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

Application Type	Supplemental New Drug Application (sNDA), S-11
Application Number(s)	214787
Priority or Standard	Priority
Submit Date(s)	November 30, 2021
Received Date(s)	November 30, 2021
PDUFA Goal Date	May 30, 2022
Division/Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)	Division of Antivirals Yodit Belew, MD, Deputy Director (Acting) Kimberly Struble, PharmD, CDTL Kirk Chan-Tack, MD, Medical Officer Division of Infectious Disease Pharmacology /Office of Clinical Pharmacology/Office of Translational Sciences Mario Sampson, PharmD, Clinical Pharmacology Reviewer Justin Earp, PhD, Pharmacometrics Reviewer Vikram Arya, PhD, Associate Director for Therapeutic Review
Review Completion Date	April 11, 2022
Established Name	Remdesivir (RDV)
(Proposed) Trade Name	Veklury®
Applicant	Gilead Sciences, Inc.
Formulation(s)	Lyophilized formulation for injection, 100 mg Solution formulation for injection, 5 mg/mL
Dosing Regimen	Single intravenous (IV) loading dose of remdesivir 5 mg/kg on Day 1, followed by once-daily maintenance doses of RDV 2.5 mg/kg from Day 2 via IV infusion. The treatment duration depends upon the patient population, is unchanged from the currently approved label: • The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation (IMV) and/or extracorporeal membrane oxygenation (ECMO) is 10 days. • The recommended treatment duration for hospitalized patients not requiring IMV and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days. • The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

Applicant Proposed Indication(s)/Population(s)	Treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are: • Hospitalized, or • Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are: • Hospitalized, or • Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Remdesivir (RDV) is an intravenous (IV) antiviral drug approved for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:
• Hospitalized, or
• Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

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

COVID-19 is a potentially serious or life-threatening disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. Globally, according to the World Health Organization, 485,243,022 confirmed cases of COVID-19 have been reported, including 6,137,553 deaths as of March 30, 2022. In the United States, according to the Centers for Disease Control and Prevention, 79,904,464 confirmed cases of COVID-19 have been reported, including 977,495 deaths as of March 30, 2022. RDV is currently the only approved treatment for COVID-19.

In this supplemental new drug application (sNDA), the Applicant's proposed indication is treatment of adults and pediatric patients (28 days and older and weighing at least 3 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:
• Hospitalized, or
• Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

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

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

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

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

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

The overall benefit-risk profile of RDV is favorable to support extending the indicated population to include pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:
• Hospitalized, or
• Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

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

<u>Hospitalized patients:</u>
The treatment course of RDV should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made.
• The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation (IMV) and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
• The recommended treatment duration for hospitalized patients not requiring IMV and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.

<u>Non-hospitalized patients:</u>
The treatment course of RDV should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.
• The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td>Analysis of Condition</td><td>• Coronavirus disease 2019 (COVID-19) is a potentially serious or life-threatening disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 can cause severe disease which can result in pneumonia, respiratory failure, multi-organ failure, and death.
• Globally, 485,243,022 confirmed cases of COVID-19 have been reported as of March 30, 2022, including 79,904,464 people in the United States (US).
• Globally, 6,137,553 deaths due to COVID-19 have been reported as of March 30, 2022, including 977,495 deaths in the US.</td><td>The ongoing COVID-19 pandemic is a significant and ongoing public health concern, one that affects a large population in the United States and worldwide. When infected with SARS-CoV-2, patients can experience symptoms that are severe, debilitating, and can be fatal.</td></tr>
<tr><td>Current Treatment Options</td><td>• RDV is currently the only approved treatment for COVID-19. The current RDV approval encompasses pediatric patients 12 years of age and older and weighing at least 40 kg.
• The following products are authorized for emergency use for the treatment of COVID-19 in the following hospitalized patient populations:
<table>
<tr><th>Hospitalized Patient Population</th><th>EUA</th></tr>
<tr><td>Pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age and weighing at least 3.5 kg with positive results of direct SARS-CoV-2 viral testing and who are hospitalized</td><td>Remdesivir</td></tr>
<tr><td>Hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)</td><td>Baricitinib</td></tr>
<tr><td>Adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO</td><td>Tocilizumab</td></tr>
</table>
• The following products are authorized for emergency use for the treatment of mild-to moderate COVID-19 in the following nonhospitalized patient populations:</td><td>An unmet medical need exists for effective antiviral regimens for pediatric patients with COVID-19, including younger ages/lower weights.</td></tr>
</table>

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the Omicron BA.2 sub-variant. • Due to the mortality and severe morbidity associated with COVID-19, there is an urgent need to develop effective treatments.	
Benefit	• The efficacy of RDV was assessed in three Phase 3 clinical trials in hospitalized patients and one Phase 3 clinical trial in non-hospitalized patients who are at high risk for progression to severe COVID-19, including hospitalization or death. • Despite the inherent limitations of its small sample size and single-arm, open-label design, GS-US-540-5823 provided supportive evidence for the efficacy of RDV in pediatric patients hospitalized with COVID-19. A total of 32 subjects (60%) were discharged alive by Day 10, and a total of 44 subjects (83%) were discharged alive by Day 30. Three subjects (6%) died during the study.	Based on the totality of the data, including extrapolation of efficacy from the four Phase 3 clinical trials in the approved label, and the pharmacokinetic/pharmacodynamic and safety data from GS-US-540-5823, it is reasonable to extend the indication to include the pediatric population 28 days and older and weighing at least 3 kg to less than 40 kg, with positive results of direct SARS-CoV-2 viral testing, who are: • Hospitalized, or • Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. RDV fills an important unmet medical need for pediatric patients with COVID-19, including 28 days and older and weighing at least 3 kg to less than 40 kg.
Risk	• No major safety issues were encountered during this review. • ALT increased (6%) was the most commonly reported adverse drug reaction (ADR) reported in GS-US-540-5823. All other ADRs occurred in less than 5% of subjects.	The overall safety profile in the GS-US-540-5823 pediatric population is consistent with the known safety profile of RDV as observed from adult and adolescent subjects in the hospitalized and non-hospitalized Phase 3 clinical trials.
Risk Management	• No significant safety signals were identified in this trial conducted in pediatric patients.	Safety concerns associated with RDV are adequately addressed in product labeling.

2. Background

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

The predominant signs and symptoms of COVID-19 include fever, cough, and shortness of breath. Clinical severity ranges widely, from asymptomatic infection to critical illness. Mild illness is defined by the presence of symptoms without shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as the presence of symptoms and evidence of lower respiratory tract disease by clinical examination or chest imaging accompanied by oxygen saturation ≥94% on room air. Severe and critical illness are defined as worsening pulmonary status requiring hospitalization, supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation (IMV), or extra-corporeal membrane oxygenation (ECMO). Risk factors for hospitalization include, but are not limited to, age > 65 years, hypertension, obesity, diabetes, cardiovascular disease, and chronic lung disease.[3]

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

RDV, a direct acting antiviral drug that inhibits viral RNA synthesis, is currently the only approved antiviral treatment regimen for COVID-19 caused by SARS-CoV-2 virus. Approved on October 22, 2020, RDV is indicated for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. The original NDA approval was based on efficacy and safety data from three Phase 3 randomized clinical trials in hospitalized adult subjects with COVID-19 treated with 5-10 days of RDV. The initial indication included patients 12 years of age and older and weighing at least 40 kg. The inclusion of this pediatric sub-population in the indication was supported by the following: 1) the systemic exposure and clearance of drugs are generally similar in adolescent

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

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

On January 21, 2022, the indication was expanded to include treatment of COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. The outpatient sNDA approval was based on efficacy and safety data from a Phase 3 randomized, double-blind, placebo-controlled clinical trial evaluating 3 days of RDV in non-hospitalized adults and adolescents with mild-to-moderate COVID-19 who are at high risk of progression to severe COVID-19, including hospitalization or death.[7] The inclusion of this pediatric sub-population (12 years of age and older and weighing at least 40 kg) in the non-hospitalized indication is based on extrapolation of pediatric efficacy from the aforementioned adequate and well-controlled study.

In this supplemental new drug application (sNDA), the Applicant's proposes to expand the indication to encompass treatment of pediatric patients (28 days and older and weighing at least 3 kg to less than 40 kg) with positive results of direct SARS-CoV-2 viral testing, who are:
• Hospitalized, or
• Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

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

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

3. Product Quality

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

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

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

4. Nonclinical Pharmacology/Toxicology

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

5. Clinical Pharmacology

Background

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

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

Exposure comparison in pediatric subjects vs adults

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

Exposure comparison in pediatric subjects vs adults: enrolled subjects

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

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

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

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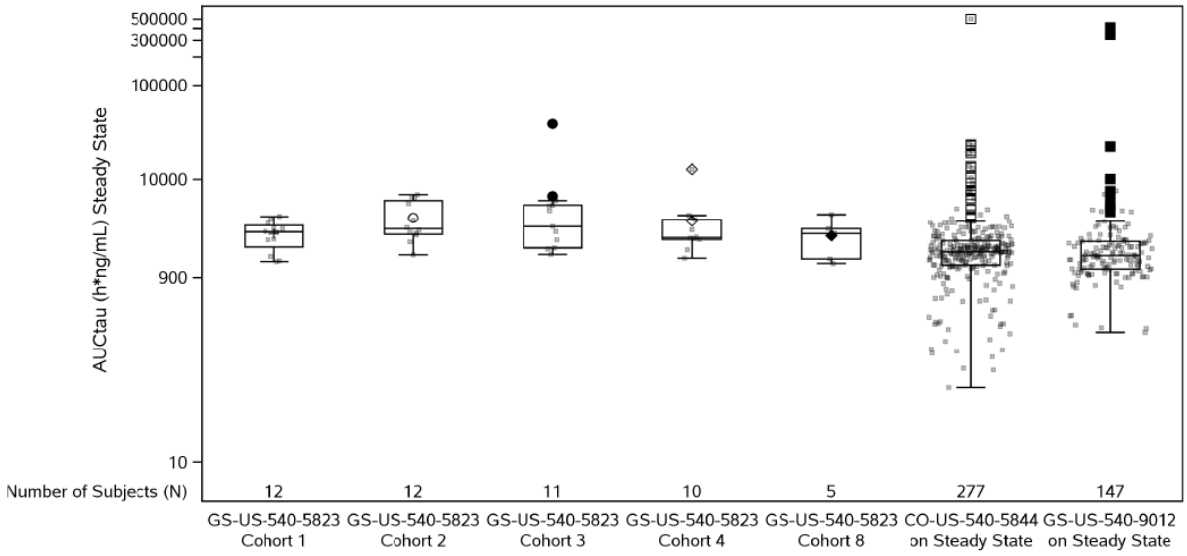
Table 1. RDV and metabolite exposures in enrolled pediatric subjects (study 5823) and adults (study 9012)

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

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

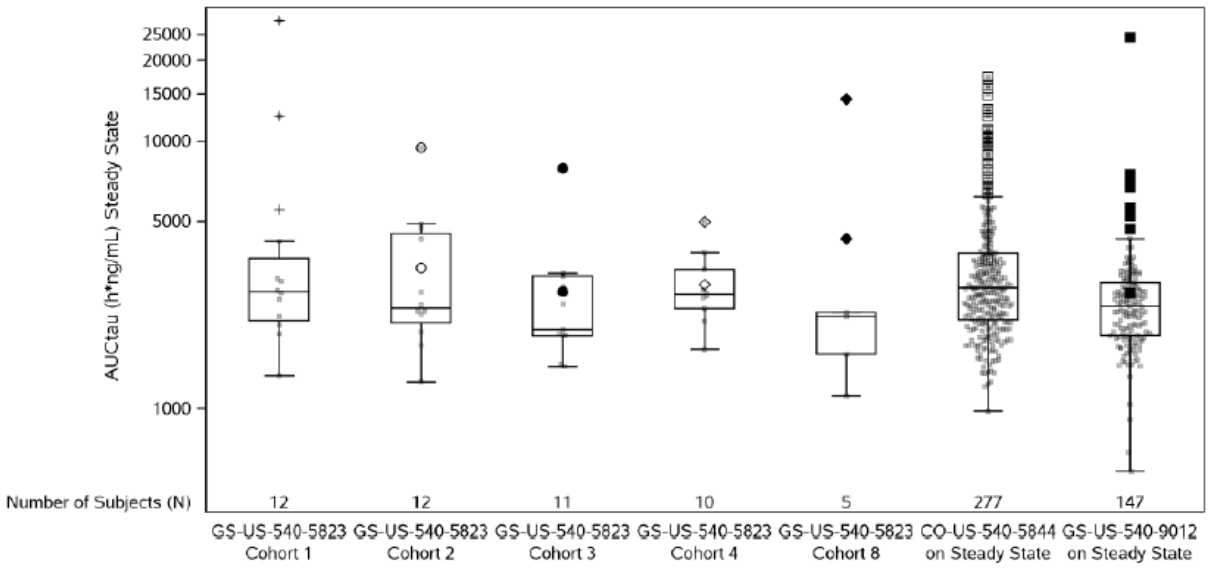
Figure 1. RDV AUC in enrolled pediatric subjects (study 5823) and adults (study 9012)



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

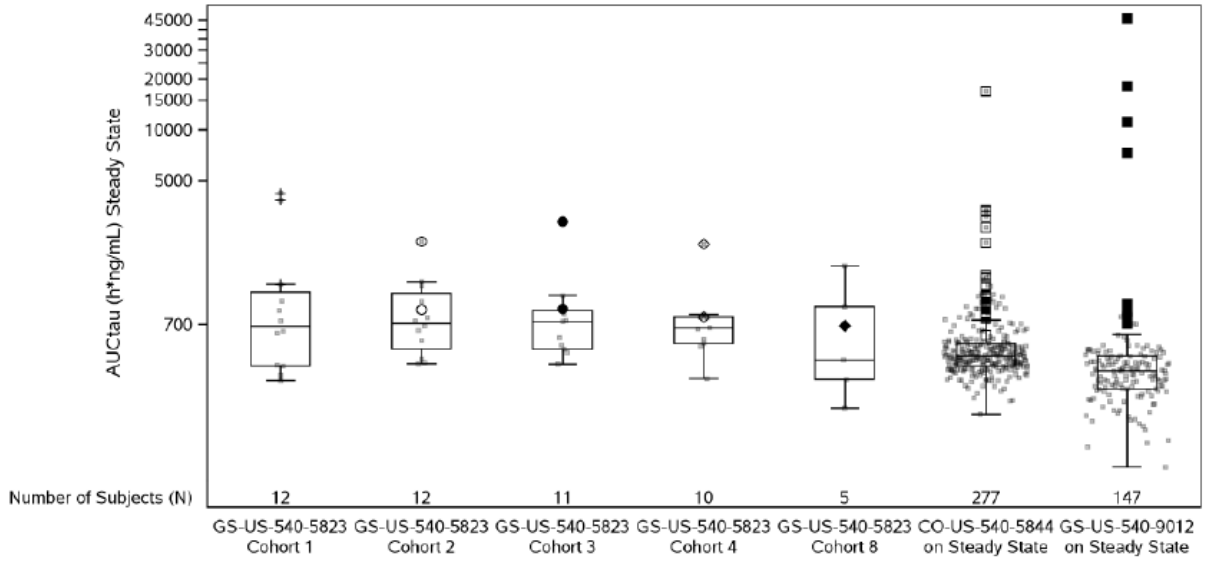
Source: Clinical Pharmacology Summary, p18. Note adult study 5844 was not included in the FDA analysis; however, is included in Figures 1-3 as provided by the Applicant.

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



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

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



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

Exposure comparison in pediatric subjects vs adults: virtual population

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

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

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

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

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

Source: NDA 214787 SDN 247, p17.

Study GS-US-540-5823 summary

Methods

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

Table 3. Cohort age and weight definitions and dosing for study 5823

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

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

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

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

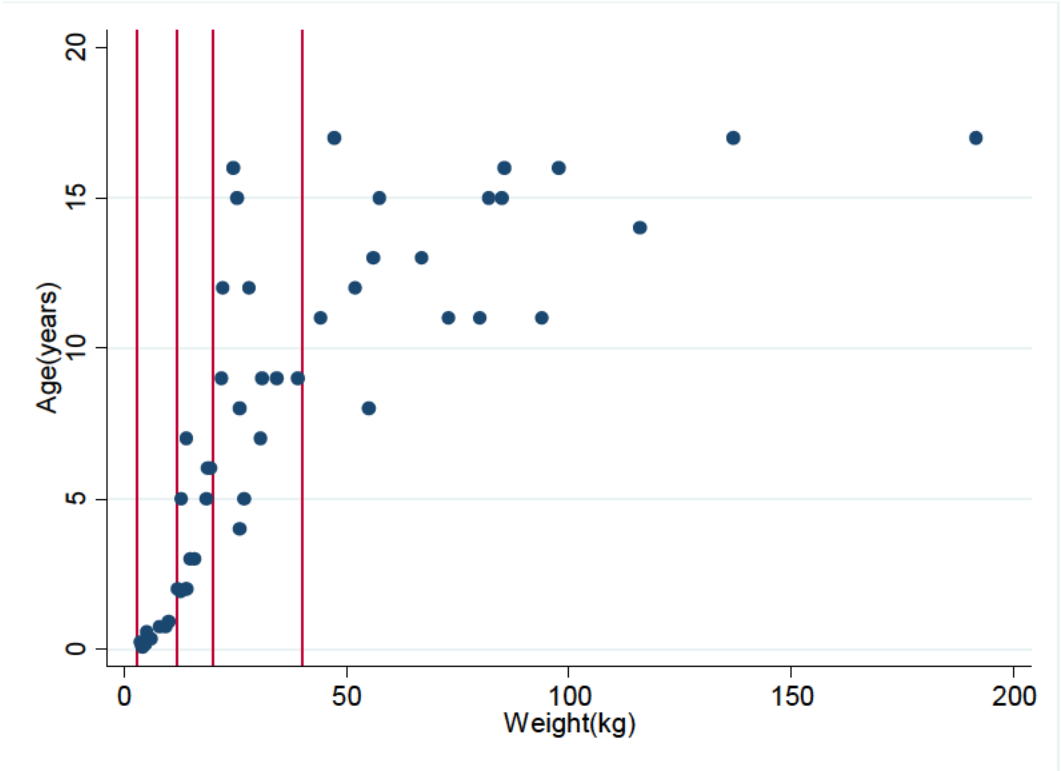
Prohibited concomitant medications included unapproved COVID-19 treatments with direct antiviral effect such as LPV/RTV, chloroquine, interferon, etc. in addition to P-gp inducers (e.g. rifampin, rifabutin, carbamazepine, phenytoin or herbal medications).

Results

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

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

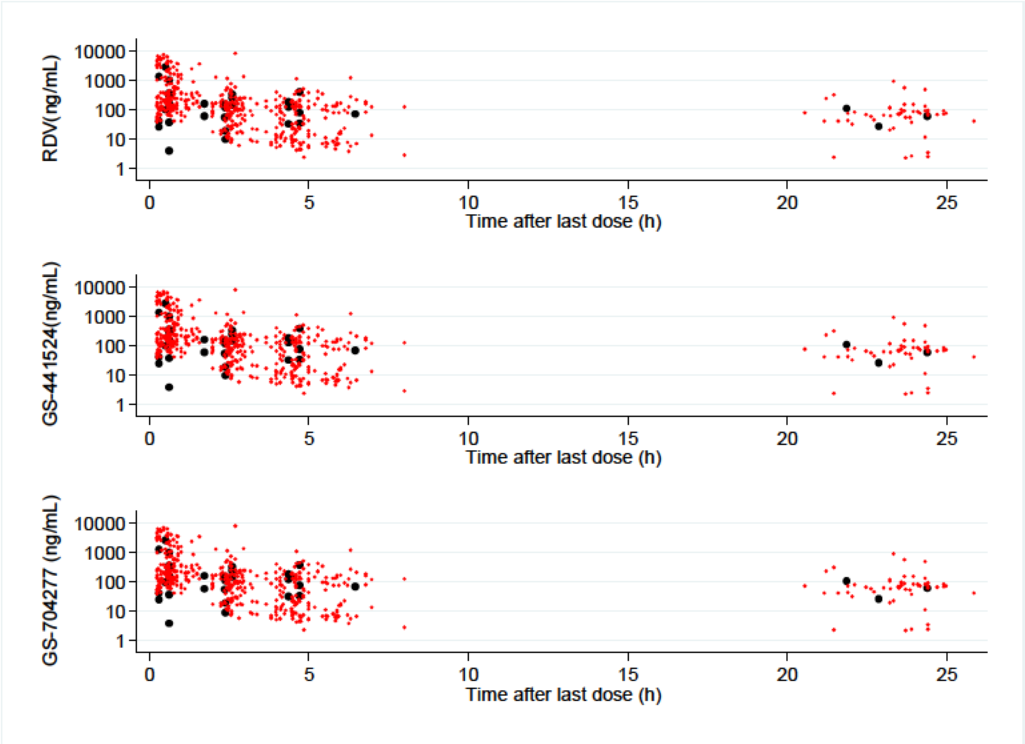
Figure 4. Baseline age vs weight among pediatric subjects in study 5823 with at least one PK sample with a detectable concentration



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

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

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



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

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

Population PK models

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

Table 4. Initial popPK model parameters

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

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

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

Source: RDV new NDA popPK report, p35.

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

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

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

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

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

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

Table 5. Final model parameters for the revised models

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

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

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

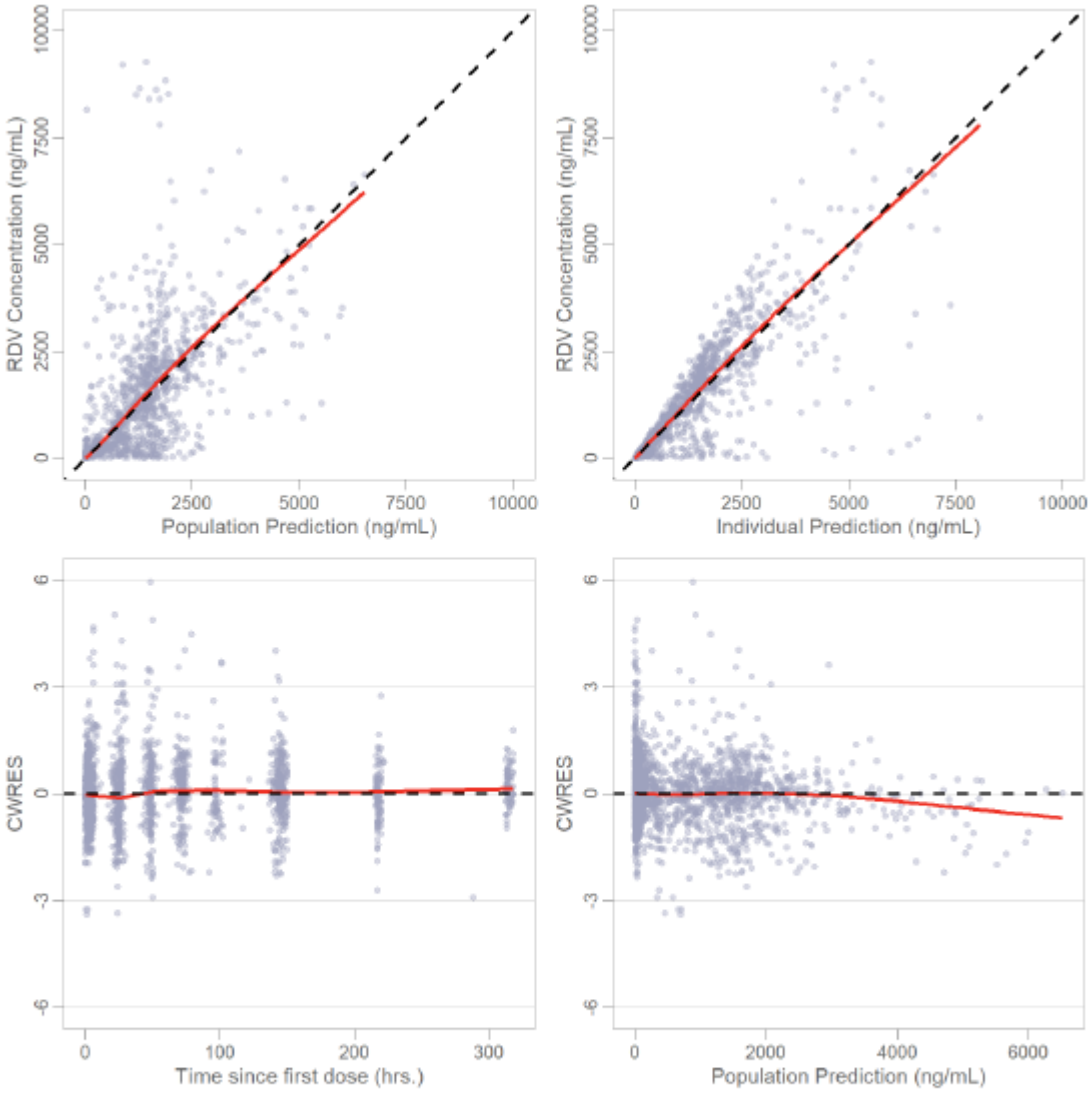
OFV–remdesivir = 25248.242, OFV–GS-704277= 20924.235, OFV–GS-441524 = 26379.828

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

Source: PPK-Diagnostics.html

Source: RDV popPK report for revised models, p60.

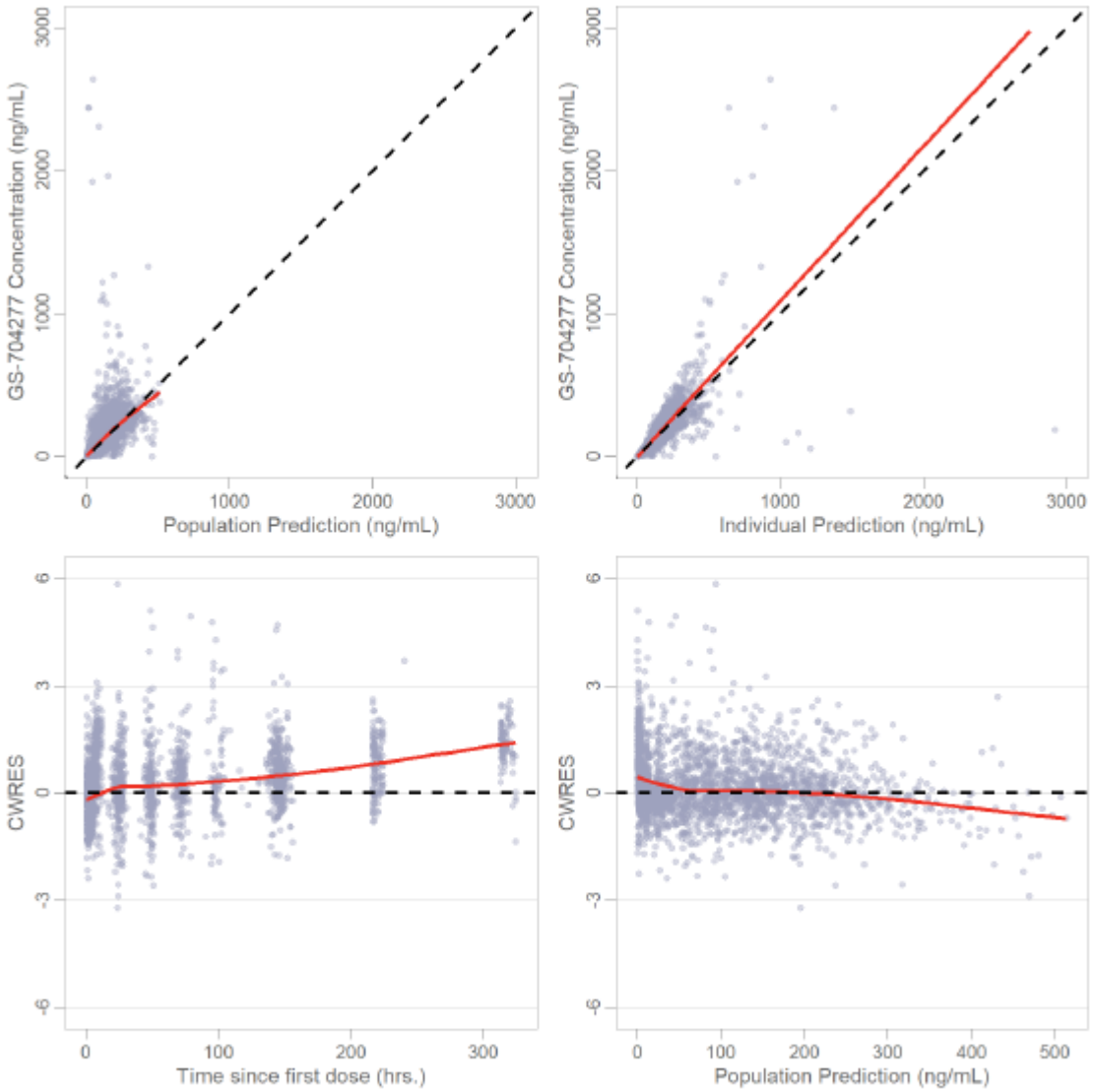
Figure 6. RDV final model GOF plots



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

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

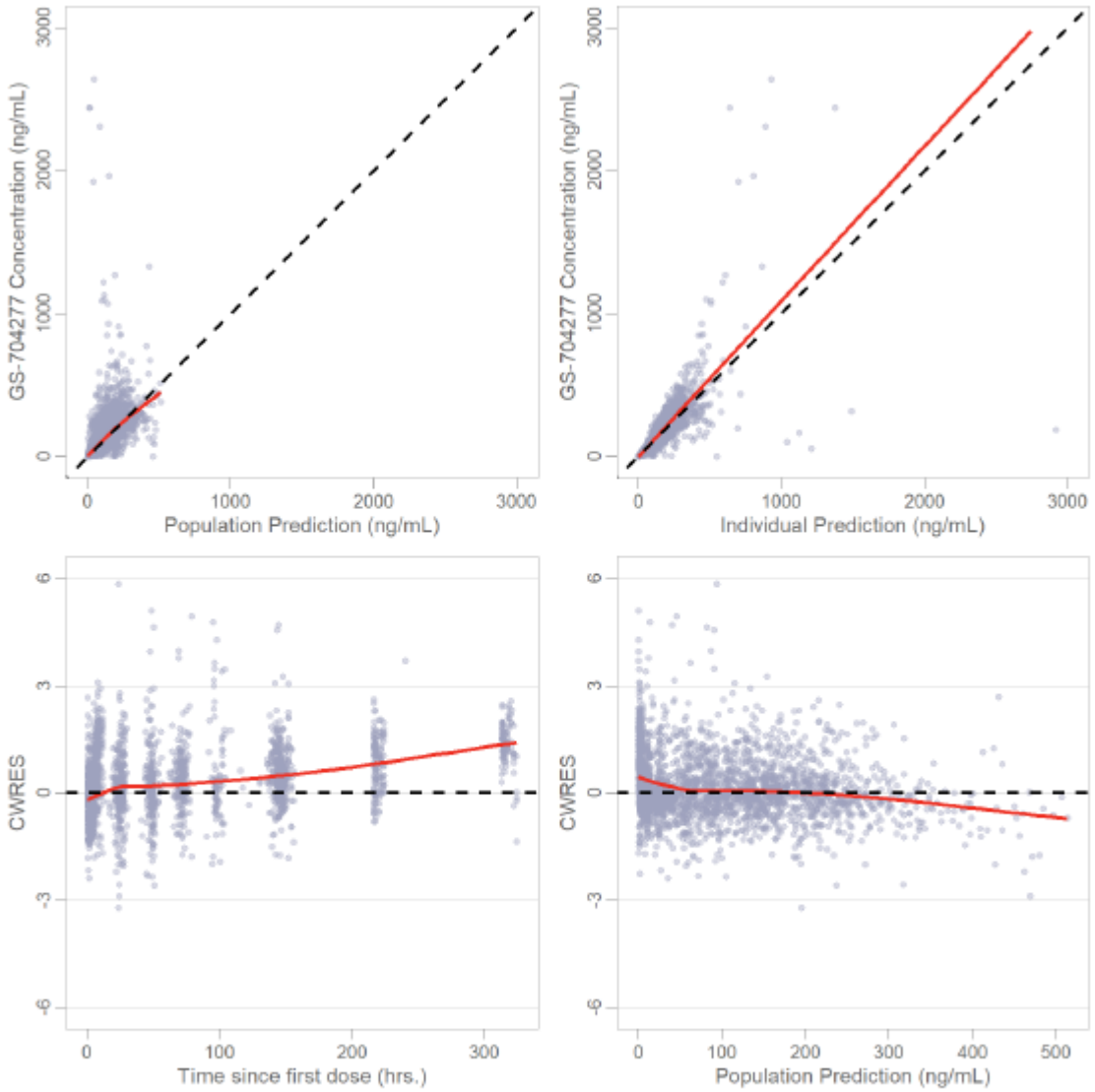
Figure 7. GS-441524 final model GOF plots



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

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

Figure 8. GS-704277 final model GOF plots



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

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

Table 6. Shrinkage values for the revised popPK models

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

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

Source: RDV popPK report for revised models, p171.

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

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

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

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

6. Clinical Virology

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

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

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

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

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

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

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

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

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

7. Clinical – Descriptive Efficacy

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

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

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

Study design, baseline characteristics, and key efficacy results

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

Table 8: GS-US-540-5823

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

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

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

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

Routine clinical tests

In GS-US-540-5823, routine clinical evaluation and laboratory testing occurred at pre-specified intervals: Screening; Day 1 (Baseline); Days 2-10, or until discharge, whichever comes earlier; Follow-Up on Day 30 (±5). The frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurement, physical examinations, and standard laboratory safety tests. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

Study Endpoints

The primary endpoints are as follows:

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

The secondary endpoints are as follows:

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

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

Statistical Analysis Plan (SAP)

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

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

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

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

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

(b) (4)

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

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

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

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

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

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

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

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

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

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

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

Table 9: Subject Disposition, FAS

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

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

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

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

Baseline demographics

The table below summarizes baseline demographics.

Table 10: Demographics, FAS

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

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

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

Baseline disease characteristics

The table below summarizes baseline disease characteristics.

Table 11: Baseline disease characteristics, FAS

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

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

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

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

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

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

Treatment duration

The table below summarizes the treatment duration.

Table 12: Treatment Duration, SAS

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

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

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

Hospital discharge

The table below summarizes clinical outcomes for hospitalization.

Table 13: Proportion of subjects who were hospitalized, FAS

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

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

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

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

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

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

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

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

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

Change from baseline in clinical status

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

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

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

Source: ADEFF dataset,

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

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

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

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

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

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

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

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

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

Conclusions on effectiveness

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

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

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

Based on the totality of data, the review team supports expanding the indication to encompass treatment of pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg with positive results of direct SARS-CoV-2 viral testing, who are:
• Hospitalized, or
• Not hospitalized and have mild-to-moderate COVID-19 and are at high risk for progression to severe COVID-19, including hospitalization or death.

8. Safety

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

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

The safety database is considered adequate to assess the safety of RDV for the proposed indication, dosage regimen, duration of treatment, and patient population – pediatric patients 28 days and older and weighing at least 3 kg to less than 40 kg with positive results of direct SARS-CoV-2 viral testing, who are:
• Hospitalized, or
• Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Nontreatment-emergent deaths

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

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

Serious Adverse Events (SAEs)

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

Table 17: SAEs

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

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

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

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

Discontinuations due to AEs

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

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

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

Significant AEs

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

Adverse events are treatment-emergent and regardless of causality. Adverse drug reactions are treatment-emergent and at least possibly related as assessed by the investigator. Some of these events were also considered SAEs; hence, there is some overlap between events reported in this section and in the SAE subsection (above).

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

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

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

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

Treatment-emergent AEs (TEAEs)

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

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

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

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

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

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

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

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

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

The following table summarizes graded chemistry and urinalysis results.

Table 19: Chemistry and Urinalysis Laboratory Results, All Grade

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

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

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

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

Reviewer Comment: Nonclinical studies in rats and cynomolgus monkeys identified the kidney as the target organ of toxicity, mainly driven by the sulfobutylether-β-cyclodextrin sodium salt (SBECD) excipient. Similar effects were seen in humans in Study GS-US-540-5823 with Grade 3/4 creatinine clearance decreased (18%) and Grade 3/4 increased creatinine (10%) observed in this hospitalized trial in pediatric subjects. None of these renal laboratory abnormalities resulted in RDV discontinuation. These laboratory abnormalities were also noted in the hospitalized trials in adults but occurred at similar or slightly higher rates in the PBO or SOC groups compared to the RDV group.

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

There were no Grade 3/4 bilirubin elevations.

The following table summarizes graded hematology and coagulation results.

Table 20: Hematology and Coagulation Laboratory Results, All Grade

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

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

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

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

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

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

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

Submission-specific safety issues

Nephrotoxicity:

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

There were no renal ADRs.

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

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

Hepatotoxicity:

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

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

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

Hypersensitivity Reactions

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

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

Hemorrhagic events:

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

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

Rash events

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

Overall Assessment: Based on these findings, no additional labeling regarding rash events is warranted at this time. Any potential signals of serious rash events associated with RDV use will be closely monitored in the postmarketing setting.

Conclusions on safety

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

9. Advisory Committee Meeting

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

10. Pediatrics

The Applicant submitted an initial Pediatric Study Plan (iPSP) for RDV in advance of the original NDA submission. The document was reviewed by the Division of Pediatrics and Maternal Health (DPMH), the Division of Antivirals, and the Pediatric Review Committee (PeRC). The Applicant proposed to use an extrapolation approach leveraging PK, safety, and efficacy data, wherever applicable, in adults and adolescents to guide dosing and assessment of RDV efficacy in the pediatric population. The Agency concurred that SARS-CoV-2 is expected to respond similarly to RDV in pediatric patients as it does in adults, and therefore pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, supplemented with information obtained in pediatric patients, such as PK and safety from Study GS-US-540-5823. The Applicant requested a deferral of required pediatric assessments in pediatric patients' birth to <12 years of age, until data from Study GS-US-540-5823 (including the preliminary PK data) are available and have been reviewed by the Agency. The Division agreed with this proposal. The deferral request was presented to the PeRC, and the PeRC agreed with the Applicant's proposal and the Division's recommendations. The Agency's recommendations for revisions were conveyed to the Applicant. The Applicant accepted the Agency's recommendations, and the Agency issued a formal notice of agreement in July 2020.

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

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

The Applicant is planning a (b) (4)

11. Other Relevant Regulatory Issues

- *Financial disclosures*

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

- *Other Good Clinical Practice (GCP) issues*

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

- *Office of Scientific Investigations (OSI) audits*

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

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

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

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

- *Office of Surveillance and Epidemiology (OSE)*

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

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

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

12. Labeling

Prescribing Information

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

- INDICATIONS AND USAGE section:

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

The revised indication is treatment of adults and pediatric patients (28 days and older and weighing at least 3 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:
• Hospitalized, or
• Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

- DOSAGE AND ADMINISTRATION section

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

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

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

- ADVERSE REACTIONS section:

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

Adverse reactions leading to RDV discontinuation will be displayed.

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

- USE IN SPECIFIC POPULATIONS section

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

- CLINICAL PHARMACOLOGY section:

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

- CLINICAL STUDIES section:

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

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

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

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

Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

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

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

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

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

14. Recommended Comments to the Applicant

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

Appendix 1 – Financial Disclosure

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

Covered Clinical Study (Name and/or Number): GS-US-540-5823

Was a list of clinical investigators provided:	Yes X	No __ (Request list from Applicant)
Total number of investigators identified: 126 Overall: 19 Principal Investigators, 107 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/ arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes	No __ (Request explanation from Applicant)

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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