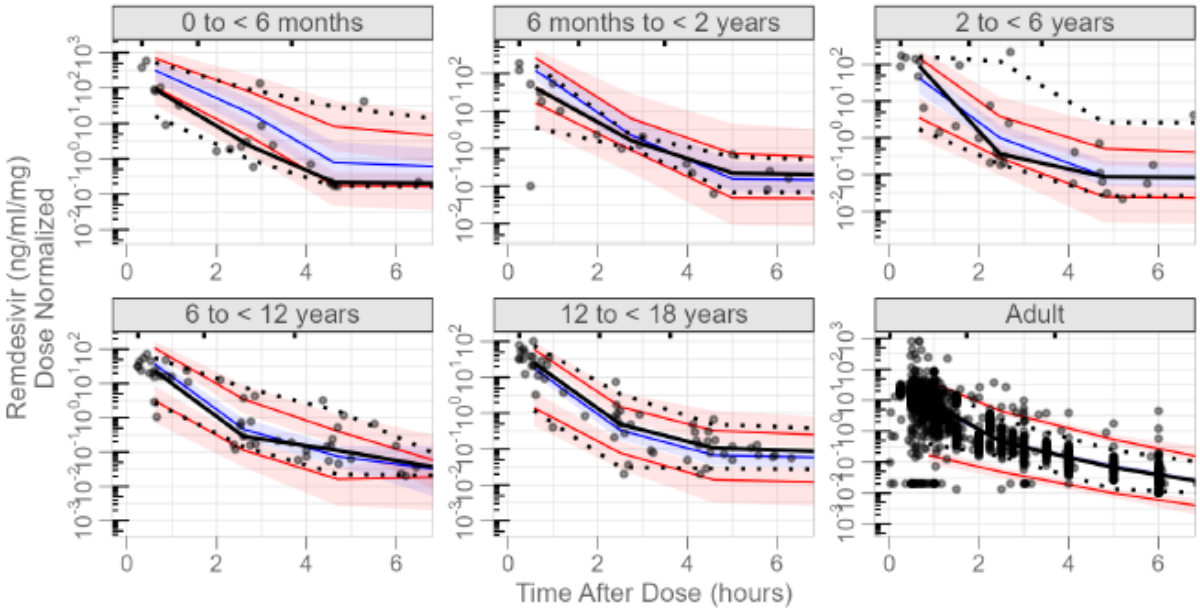
CWRES = conditional weighted residuals; PopPK = population pharmacokinetic.
Source: PopPK report, p40.

Figure 16. GS-441524 final model GOF plots.



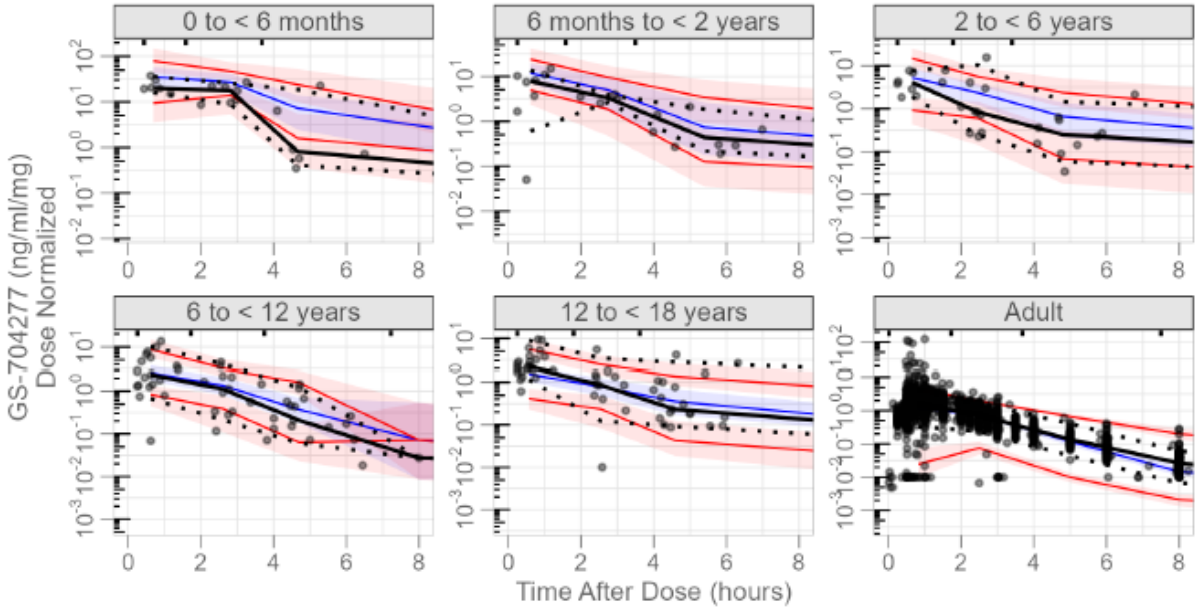
CWRES = conditional weighted residuals; PopPK = population pharmacokinetic.
Source: PopPK report, p41.

Figure 17. Dose-Normalized VPC Stratified by Age of the Final RDV Model.



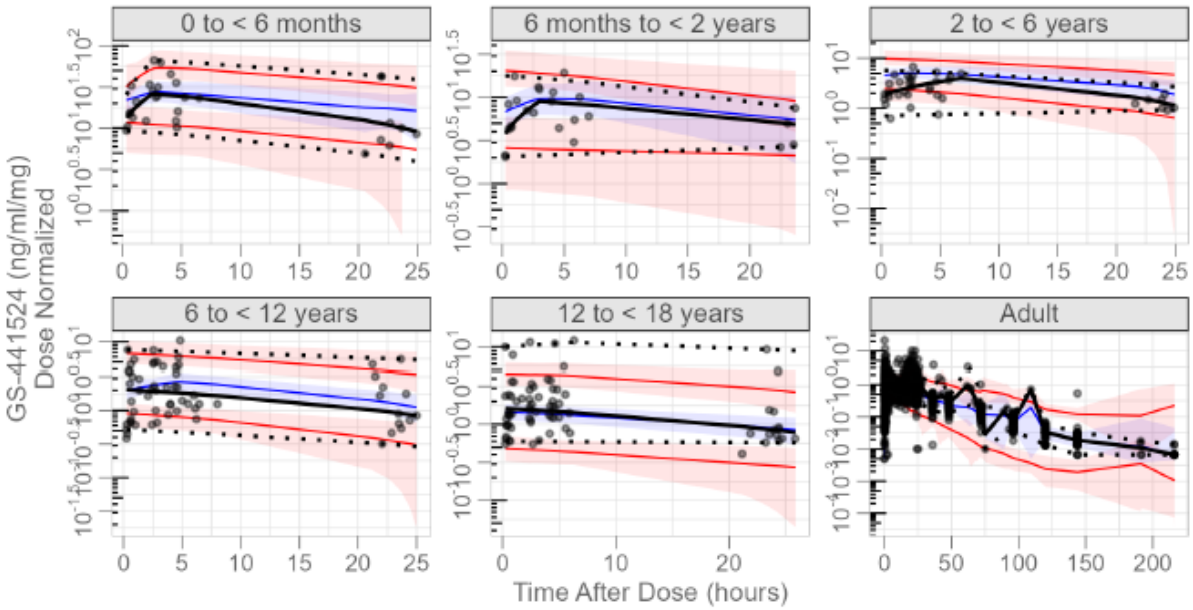
Source: PopPK report, p225.

Figure 18. Dose-Normalized VPC Stratified by Age of the Final GS-704277 Model.



Source: PopPK report, p226.

Figure 19. Dose-Normalized VPC Stratified by Age of the Final GS-441524 Model.



Source: PopPK report, p227.

Table 12. Shrinkage Estimates of the Final RDV, GS-704277, and GS-441524 PopPK Models

Parameter	Parameter Description	Shrinkage (%)
ω^2_{11} - remdesivir	IIV on CL-remdesivir, Phases 1 and 2/3 (%CV)	3
ω^2_{22} - remdesivir	IIV of V1 -remdesivir, Phases 1 and 2/3 (%CV)	23
ω^2_{33} - remdesivir	IIV of CL -remdesivir, Phase 3 (%CV)	14
ω^2_{44} - remdesivir	IIV of V1 -remdesivir, Phase 3 (%CV)	57
ω^2_{11} - GS-704277	IIV on CL-GS-704277, Phases 1 and 2/3 (%CV)	2
ω^2_{22} - GS-704277	IIV of V1 -GS-704277, Phases 1 and 2/3 (%CV)	9
ω^2_{33} - GS-704277	IIV of CL-GS-704277, Phase 3 (%CV)	16
ω^2_{44} - GS-704277	IIV of V1 -GS-704277, Phase 3 (%CV)	21
ω^2_{11} - GS-441524	IIV on CL-GS-441524, Phases 1 and 2/3 (%CV)	4
ω^2_{22} - GS-441524	IIV of V1 -GS-441524, Phases 1 and 2/3 (%CV)	13
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524, Phases 1 and 2/3 (%CV)	11
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524, Phases 1 and 2/3 (%CV)	23
ω^2_{55} - GS-441524	IIV on CL-GS-441524, Phase 3 (%CV)	10
ω^2_{66} - GS-441524	IIV of V1 -GS-441524, Phase 3 (%CV)	49
ω^2_{77} - GS-441524	IIV of Vp1-GS-441524, Phase 3 (%CV)	52
ω^2_{88} - GS-441524	IIV of Vp2-GS-441524, Phase 3 (%CV)	54
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	6
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 = variance of residual error; ω = interindividual variability; %CV = percentage of the coefficient of variation; CL = clearance; IIV = interindividual variability; PopPK = population pharmacokinetic(s); RDV = remdesivir; V1 = central volume of distribution; Vp1 = first peripheral volume of distribution; Vp2 = second peripheral volume of distribution.

Source: PopPK report, p94.

Reviewer's Comments:
The maturation functions for RDV and its metabolite CL are acceptable. The CES1-based maturation function used for RDV and GS-704277 metabolism is based on samples from all ages. There is no information available regarding the maturation of HINT1. While the equation is based on CES1 samples and GS-704277 is metabolized by HINT1, the equation was acceptable for estimation of individual subject exposures in the prior pediatric supplement (≥28 days and ≥3 kg). The maturation function for renal elimination of GS-441524 is acceptable. The equation has been widely used and is based on samples from all ages including a large number of neonates and infants.

Overall, the Applicant's models are acceptable as demonstrated by GOF and VPC plots. In addition, the reviewer ran the Applicant's models and no discordance was identified with the objective function or model parameter estimates.

SBECD Population PK model

Review Summary

The Applicant's popPK analysis is acceptable for the purpose of describing SBECD concentrations. The Applicant's final model parameters were verified by the reviewer.

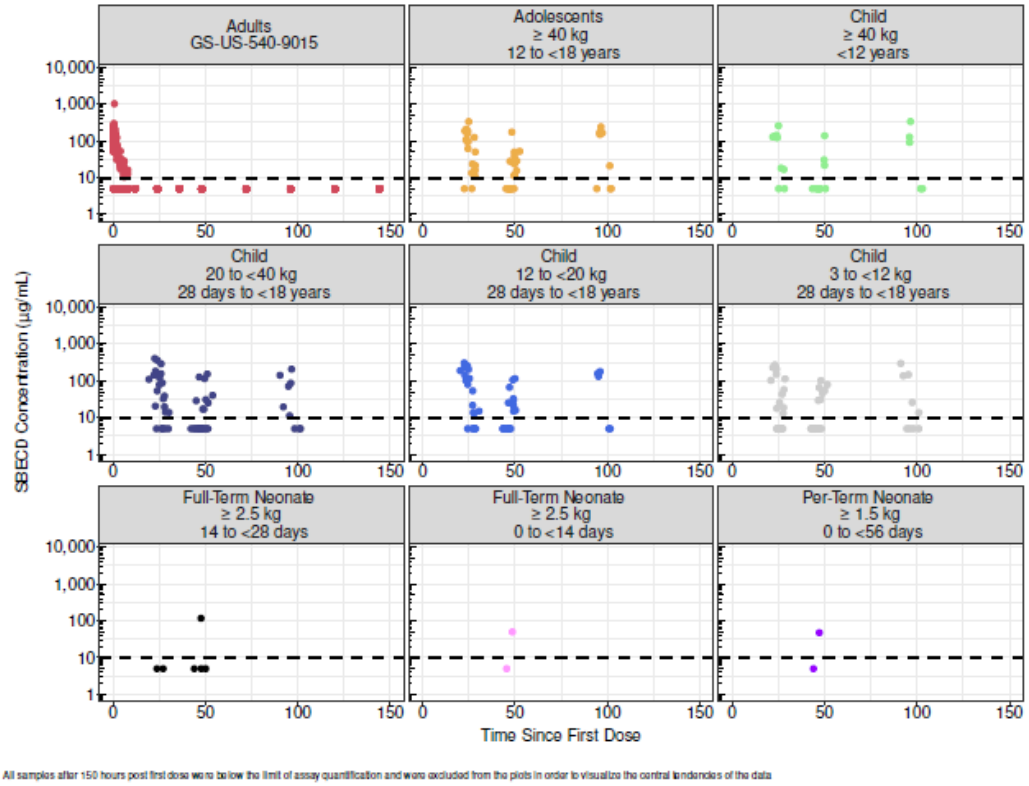
Introduction

The objectives were to identify a popPK model to describe SBECD concentrations in adults with normal renal function and pediatric subjects, identify covariates for accounting for interindividual variability in SBECD PK parameters, and to determine SBECD model-based exposure metrics (Cmax and AUC).

Model development

There were three samples with detectable concentrations in neonates (Figure 20). SBECD PK was best described by a two-compartment model with first-order elimination. Model parameters had acceptable precision and interindividual variability parameters had acceptable shrinkages (Table 13). The models demonstrated acceptable performance in goodness-of-fit and visual predictive check plots (Figure 21, Figure 22).

Figure 20. SBECD concentrations by age.



Source: popPK report, p21.

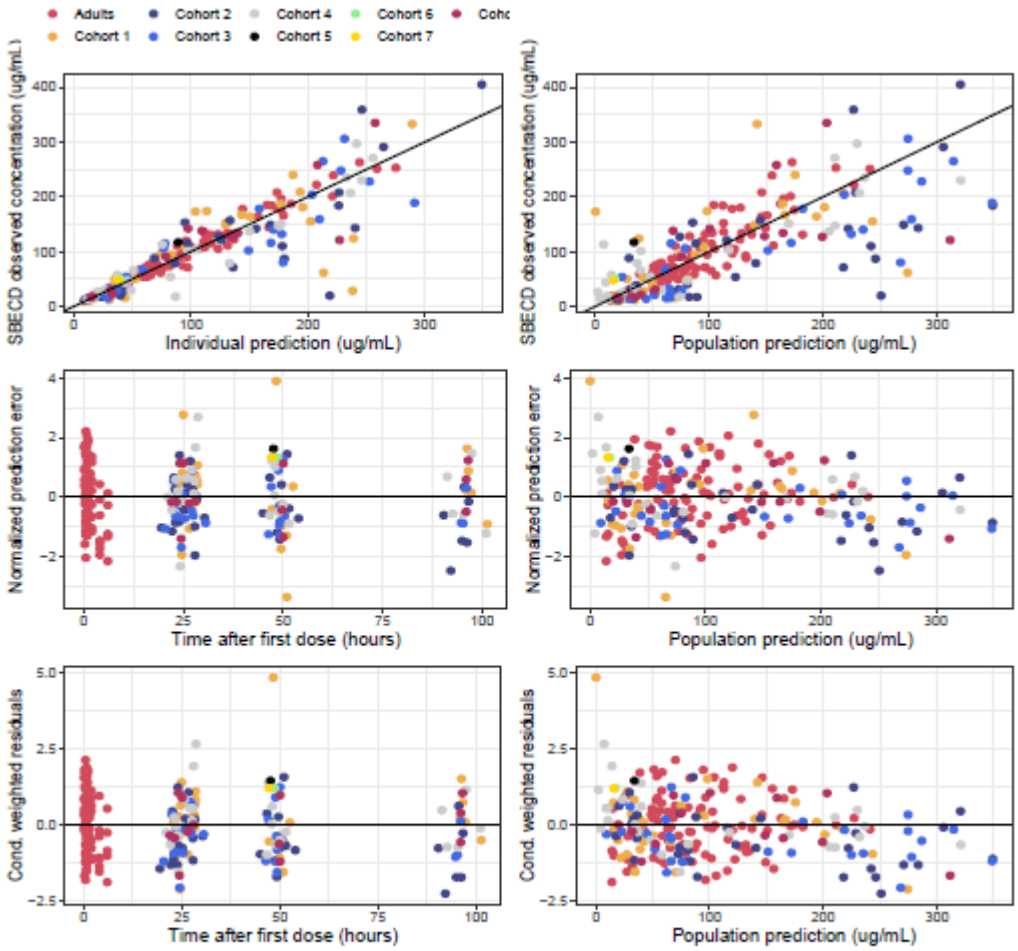
Table 13. SBECD final model parameter estimates

Parameter	Units	Estimate	RSE (%)	Shrinkage (%)	SIR 50th	SIR 10th-90th
CL	L/hr/70kg	7.17	7.12	-	7.43	[6.86;8.07]
Vc	L/70kg	8.81	8.83	-	8.97	[8.04;10.1]
Q	L/hr/70kg	11.9	14.3	-	11.9	[9.78;14.4]
Vp	L/70kg	8.41	7.45	-	8.41	[7.64;9.30]
σ^2 Adults	$\sqrt{\sigma^2}$, CV	0.136	10.4	-	0.137	[0.121;0.157]
σ^2 Peds	$\sqrt{\sigma^2}$, CV	0.364	7.95	-	0.362	[0.330;0.400]
ω^2 [CL]	$\sqrt{\omega^2}$, CV	0.519	10.9	14.8	0.523	[0.457;0.593]
ω^2 [Vc]	$\sqrt{\omega^2}$, CV	0.410	18.2	38.6	0.401	[0.317;0.505]

Drug clearance (CL); Central volume of distribution (Vc); Intercompartmental clearance (Q); Peripheral volume of distribution (Vp); Residual variability variance (σ^2); Interindividual variability variance (ω^2); Percent coefficient of variation (CV%); Relative standard error (RSE); Sampling importance resampling (SIR).

Source: popPK report, p15.

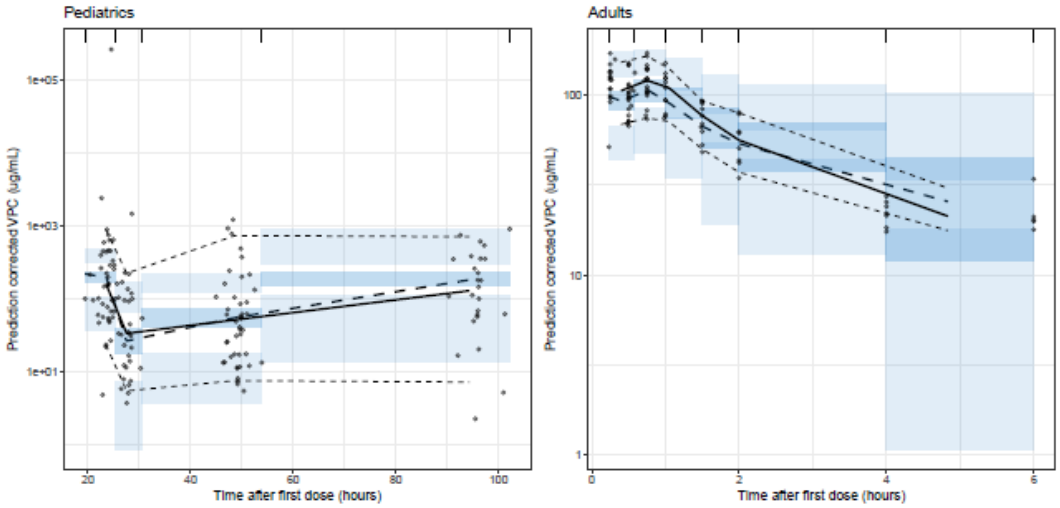
Figure 21. SBECD final model GOF plots.



Upper panel present the observed concentration versus individual prediction and population prediction, respectively.
The middle panel presents the normalized prediction errors versus time after first dose and population prediction, respectively
The lower panel presents the conditional weighted residuals versus time after first dose and population prediction, respectively

Source: popPK report, p24.

Figure 22. VPC by population (pediatrics vs adults).



VPC, Visual Predictive Check
Blue shaded area represent 90th prediction interval for the 5th, 50th and 95th confidence interval
Black dots represent observed SBECD concentrations
Dashed lines represent the observed SBECD predicited 5th, 50th and 95th percentiles.
Solid line represent model predicted median.

Source: popPK report, p25.

Reviewer's Comments: *The Applicant's models are acceptable as demonstrated by GOF and VPC plots. In addition, we ran the Applicant's SBECD final model and obtained nearly identical objective function and model parameter values.*

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 26 virology review by Dr. Ince for a detailed assessment of the clinical virology data.

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 weighing at least 1.5 kg to less than 3 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). 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.

Please refer to the sNDA-11 review (action date April 25, 2022) for full details of GS-US-540-5823 Cohorts 1-4 and Cohort 8, and the assessments that supported use of RDV in pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg.

This section summarizes the descriptive efficacy analyses of GS-US-540-5823 Cohorts 5-7. The study design, subject characteristics, and descriptive efficacy results are summarized below.

Study design, baseline characteristics, and key efficacy results

GS-US-540-5823 (clinicaltrials.gov identifier NCT04431453) is 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 6 and 7 were enrolled after RDV exposures from the preceding cohorts were included in a population PK model and the dose for these cohorts had been selected. Cohorts 1-4 and Cohort 8 were submitted in sNDA-11 (action date April 25, 2022). Cohorts 5-7 (bold font) are submitted in this sNDA.

Table 14: GS-US-540-5823

Cohort	N[c]	Description	Dosing
Pediatrics ≥ 28 days to < 18 years old			
1[a]	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[f]
2[a]	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[f]
3[a]	12	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg	
4[a]	12	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg	
Term neonates 0 days to < 28 days old			
5[a]	**4**	**≥ 14 days to < 28 days of age, gestational age > 37 weeks and weight at Screening ≥ 2.5 kg**	**5 mg/kg IV on Day 1 followed by 2.5 mg/kg IV QD for up to 10 days[f]**
6[b]	**d**	**0 days to < 14 days of age, gestational age > 37 weeks and birth weight ≥ 2.5 kg**	**2.5 mg/kg IV on Day 1 followed by 1.25 mg/kg IV QD for up to 10 days[f]**
Preterm neonates and infants 0 days to < 56 days old			
7[b]	**d**	**0 days to < 56 days of age, gestational age ≤ 37 weeks and birth weight ≥ 1.5 kg**	**2.5 mg/kg IV on Day 1 followed by 1.25 mg/kg IV QD for up to 10 days[f]**
Exploratory cohort for pediatrics < 12 years			
8[a]	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[f]

[a]Cohorts 1-5 and 8 were enrolled in parallel.
[b]Cohorts 6 and 7 were enrolled after RDV exposures from preceding cohorts were included in a population PK model and the dose for these cohorts had been selected.
[c]Planned sample size.
[d]No minimum number.
[e]Exploratory cohort 8 was added in the September 22, 2020 protocol amendment.
[f]Treatment with RDV was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

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])

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: 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.

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 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.
• Final Analysis will be performed after all subjects from Cohort 5, 6 and 7 (if available) have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been finalized.

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.
- 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
Overall, GS-US-540-5823 was conducted from July 22, 2020 to May 3, 2023, and enrolled across 16 centers in the United States, 3 in Spain, 2 in Italy, and 1 in the United Kingdom.

For this sNDA (Cohorts 5-7), the first subject was enrolled on April 1, 2021, and the last subject visit was completed on February 10, 2023. Study enrollment closed on May 3, 2023.

Of the 6 subjects (US [n=3], Italy [n=2], Spain [n=1]) who were screened for Cohorts 5-7, a total of 5 subjects (US [n=2], Italy [n=2], Spain [n=1]) were enrolled and received at least one dose of study medication, and consequently were included in the full analysis set. One subject in Cohort 5 enrolled but did not receive treatment due to withdrawal of parental consent.

Reviewer Comment: Of the 6 subjects, 3 subjects were from the US, 3 subjects were ex-US.

One important protocol deviation (in one subject in Cohort 5; SAE not reported to the Applicant within 24 hours of identification) occurred during the study through the Day 30 follow-up visit. This protocol violation 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 15: Subject Disposition, FAS

Cohort	**5**	**6**	**7**	**Total**
Age/weight groups	**14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg**	**< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg**	**< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg**	
Subjects enrolled	4	1	1	6
Subjects treated (FAS)	3	1	1	5
Subjects completed study drug	2 (67%)	1 (100%)	1 (100%)	4 (80%)
Subjects prematurely discontinuing study drug	1 (33%)	0	0	1 (20%)
Adverse Event	0	0	0	0
Hospital Discharge	1 (33%)	0	0	1 (20%)
Investigator's Discretion	0	0	0	0
Subject Decision	0	0	0	0
Parent/Guardian Decision	0	0	0	0
Subjects completed study	3 (100%)	1 (100%)	1 (100%)	5 (100%)
Subjects prematurely discontinuing from study	0	0	0	0
Death	0	0	0	0
Withdrew Consent	0	0	0	0
Lost to Follow-Up	0	0	0	0

Disposition is as of the Day 30 follow-up visit.
Source: ADSL dataset; GS-US-540-5823 Clinical Study Report, Table 6.
Notes: The denominator for percentages is the number of subjects in the full analysis set (FAS).

Reviewer Comment: Of the 5 subjects, one subject (20%) prematurely discontinued RDV due to hospital discharge (following clinical recovery). The other 4 subjects completed the RDV course outlined by the investigators.

Baseline demographics
The table below summarizes baseline demographics.

Table 16: Demographics, FAS

Cohort	**5**	**6**	**7**	**Total**
Age/weight groups	**14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)**	**< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)**	**< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)**	**5**
Age* (years)				
Mean	0.0	0.0	0.1	0.0
Median	0.0	0.0	0.1	0.0
Minimum, maximum	0.5, 0.5	0.0, 0.0	0.1, 0.1	0.0, 0.1
Sex at birth				
Male	2 (67%)	0	0	2 (40%)
Female	1 (33%)	1 (100%)	1 (100%)	3 (60%)
Race				
White	3 (100%)	0	1 (100%)	4 (80%)
Black	0	1 (100%)	0	1 (20%)
Ethnicity				
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	3 (100%)	1 (100%)	1 (100%)	5 (100%)
Baseline weight (kg)				
Mean	3.3	3.5	2.2	3.1
Median	3.5	3.5	2.2	3.5
Minimum, maximum	2.8, 3.5	3.5, 3.5	2.2, 2.2	2.2, 3.5

*Cohort 5 (15 day-old male weighing 2.8 kg; 16 day-old male weighing 3.5 kg; 16 day-old female weighing 3.5 kg); Cohort 6 (12 day-old female weighing 3.5 kg); Cohort 7 (30 day-old female weighing 2.2 kg).
Source: ADSL dataset; GS-US-540-5823 Clinical Study Report, Table 8.

Reviewer Comment: The median age was 16 days old (range: 12 to 30 days); 60% of subjects were female, 80% of subjects were White and 20% of subjects were Black; no subjects were Hispanic or Latino; median weight was 3.5 kg (range: 2.2 to 3.5 kg).

Baseline disease characteristics
The table below summarizes baseline disease characteristics.

Table 17: Baseline disease characteristics, FAS

Cohort	5	6	7	Total
Age/weight groups	**14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)**	**< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)**	**< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)**	**5**
Duration of symptoms prior to first dose of RDV (days)				
Mean	6	2	9	6
Median	6	2	9	6
Minimum, maximum	2, 9	2, 2	9, 9	2, 9
Oxygen support status (ordinal scale)				
High-flow oxygen (OS-3)	1 (33%)	1 (100%)	0	2 (40%)
IMV (OS-2)	2 (67%)	0	1 (100%)	3 (60%)
Duration of hospitalization prior to first dose of RDV (days)				
Mean	5	1	3	4
Median	5	1	3	3
Minimum, maximum	1, 9	1, 1	3, 3	1, 9

Source: ADSL dataset; GS-US-540-5823 Clinical Study Report, Table 9.
Abbreviations: OS, ordinal scale; IMV, invasive mechanical ventilation.

Reviewer Comment: The median duration of symptoms prior to treatment initiation was 6 days (range: 2 to 9 days). The median duration of hospitalization prior to treatment initiation was 3 days (range: 1 to 9 days).

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

- *2 subjects (40%) had a clinical status of 3 (hospitalized, receiving noninvasive ventilation or high-flow oxygen devices)*
- *3 subjects (60%) had a clinical status of 2 (hospitalized, receiving IMV or ECMO)*

Treatment duration

The table below summarizes the treatment duration.

Table 18: Treatment Duration, SAS

Cohort	5	6	7	Total
Age/weight groups	14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)	< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)	< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)	5
Number of doses				
Mean	9	5	10	9
Median	10	5	10	10
Minimum, maximum	8, 10	5, 5	10	5, 10
Number of doses				
1	0	0		0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	1 (100%)	0	0
6	0	0	0	0
7	0	0	0	0
8	1 (33%)*	0	0	0
9	0	0	0	0
10	2 (67%)	0	1 (100%)	0

*Prematurely discontinued RDV due to hospital discharge.
Source: ADAE dataset, GS-US-540-5823

Reviewer Comment:Treatment duration was based on the clinical judgment of the investigator.
• Cohort 5: Two 5 subjects received RDV for 10 days; the other subject received RDV for 8 days, had clinical improvement and was discharged.
• The subject in Cohort 6 received RDV for 5 days (as determined by the investigator).
• The subject in Cohort 7 received RDV for 10 days.

Hospital discharge
The table below summarizes clinical outcomes for hospitalization.

Table 19: Proportion of subjects who were hospitalized, FAS

Cohort	5	6	7	Total
Age/weight groups	14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)	< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)	< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)	5
Day 10				
Number of subjects discharged alive by Day 10	1 (33%)	0	0	1 (20%)
Number of subjects still hospitalized at Day 10	2 (67%)	1 (100%)	1 (100%)	4 (80%)
Number of subjects who died on or prior to Day 10	0	0	0	0
Day 30				
Number of subjects discharged alive by Day 30	1 (33%)	1 (100%)	1 (100%)	3 (60%)
Number of subjects still hospitalized at Day 30	2 (67%)	0	0	0
Number of subjects who died on or prior to Day 30	0	0	0	0

Source: ADEFF dataset, GS-US-540-5823

Reviewer Comment: One subject (in Cohort 5) was discharged alive by Day 10. Three subjects (one each in Cohorts 5 to 7, respectively) were discharged alive by Day 30; for these three subjects, the duration of hospitalization is summarized below:

- *Cohort 5: 9 days*
- *Cohort 6: 13 days*
- *Cohort 7: 19 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.

Table 20: Clinical status (based on the 7-point ordinal scale), FAS

Cohort	5	6	7	Total
Age/weight groups	**14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)**	**< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)**	**< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)**	**5**
Clinical status (based on the 7-point ordinal scale) on Day 10				
1 (Death)	0	0	0	0
2 (IMV or ECMO)	2 (67%)	0	0	2 (40%)
3 (Noninvasive ventilation or high-flow oxygen devices)	0	0	0	0
4 (Hospitalized, requiring low-flow supplemental oxygen)	0	0	1 (100%)	1 (20%)
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	0	1 (100%)	0	1 (20%)
6 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, other than per protocol RDV administration)	0	0	0	0
7 (Not hospitalized)	1 (33%)	0	0	1 (20%)
Clinical status (based on the 7-point ordinal scale) on the last available assessment				
1 (Death)	0	0	0	0
2 (IMV or ECMO)	2 (67%)	0	0	2 (40%)
3 (Noninvasive ventilation or high-flow oxygen devices)	0	0	0	0
4 (Hospitalized, requiring low-flow supplemental oxygen)	0	0	0	0
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	0	0	0	0
6 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, other than per protocol RDV administration)	0	0	0	0
7 (Not hospitalized)	1 (33%)	1 (100%)	1 (100%)	3 (60%)

Source: ADEFF dataset, GS-US-540-5823
Abbreviations: IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

Reviewer Comment: One subject (20%) achieved an ordinal scale score of 7 (i.e., not hospitalized) on Day 10. Three subjects (60%) achieved an ordinal scale score of 7 (i.e., not hospitalized) on the last available assessment.

Regarding the change from baseline in clinical status
On Day 10, the change from baseline in clinical status (based on the 7-point ordinal scale) was as follows:
• Cohort 5: One subject improved by 4 points, from OS-3 (high-flow oxygen) to OS-7 (not hospitalized). The other two subjects had no change in clinical status and remained at OS-2 (IMV).
• Cohort 6: The subject improved by 2 points, from OS-3 (high-flow oxygen) to OS-5 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise]).
• Cohort 7: The subject improved by 2 points, from OS-2 (IMV) to OS-4 (hospitalized, requiring low-flow supplemental oxygen).

At the time of the last assessment:
• Cohort 5: The other two subjects had no change in clinical status.
• Cohort 6: The subject had overall improved by 4 points, from OS-3 (high-flow oxygen) to OS-7 (not hospitalized).
• Cohort 7: The subject had overall improved by 5 points, from OS-2 (IMV) to OS-7 (not hospitalized).

Clinical improvement (≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale)
• All 5 subjects had baseline ordinal score of ≤ 5 points.
• On Day 10, 3 subjects (60%) had a ≥ 2-point improvement in clinical status.
• At the time of the last assessment, these same 3 subjects (60%) had a ≥ 2-point improvement in clinical status.

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)
• One subject (in Cohort 5) met the definition for recovery by Day 10.
• Three subjects (one each in Cohorts 5 to 7, respectively) met the definition for recovery by the time of the last assessment. These same 3 subjects had been discharged (i.e., achieved an ordinal scale score of 7) by the time of the last assessment.

Conclusions on effectiveness

The disease process of 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 weighing at least 1.5 kg to less than 3 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 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 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 weighing at least 1.5 kg to less than 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.

8. Safety

This section summarizes the safety findings of GS-US-540-5823 Cohorts 5-7.

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 weighing at least 1.5 kg to less than 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.

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.

Treatment-emergent AEs (TEAEs) were defined as any AE that began on or after the first dose of study drug up to the date of the last dose of study drug plus 30 days, *OR* any AE leading to premature discontinuation of study drug.

Treatment-emergent death referred to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Adverse events (AEs) are treatment-emergent and regardless of causality. Adverse drug reactions (ADRs) are treatment-emergent and at least possibly related as assessed by the investigator. For ADR assessment, the investigator's determination of causality is the basis for classification. The limitations of this approach to causality assessment are acknowledged.

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 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 21. Overview of Adverse Events, GS-US-540-5823

Cohort	5	6	7	Total
Subjects Experiencing Event	**14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)**	**< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)**	**< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)**	**5**
Any AE	2 (67%)	1 (100%)	0	3 (60%)
Related AE	0	0	0	0
Grade 3 or 4 AE	1 (33%)	0	0	1 (20%)
Related Grade 3 or 4 AE	0	0	0	0
SAE	1 (33%)	1 (100%)	0	2 (40%)
Related SAE	0	0	0	0
Death	0	0	0	0
Related deaths	0	0	0	0
Discontinuation of study drug due to AE	0	0	0	0
D/c of study drug due to related AEs	0	0	0	0

Source: ADAE dataset, GS-US-540-5823
Abbreviations: AE, adverse event; SAE, serious adverse event.

Reviewer Comment: There were no deaths in Cohorts 5-7. All AEs, SAEs, and Grade 3/4 AEs in Cohorts 5-7 were assessed as unrelated to study drug by the study investigators.

Deaths
There were no deaths in Cohorts 5-7.

Serious Adverse Events (SAEs)

In GS-US-540-5823, SAEs were overall consistent with those observed in a hospitalized patient population. SAEs occurred in two subjects (one subject in Cohort 5; one subject in Cohort 6). All SAEs were assessed by investigators as not related to study drug. The following table provides a summary of SAEs by Preferred Term (PT).

Table 22: SAEs (*note: subjects could have more than one event*)

Cohort	**5**	**6**	**7**	**Total**
Preferred Term	**14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)**	**< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)**	**< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)**	**5**
Total subjects w/any SAE	1 (33%)	1 (100%)	0	2 (40%)
Acidosis*	1 (33%)	0	0	1 (20%)
Cardiopulmonary failure*	1 (33%)	0	0	1 (20%)
Pneumothorax*	1 (33%)	0	0	1 (20%)
Seizure*	1 (33%)	0	0	1 (20%)
Urinary tract infection	0	1 (100%)	0	1 (20%)

Source: ADAE dataset, GS-US-540-5823; *Grade 3/4 AEs

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

There were no discontinuations due to AEs in Cohorts 5-7

Significant AEs

In GS-US-540-5823, Grade 3/4 AEs were overall consistent with those observed in a hospitalized patient population. All of these events were also considered SAEs; please refer to the SAE subsection (above). As summarized in Table 16 (above), Grade 3/4 AEs occurred in one subject in Cohort 5. All Grade 3/4 AEs were assessed by investigators as not related to study drug.

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 three subjects (two subjects in Cohort 5; one subject in Cohort 6). All AEs were assessed by investigators as not related to study drug.

Table 23: Treatment-Emergent AEs by Preferred Term, All Grade and All Causality

Cohort	**5**	**6**	**7**	**Total**
Preferred Term	**14 to < 28 Days, Gest. Age > 37 Weeks,**	**< 14 Days, Gest. Age > 37 Weeks,**	**< 56 Days, Gest. Age ≤ 37 Weeks,**	

	and Weight ≥ 2.5 kg (n=3)	and Birth Weight ≥ 2.5 kg (n=1)	and Birth Weight ≥ 1.5 kg (n=1)	5
Total subjects w/any AE	2 (67%)	1 (100%)	0	3 (60%)
Acidosis*	1 (33%)	0	0	1 (20%)
Cardiopulmonary failure*	1 (33%)	0	0	1 (20%)
Pneumothorax*	1 (33%)	0	0	1 (20%)
Seizure*	1 (33%)	0	0	1 (20%)
Hypertension	1 (33%)	0	0	1 (20%)
Anaemia	1 (33%)	0	0	1 (20%)
Infusion site extravasation	1 (33%)	0	0	1 (20%)
Bacterial disease carrier	1 (33%)	0	0	1 (20%)
Chest wall haematoma	1 (33%)	0	0	1 (20%)
Conjunctivitis	1 (33%)	0	0	1 (20%)
Urinary tract infection	0	1 (100%)	0	1 (20%)

Source: ADAE dataset, GS-US-540-5823; *Grade 3/4 AEs

The majority of AEs were Grades 1 or 2 in severity. No AE occurred more than once.

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.

There were no ADRs in Cohorts 5-7.

Reviewer Comment: There are no ADRs from Cohorts 5-7 to display in product labeling.

Laboratory abnormalities
Graded laboratory abnormalities occurred in all 5 subjects. Grade 3/4 laboratory abnormalities occurred in the subjects in Cohorts 5 and 7, respectively.

The following table summarizes graded chemistry and urinalysis results.

Table 24: Chemistry and Urinalysis Laboratory Results, All Grade

Cohort	5	6	7	Total
Parameter and Max Analysis Toxicity Grade	14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)	< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)	< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)	5
Increased alanine aminotransferase (U/L)				
N	3	1	1	5
Grade 1 (1.25 to <2.5x ULN)	0	0	0	0
Grade 2 (2.5 to <5x ULN)	0	0	0	0
Grade 3 (5 to <10x ULN)	0	0	0	0
Grade 4 (>10x ULN)	0	0	0	0
Increased aspartate aminotransferase (U/L)				
N	3	1	1	5

Grade 1 (1.25 to <2.5x ULN)	0	0	0	0
Grade 2 (2.5 to <5x ULN)	0	0	0	0
Grade 3 (5 to <10x ULN)	0	0	0	0
Grade 4 (>10x ULN)	0	0	0	0
Increased total bilirubin (mg/dL)				
N	3	1	1	5
Grade 1 (1.1 to <1.6x ULN)	1 (33%)	0	0	0
Grade 2 (1.6 to <2.6x ULN)	0	0	0	0
Grade 3 (2.6 to <5x ULN)	0	0	0	0
Grade 4 (≥5x ULN)	0	0	0	0
Increased direct bilirubin (mg/dL)				
N	2	1	1	4
Grade 1 (ULN to ≤ 1 mg/dL)	0	0	0	0
Grade 2 (> 1 to ≤ 1.5 mg/dL)	0	0	0	0
Grade 3 (> 1.5 to ≤ 2 mg/dL)	1 (50%)	0	0	1 (25%)
Grade 4 (> 2 mg/dL)	0	0	0	0
Increased creatinine (mg/dL)				
N	3	1	1	5
Grade 1 (1.1 to 1.3x ULN)	0	0	0	0
Grade 2 (>1.3 to 1.8x ULN *OR* increase to 1.3 to <1.5x subject's baseline)	0	0	0	0
Grade 3 (>1.8 to <3.5x ULN *OR* increase to 1.5 to <2.0x subject's baseline)	1 (33%)	0	0	1 (20%)
Grade 4 (≥3.5x ULN *OR* increase of ≥2.0x subject's baseline)	0	0	0	0
Decreased eGFR (mL/min/1.73m^2)				
N	0	0	0	0
Grade 1 (NA)	0	0	0	0
Grade 2 (<90 to 60 mL/min/1.73m^2 *OR* 10 to <30% decrease from subject's baseline)	0	0	0	0
Grade 3 (<60 to 30 mL/min/1.73m^2 *OR* 30 to <50% decrease from subject's baseline)	0	0	0	0
Grade 4 (<30 mL/min/1.73m^2 *OR* ≥50% decrease from subject's baseline or dialysis needed)	0	0	0	0
Increased glucose (mg/dL)				
N	3	1	0	4
Grade 1 (116 to 160 mg/dL)	0	0	0	0
Grade 2 (>160 to 250 mg/dL)	0	0	0	0
Grade 3 (>250 to 500 mg/dL)	0	0	0	0
Grade 4 (≥500 mg/dL)	0	0	0	0
Increased potassium (mEq/L)				
N	3	1	1	5
Grade 1 (5.6 to <6.0 mEq/L)	0	1 (100%)	1 (100%)	2 (40%)
Grade 2 (6.0 to <6.5 mEq/L)	0	0	0	0
Grade 3 (6.5 to <7.0 mEq/L)	1 (33%)	0	0	1 (20%)
Grade 4 (≥7.0 mEq/L)	0	0	0	0
Decreased potassium (mEq/L)				

N	3	1	1	5
Grade 1 (3.0 to 3.4 mEq/L)	2 (67%)	0	0	2 (40%)
Grade 2 (2.5 to <3.0 mEq/L)	0	0	0	0
Grade 3 (2.0 to 2.5 mEq/L)	0	0	0	0
Grade 4 (<2.0 mEq/L)	0	0	0	0
Urine glucose (mg)				
N	3	0	1	4
Grade 1 (≤250 mg)	0	0	0	0
Grade 2 (250 to ≤500 mg)	0	0	0	0
Grade 3 (>500 mg)	0	0	0	0
Grade 4 (NA)	0	0	0	0
Urine protein				
N	2	0	1	3
Grade 1 (1+)	1 (50%)	0	0	1 (33%)
Grade 2 (2+)	0	0	0	0
Grade 3 (3+ or higher)	0	0	0	0
Grade 4 (NA)	0	0	0	0

Source: ADLB dataset, 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: None of these chemistry or urinary laboratory abnormalities resulted in RDV discontinuation.

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. Grade 3/4 creatinine increase occurred in one subject.

There were no Grade 3/4 ALT or AST elevations. There was one Grade 3/4 direct bilirubin elevation.

The following table summarizes graded hematology and coagulation results.

Table 25: Hematology and Coagulation Laboratory Results, All Grade

Cohort	**5**	**6**	**7**	**Total**
Parameter and Max Analysis Toxicity Grade	**14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (n=3)**	**< 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (n=1)**	**< 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (n=1)**	**5**
Decreased hemoglobin (g/dL)				
N	3	1	1	5
Grade 1 (11 to <13 g/dL)*	0	1 (100%)*	0	1 (20%)
Grade 2 (9 to <11 g/dL)*	2 (67%)*	0	1 (100%)‡	3 (60%)
Grade 3 (8 to <9 g/dL)*	0	0	0	0
Grade 4 (<8 g/dL)*	0	0	0	0
Decreased neutrophils (cells/mm^3)				

N	3	1	1	5
Grade 1 (800 to 1000/mm^3)	1 (33%)	0	1 (100%)	2 (40%)
Grade 2 (600 to 799/mm^3)	0	0	0	0
Grade 3 (400 to 599/mm^3)	0	0	0	0
Grade 4 (<400/mm^3)	0	0	0	0
Decreased platelets (cells/mm^3)				
N	3	1	1	5
Grade 1 (100,000 to <125,000/mm^3)	0	0	0	0
Grade 2 (50,000 to <100,000/mm^3)	0	0	0	0
Grade 3 (25,000 to <50,000/mm^3)	0	0	0	0
Grade 4 (<25,000/mm3)	0	0	0	0
Decreased WBC (cells/mm^3)				
N	3	1	1	5
Grade 1 (2000 to 2499/mm^3)	0	0	0	0
Grade 2 (1500 to <1999/mm^3)	0	0	0	0
Grade 3 (1000 to <1499/mm^3)	0	0	0	0
Grade 4 (<1000/mm^3)	0	0	0	0
Prothrombin time (PT) increased				
N	3	0	1	4
Grade 1 (1.1 to <1.25x ULN)	0	0	0	0
Grade 2 (1.25 to <1.5x ULN)	1 (50%)	0	0	1 (25%)
Grade 3 (1.5 to <3x ULN)	0	0	0	0
Grade 4 (≥3x ULN)	1 (50%)	0	0	1 (25%)
INR increased				
N	3	1	1	5
Grade 1 (1.1 to < 1.5x ULN)	1 (33%)	0	0	1 (20%)
Grade 2 (1.5 to < 2.0x ULN)	0	0	0	0
Grade 3 (2.0 to < 3.0x ULN)	0	0	0	0
Grade 4 (≥3x ULN)	1 (33%)	0	0	1 (20%)
Activated Partial Thromboplastin Time (aPTT) increased				
N	3	1	1	5
Grade 1 (1.1 to <1.66x ULN)	1 (33%)	1 (100%)	0	2 (40%)
Grade 2 (1.66 to <2.33x ULN)	0	0	0	0
Grade 3 (2.33 to <3x ULN)	0	0	0	0
Grade 4 (≥3x ULN)	2 (67%)	0	0	2 (40%)

Source: ADLB dataset, GS-US-540-5823
For each laboratory parameter, N represents the number of subjects who had at least one post-baseline value for the specified test.
*Hemoglobin grading for pediatrics 8 to ≤ 21 days of age (i.e., subjects enrolled in Cohorts 5 and 6).

‡Hemoglobin grading for pediatrics 22 to 35 days of age: Grade 1 (9.5 to <11 g/dL); Grade 2 (8 to <9.5 g/dL); Grade 3 (6.7 to <8 g/dL); Grade 4 (<6.7 g/dL).
‡Hemoglobin grading for pediatrics 36 to 56 days of age: Grade 1 (8.5 to 9.6 g/dL); Grade 2 (7 to <8.5 g/dL); Grade 3 (6 to <7 g/dL); Grade 4 (<6 g/dL).
‡Subject enrolled in Cohort 7 was 30 days of age at baseline, and 40 days of age on Day 10 when Grade 2 hemoglobin decreased (7.1 g/dL) occurred,
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, PT elevations occurred in one subject, INR elevations occurred in one subject, and aPTT elevations occurred in two subjects.

Overall Assessment: The laboratory abnormalities observed in pediatric subjects were consistent with those observed in clinical trials in adults.

In GS-US-540-5823 Cohorts 5-7, the following Grade 3/4 laboratory abnormalities occurred: aPTT increased (2 out of 5 subjects); prothrombin time increased (1 out of 5 subjects); INR increased (1 out of 5 subjects); direct bilirubin increased (1 out of 5 subjects); creatinine increased (1 out of 5 subjects); and potassium increased (1 out of 5 subjects).

These findings will be displayed in product labeling. Of note, the approved label already outlines that monitoring of hepatic function and prothrombin time are recommended while receiving RDV.

Submission-specific safety issues
Nephrotoxicity:
- There were no renal AEs.
- Grade 3/4 creatinine increase occurred in one subject.
- 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:
- There were no hepatic AEs.
- There were no Grade 3/4 ALT or AST or total bilirubin elevations.
- Grade 3/4 direct bilirubin elevations occurred in one subject.
- No hepatic laboratory abnormalities led to RDV discontinuation.

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
- There were no 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:
- One hemorrhagic AE (Grade 2 chest wall haematoma) occurred.
- There were no hemorrhagic ADRs.
- No hemorrhagic AEs led to RDV discontinuation.
- Grade 3/4 PT elevations occurred in one subject.
- Grade 3/4 INR elevations occurred in one subject.
- Grade 3/4 aPTT elevations occurred in two 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
- There were no rash events.

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.

Seizure (please refer to the SAE subsection [above])
- One seizure event was reported (Grade 4 [onset on Day 4, resolved on Day 4]; assessed by investigators as not related to study drug); this event did not lead to RDV discontinuation. Of note, this patient also had the following additional SAEs: progressive cardiopulmonary failure requiring vasopressor support (first episode – onset on Day 1, resolved on Day 4); acidosis (onset on Day 7, resolved on Day 9); progressive cardiopulmonary failure requiring ECMO (second episode – onset on Day 7, resolved on Day 25); pneumothorax (onset on Day 7, resolved on Day 25).

Overall Assessment: Causality assessment is confounded by underlying COVID-19, hypoxia (leading to respiratory failure), and electrolyte abnormalities (Grade 1 hypernatremia). Based on these findings, no additional labeling regarding seizure events is warranted at this time. Routine pharmacovigilance will be in place to detect postmarketing signals.

Pancytopenia
- There were no pancytopenia events.

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

Rhabdomyolysis
- There were no cases of rhabdomyolysis.

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

Pancreatitis
- No clinical cases of pancreatitis were reported.

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

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

I. Sulfobutylether-β-cyclodextrin sodium salt (SBECD)

IA. Background

In NDA 214787/S-19 (action date: July 13, 2023; DARRTS Reference ID: 5203171):
- Data from GS-US-540-5912 (Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19) and GS-US-540-9015 (Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of Remdesivir and Metabolites in Participants with Normal Renal Function and Renal Impairment) were reviewed.
- FDA assessed the PK and safety data from GS-US-540-5912 and GS-US-540-9015 support no dosage adjustment for patients with any degree of renal impairment, including patients on dialysis. The data also supported removal of renal function monitoring from product labeling. GS-US-540-9015 fulfilled PMR 3919-6 (*Conduct a clinical trial to evaluate the pharmacokinetics and safety of remdesivir in subjects with mild, moderate, and severe renal impairment to inform appropriate dosage recommendations in patients with COVID-19 with impaired renal function*.)
- Although no adolescents were enrolled in GS-US-540-5912 and no pediatric data were included in NDA 214787/S-19, FDA assessed that use of RDV in patients with severe renal insufficiency or ESRD can be extended to the pediatric population, based on the totality of the data used to support the prior regulatory actions and the safety and PK data submitted in NDA

214787/S-19 (that includes adults with severe insufficiency and adults with ESRD on dialysis, respectively). Given the low prevalence of pediatric patients with severe renal insufficiency or ESRD on dialysis, and feasibility challenges to conduct a clinical trial in this population, FDA assessed that extending the dosing recommendations to the pediatric population will provide a treatment option to this pediatric population with unmet medical need.
- The adult safety data in patients with renal impairment (including those requiring dialysis) did not identify any new safety concerns compared to adults with normal renal function. The label outlined that the use of RDV in pediatric patients with renal impairment is supported by safety data in adults.
- The label included a statement regarding no safety data are available in pediatric patients with severe renal impairment and outlined that the use of RDV in pediatric patients with renal impairment is supported by safety RDV contains SBECD which, when administered intravenously, is eliminated through glomerular filtration and may be reduced in pediatric patients with renal immaturity or renal impairment, resulting in higher exposure to SBECD.

IB. Current sNDA

Although limited clinical data are available in pediatric patients weighing ≥ 1.5 kg to < 3 kg, the Division believes that use of RDV can be extended to this pediatric subgroup, based on the totality of the data used to support the prior regulatory actions (outlined in Section 2 of this review, as well as NDA 214787/S-19 [please refer to Section 10, IA above]) and the PK and safety data submitted in this sNDA (please refer to Sections 5 and 8 of this review).

Plasma exposures of excipient SBECD were generally similar for all pediatric patients at the doses administered in GS-US-540-5823 and were similar compared to adults with normal renal function, although data are very limited.

The current submission contains PK data for all cohorts of GS-US-540-5823. Compared to healthy adults with normal renal function in GS-US-540-9015 administered a single RDV dose of 100 mg, plasma concentrations of SBECD in all pediatric subjects in GS-US-540-5823 were largely within the range of those in adults (Figure 10), and the three detectable concentrations from neonates were within the range of adults (Figure 11).

Per EMA, the maximum recommended dose of SBECD is 250 mg/kg/day. The ratio of SBECD (mg) to RDV (mg) in the RDV formulation is 30:1. Enrolled neonates receiving RDV 5 mg/kg on day 1 received SBECD 150 mg/kg/day. Per proposed labeling, maximum RDV dosing for neonates is 2.5 mg/kg, which amounts to 75 mg/kg/day SBECD.

As discussed in the Pharmacology/Toxicology review of the original NDA, to support use of RDV in subjects < 2 years of age during clinical trials and the EUA, the Applicant provided toxicity data for SBECD administered to juvenile animals in DMF # (b) (4). IV doses of up to 4500 mg/kg/day for 2 weeks were well tolerated in juvenile rats. SBECD produced known renal effects; tubular vacuolation was similar to that produced in adult rats. There was no evidence that the juvenile kidney was more sensitive than adult kidney, and effects were fully

reversible.[9] The calculations of SBECD (mg/kg/day) with IV RDV for pediatric patients weighing ≥ 1.5 kg to < 3 kg is up to 75 mg/kg/day SBECD and is far less than the 250 mg/kg/day cited by EMA.

Acknowledging the nonclinical findings with SBECD, which are reversible and at higher exposures than the 5-10 day IV treatment, along with the ability to leverage existing PK and safety data in adults to pediatric patients, the review team concluded the totality of the data are reasonable to support RDV use in pediatric patients weighing ≥ 1.5 kg to < 3 kg given the severity of disease, short term treatment (5 to 10 days) and lack of approved or authorized products for this pediatric subgroup.

II. Postmarketing requirement (PMR)

Under the Pediatric Research Equity Act (PREA), the following postmarketing requirement (PMR) was issued in the original approval letter, dated October 22, 2020:

3919-1 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response to remdesivir in pediatric subjects from birth to less than 18 years of age including neonates, with coronavirus disease 2019 (COVID-19).

Study Completion:	03/2021
Final Report Submission:	10/2021

On April 29, 2021, the Applicant submitted a deferral extension because of difficulties encountered in enrolling pediatric subjects in the youngest cohorts. On June 11, 2021, the Division of Antivirals (DAV) granted the deferral extension as follows:

Study Completion:	02/2022 (revised date)
Final Report Submission:	09/2022 (deferral extension date)

Reference is made to the supplemental NDA (sNDA) submitted on October 21, 2021, and the approval letter dated January 21, 2022: sNDA-11 provides for the use of RDV as a 3-day dosing regimen for the 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Given that the sNDA triggered PREA for a new dosing regimen, FDA determined that the Applicant was required, pursuant to section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) to conduct the following PREA PMR:

4220-1 Conduct a study to evaluate the safety, tolerability, and pharmacokinetics of remdesivir in non-hospitalized pediatric subjects from birth to less than 12 years of age with coronavirus disease 2019 (COVID-19). A dedicated

[9] Center for Drug Evaluation and Research. Non-Clinical Review for NDA 214787; action date, October 22, 2020 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214787Orig1s000PharmR.pdf).

outpatient pediatric study is not required if pharmacokinetics and safety can be obtained from the ongoing trial in hospitalized pediatric population.

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

On March 28, 2022, the Applicant submitted a deferral extension because of difficulties encountered in enrolling pediatric subjects in the youngest cohorts. The Applicant proposed the following revised milestone dates for PMR 3919-1 and PMR 4220-1 based on updated projections for the study enrollment:

Final Protocol Submission:	submitted
Study Completion:	02/2023
Final Report submission:	08/2023

The Division of Antivirals (DAV) agreed with the Applicant that multiple factors, such as the spectrum of COVID-19 disease in children, challenges with accruing clinical trial data in neonates and preterm neonates, and the decreased number of sites that are willing to continue to try to enroll these pediatric subjects, present logistical challenges and the revised timelines are acceptable. DAV assessed that the deferral extension request for PREA PMR 3919-1 and PREA PMR 4220-1 should be granted. The above issues were presented before the Pediatric Research Committee (PeRC) on May 3, 2022, who agreed with DAV's recommendation. On May 6, 2022, DAV granted the deferral extension.

As outlined in this review, Cohorts 5-7 are submitted in this sNDA (please refer to Section 7, Table 14 [above]), thereby completing GS-US-540-5823. The Agency (including discussions between DAV and PeRC) concluded that PMR 3919-1 and PMR 4220-1 have been fulfilled.

III. Written Request (WR)

On October 28, 2021, FDA issued a Written Request (under IND 147753 and NDA 214787) in order to obtain needed pediatric information on RDV, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007. The Applicant was requested to submit the pediatric study report by September 30, 2022.

On May 20, 2022, the Applicant submitted a proposed amendment to Written Request to revise the timeframe for submitting the pediatric study report from September 30, 2022 to August 31, 2023 due to enrollment difficulties in the pediatric study intended to fulfil the Written Request. On May 26, 2022, FDA issued a revised Written Request outlining that the Applicant submit the pediatric study report by August 31, 2023.

As outlined in this review, Cohorts 5-7 are submitted in this sNDA (Table 14), thereby completing GS-US-540-5823. The Agency (through discussions with DAV and the Pediatric Exclusivity Board) concluded that the Written Request has been fulfilled and determined that pediatric exclusivity should be granted (Reference ID: 5314908).

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, bioanalytical site inspections were conducted. No objectional conditions were observed.

- *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 memorandum for this supplement (Reference ID: 5313326) and to the OSE memorandum for the Pediatric Advisory Committee (Reference ID: 5313166) 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 weighing at least 1.5 kg to less than 3 kg.

The revised indication is treatment of adults and pediatric patients (birth to less than 18 years of age weighing at least 1.5 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.

- DOSAGE AND ADMINISTRATION section

The review team recommends the following dosages for pediatric patients weighing at least 1.5 kg to less than 3 kg: single loading dose of RDV 2.5 mg/kg on Day 1 via IV infusion followed by once-daily maintenance doses of RDV 1.25 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.
- 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 is limited to those events for which there was at least a possible causal relationship with the drug (i.e., adverse reactions). No adverse reactions occurred in Cohorts 5-7, so this information will not be described.

Laboratory data from GS-US-540-5823 will be displayed (see above Section 8).

- USE IN SPECIFIC POPULATIONS section

The data that support expanding the indication to encompass pediatric patients weighing at least 1.5 kg to less than 3 kg was described (see above Sections 5, 7, and 8).

- CLINICAL PHARMACOLOGY section:

The population pharmacokinetic data and clinical trial pharmacokinetic data that support expanding the indication to encompass pediatric patients weighing at least 1.5 kg to less than 3 kg was described (see above Section 5).

- CLINICAL STUDIES section:

Using a similar format as sNDA-11 (action date April 25, 2022), descriptive outcome analyses will be displayed (see above Section 7).

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

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

Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

The final study report for GS-US-540-5823 was submitted to fulfill PREA PMRs 3919-1 and 4220-1, issued in October 22, 2020 approval and January 21, 2022 supplement approval, respectively:

- PMR 3919-1: Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response to remdesivir in pediatric subjects from birth to less than 18 years of age including neonates, with coronavirus disease 2019 (COVID-19).
- PMR 4220-1: Conduct a study to evaluate the safety, tolerability, and pharmacokinetics of remdesivir in non-hospitalized pediatric subjects from birth to less than 12 years of age with coronavirus disease 2019 (COVID-19). A dedicated outpatient pediatric study is not required if pharmacokinetics and safety can be obtained from the ongoing trial in hospitalized pediatric population.

The Agency concluded that PMR 3919-1 and PMR 4220-1 were fulfilled.

New Clinical Virology PMR

Conduct a nonclinical virology study 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 that are 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: nsp10 A32V + nsp14 T31I (combined)

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 (Cohorts 5-7)

Was a list of clinical investigators provided:	Yes X	No _ (Request list from Applicant)
Total number of investigators identified: 39 Overall: 6 Principal Investigators, 33 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)
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.

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

/s/

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