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Considerations and Challenges in the Remdesivir COVID-19 Pediatric Development Program

The Journal of Clinical Pharmacology
2022, 0(0) 1–7

DOI: 10.1002/jcph.2158

Kirk Chan-Tack, MD[1], Mario Sampson, PharmD[2], Justin Earp, PhD[2], Vikram Arya, PhD, FCP[2], Lynne Yao, MD[3], John Alexander, MD, MPH[3], Ethan Hausman, MD[3], Yodit Belew, MD[1], Debra Birnkrant, MD[1], and Kimberly Struble, PharmD[1]

Abstract

The US Food and Drug Administration is committed to the development of effective antiviral regimens for pediatric patients with coronavirus disease 2019 (COVID-19), including infants and neonates. On April 25, 2022, the approved indication of remdesivir (RDV) was expanded to include pediatric patients 28 days and older and weighing at least 3 kg with positive results of direct severe acute respiratory syndrome coronavirus 2 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.

Given the similar course of COVID-19 in adults and pediatric patients, the approval of RDV for use in pediatric patients is supported by the safety and efficacy data from adequate and well-controlled phase 3 trials in adults and adolescents; and by the safety and pharmacokinetic data from a single-arm, open-label, phase 2/3 pediatric clinical trial of 53 pediatric patients at least 28 days of age and weighing at least 3 kg with confirmed severe acute respiratory syndrome coronavirus 2 infection and mild, moderate, or severe COVID-19. At the time of the April 25, 2022, approval action, the US Food and Drug Administration also revoked the emergency use authorization for RDV that previously covered this pediatric population. This article summarizes key issues and regulatory considerations involved in the RDV COVID-19 pediatric development program, including the evolution of the emergency use authorization issued for RDV as results from registrational studies became available, and discusses lessons learned.

Keywords

antiviral, COVID-19, pediatrics, physiologically based pharmacokinetic modeling

Coronavirus disease 2019 (COVID-19) is a potentially serious or life-threatening disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the onset of the pandemic, the US Food and Drug Administration (FDA) has been committed to expediting the development and availability of potential COVID-19 treatments.

Overview of the Differences Between an Emergency Use Authorization and an FDA Approval

Under section 564 of the federal Food, Drug & Cosmetic Act, the FDA may, pursuant to a determination and declaration by the Health and Human Services secretary, authorize an unapproved product or unapproved uses of an approved product for emergency use.

In issuing an emergency use authorization (EUA), the FDA must determine, among other things, that based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by a chemical, biological, radiological, or nuclear agent; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and

[1]Division of Antivirals, Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA
[2]Division of Infectious Disease Pharmacology, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA
[3]Division of Pediatric and Maternal Health, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA

Submitted for publication 6 July 2022; accepted 13 September 2022.

Corresponding Author:
Kirk Chan-Tack, MD, Division of Antivirals, Office of Infectious Diseases, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993
Email: Kirk.Chan-Tack@fda.hhs.gov

Table 1. Key EUA[2] and NDA (or sNDA)[3–6] Milestones for RDV

Date	EUA	NDA (or sNDA)
May 1, 2020	Treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease	
August 28, 2020	Treatment of suspected or laboratory-confirmed COVID-19 in hospitalized adult and pediatric patients	
October 22, 2020	Treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or hospitalized pediatric patients aged <12 y weighing at least 3.5 kg	Adults and pediatric patients (aged ≥12 y and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization
January 21, 2022	Treatment of COVID-19 in pediatric patients weighing 3.5 kg to <40 kg or pediatric patients aged <12 y weighing at least 3.5 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	Treatment of COVID-19 in adults and pediatric patients (aged ≥12 y and weighing at least 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
April 25, 2022	*EUA revoked because the pediatric population in the EUA is now covered by the approved label*	Treatment of COVID-19 in adults and pediatric patients (aged ≥28 days and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are • Hospitalized, or • Not hospitalized and have mild to moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death

COVID-19, coronavirus disease 2019; EUA, emergency use authorization; NDA, New Drug Application; RDV, remdesivir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sNDA, supplemental New Drug Application.

potential risks for the product; and that there are no adequate, approved, and available alternatives.

An EUA is not the same as FDA approval or licensure. The "may be effective" standard for EUAs provides for a different level of evidence than the "effectiveness" standard that FDA uses for product approvals. EUAs remain authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the authorized product under section 564(b)(1) of the Food, Drug & Cosmetic Act, 21 U.S.C. § 360bbb3(b)(1), unless the declaration is terminated or the authorization is revoked sooner.[1]

Factors That Impacted the Timeline of Key Regulatory Milestones for Remdesivir

Remdesivir (RDV) is a nucleotide prodrug that is intracellularly metabolized into its active form GS-443902, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis. Table 1 summarizes key regulatory milestones for RDV.[2–6]

RDV has been termed a *repurposed* drug because, before being evaluated for COVID-19, it was studied for other indications including Ebola virus disease (EVD).[7] The RDV COVID-19 development program represents a successful example of drug repurposing, that is, leveraging the available data (including clinical safety and pharmacokinetic [PK] data and nonclinical safety data) to help expedite drug development when exploring new uses for an existing drug (whether investigational or approved). Leveraging the existing data facilitated rapid initiation of clinical trials and reduced the time to pediatric clinical trial initiation and inclusion of pediatric dosing recommendations in labeling. Importantly, to leverage adult data for pediatric dosing with confidence, the FDA reviewed the available data and concluded that the effectiveness of RDV in pediatric patients can be extrapolated from adequate and well-controlled studies in adults because the disease process from acute COVID-19 is considered to be generally similar between adults and children. Additionally, SARS-CoV-2 is expected to respond similarly to RDV regardless of the host (ie, adults or children). As a result, the pediatric patient population covered under the EUA evolved as results from registrational studies became available (Table 1), culminating in dosing recommendations for pediatric patients aged 28 days and older and weighing at least 3 kg being included in the approved labeling 1.5 years after the initial approval in October 2020. The intravenous (IV) route of administration for RDV likely also facilitated the expedited drug development, inclusive of younger pediatric patients, as RDV could be used for all ages without additional, age-appropriate formulation development, whereas, for oral products, the development of a suitable pediatric formulation adds to the overall development timelines.

Methods

The following subsections describe the data that led to RDV approval for COVID-19 in children and discuss challenges and key considerations in the FDA's decision-making process.

Results and Discussion

RDV Dose Selection for Treatment of COVID-19

The antiviral activity data demonstrated in animal models with SARS-CoV[8] and Middle East respiratory syndrome coronavirus[9] (related coronaviruses that are similar to SARS-CoV-2), cell culture activity against SARS-CoV-2,[10] and results from the phase 1 studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505 formed the basis for selecting the dose and duration studied in phase 3 randomized clinical trials (RCTs) Adaptive COVID-19 Treatment Trial-1 (ACTT-1), GS-US-540-5773, and GS-US-540-5774.[3,11–13] Additional safety data were available from patients with EVD.[7] Of note, the only approved dosage form of RDV is IV.

Based on a review of the available data on the similarity in the disease course of COVID-19 in adults and pediatric patients, and the expected similar response to RDV, the FDA determined an RDV pediatric dosing regimen based on the collective information available. In addition to leveraging efficacy data from adults and collecting safety data in pediatrics, model-informed drug development–based quantitative approaches were effectively integrated into the development program to inform and assess the appropriateness of the proposed RDV pediatric dosing regimen. Physiologically based pharmacokinetic (PBPK) modeling of PK data from healthy adults was used to derive pediatric doses.[3] The proposed pediatric dosing regimen aimed to achieve daily exposures of RDV comparable to adults, while considering the risk : benefit profile for the renally eliminated metabolite, GS-441524, which may accumulate in pediatric patients with immature clearance pathways. PBPK models (SimCYP, version 16; SimCYP, Sheffield, UK) were developed to model adult RDV and GS-441524 exposure and predict pediatric exposure based on age-dependent physiologic changes (eg, organ volume/function, blood flow, etc). Of note, these simulations did not account for the impact of SARS-CoV-2 infection on the PK of RDV and GS-441524 because no information was available on this issue at the start of the pandemic. These initial PBPK simulations showed that:

- For pediatric patients weighing ≥40 kg, the adult dosing regimen (single loading dose of 200 mg IV on day 1 followed by 100 mg IV once daily for 9 days) was expected to maintain exposures of both RDV and the nucleoside analog GS-441524 at or below those previously observed to be generally well tolerated in the 14-day multiple-dose study in healthy adults (N = 24, GS-US-399-1954).
- For pediatric patients weighing <40 kg, a weight-based dosing regimen (single loading dose of 5 mg/kg IV on day 1 followed by 2.5 mg/kg IV once daily for 9 days) was expected to maintain RDV exposure comparable to that observed in adults while limiting the exposure of GS-441524 in very young children.

This modeling was done before the PALM RCT, which evaluated RDV (among other agents) for the treatment of EVD in adults and pediatric patients of any age; the above dosing regimen was used for pediatric patients in the PALM RCT.[7] The dosing regimen was also used by the sponsor (Gilead Sciences, Inc.) in their compassionate use program to treat pediatric cases of COVID-19.[14,15]

At the time of the May 1, 2020, EUA issuance (based on a review of topline data from ACTT-1[11] and GS-US-540-5773[12]), the PBPK model incorporated additional healthy volunteer data, and this information was described in the EUA Fact Sheet for Health Care Providers.[2] These updated PBPK simulations showed that:

- For pediatric patients weighing ≥40 kg, the adult dosing regimen (single loading dose of 200 mg IV on day 1 followed by 100 mg IV once daily for 9 days) was expected to maintain exposures of both RDV and GS-441524 generally within the expected adult steady-state exposure range following administration of the adult COVID-19 therapeutic dosage regimen in healthy volunteers (N = 20, GS-US-399-5505).
- For pediatric patients weighing <40 kg, a weight-based dosing regimen (single loading dose of 5 mg/kg IV on day 1 followed by 2.5 mg/kg IV once daily for 9 days) was expected to maintain RDV exposure comparable to that observed in adults while limiting the exposure of GS-441524 in very young children.

Data Supporting Approval of RDV in Pediatric Patients Aged ≥12 Years and Weighing ≥40 Kg

Data from the ACTT-1, GS-US-540-5773, and GS-US-540-5774 phase 3 RCTs provided substantial evidence of effectiveness and demonstration of safety to support approval of RDV for treatment of adults and pediatric patients aged ≥12 years and weighing ≥40 kg hospitalized for COVID-19.[11–13] In ACTT-1, RDV was superior to placebo (PBO) in reducing the time to recovery (median days to recovery, RDV 10 days vs PBO 15 days) in 1062 hospitalized subjects with mild, moderate, and severe COVID-19.[11] In GS-US-540-5773, treatment with 5-day and 10-day regimens of

RDV resulted in similar clinical status on day 14 in 397 hospitalized subjects with severe COVID-19.[12] In GS-US-540-5774, treatment with 5 days of RDV resulted in significantly greater odds of improved clinical status on day 11 compared to standard of care (SOC) in 584 hospitalized subjects with moderate COVID-19. The odds of improvement in clinical status did not differ significantly between the 10-day RDV group and the standard-of-care group. Cumulatively, these data supported RDV for the treatment of COVID-19 in hospitalized subjects, irrespective of oxygenation status or oxygen requirement.[13]

Although adolescents (aged 12–17) were eligible for enrollment in GS-US-540-5773 and GS-US-540-5774, only 1 adolescent subject was enrolled (in GS-US-540-5774). Furthermore, no PK data were collected in ACTT-1, GS-US-540-5773, and GS-US-540-5774.[11–13] Because these RCTs were initiated early in the pandemic, the study sponsors and investigators concluded that PK would not be collected due to logistical challenges and potential risks to health care providers. To support dosing in pediatric subjects aged ≥12 years and weighing ≥40 kg, 2 PK modeling approaches were used to predict plasma exposures of RDV and metabolites in this population:

- PBPK: A mechanistic approach that incorporates age-dependent physiology and drug physicochemical properties. PBPK model development (SimCYP, versions 17 and 18) was based on the adult phase 1 exposure data in healthy volunteers administered a 200-mg loading dose of RDV IV over 0.5 hours on day 1, then 100-mg daily maintenance doses of RDV IV over 0.5 hours starting on day 2 and continuing through day 5 or day 10 (GS-US-399-5505).
- Population PK (popPK): A compartmental model fit to observed PK data in healthy adults (n = 123). Median (min, max) body weight was 77 kg (53, 101) in this data set. The popPK model includes body weight. Allometric scaling was used to simulate exposures in patients weighing ≥40 kg.

Therefore, the October 22, 2020, initial approval and indication included patients aged ≥12 years and weighing ≥40 kg through extrapolation of efficacy from adults receiving the same dose of RDV as proposed for adolescent patients. As summarized previously, extrapolation of efficacy was acceptable because adult and pediatric populations with moderate to severe COVID-19 generally display similar symptoms, and virologic response to an antiviral drug such as RDV is expected to be similar in adults and pediatric patients.[16–20]

In summary, the inclusion of this pediatric subpopulation was supported by the following: (1) The systemic exposure and clearance of drugs are generally similar in adolescent and adult patients after accounting for the effect of body size on PK[21]; (2) using PBPK modeling and popPK modeling, the recommended dosing regimen was expected to result in comparable steady-state plasma exposures of RDV and metabolites in patients aged ≥12 years and weighing ≥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 >50 kg; and (4) 39 pediatric patients aged ≥12 years and weighing ≥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 was to be collected in patients aged 12–17 years in the ongoing RDV pediatric trial.[22,23]

Based on the results from GS-US-540-9012, on January 21, 2022, the FDA expanded the approved indication for RDV to include its use in adults and pediatric patients (aged ≥12 years and weighing ≥40 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.[4,24] In GS-US-540-9012, treatment with RDV for 3 days was superior to PBO for the primary end point, which is a composite of COVID-19–related hospitalization or all-cause mortality through day 28. Of the 562 nonhospitalized subjects who are at high risk for progression to severe COVID-19, 2 (1%) subjects in the RDV group experienced COVID-19–related hospitalizations compared to 15 (5%) subjects in the PBO group (hazard ratio, 0.13 [95%CI, 0.03–0.59]; $P = .008$). No deaths were observed through day 28 in either group. The inclusion of pediatric patients aged ≥12 years and weighing ≥40 kg in the nonhospitalized indication was based on extrapolation of efficacy from the aforementioned adequate and well-controlled study.

PK data were collected at selected study sites in GS-US-540-9012. Although no PK data were collected in the 8 adolescent subjects (RDV [n = 3], PBO [n = 5]) in GS-US-540-9012, simulations from the PBPK model indicate that in pediatric patients ≥40 kg, administration of the proposed regimen results in exposures of RDV and its metabolites, GS-704277 and GS-441524, generally within the range of exposures observed in adults, therefore supporting extrapolation of efficacy observed in adults to pediatric patients weighing ≥40 kg.

Data Supporting Approval of RDV in Pediatric Patients Aged ≥28 Days and Weighing at Least 3 kg to <40 kg

Although COVID-19 is believed to be sufficiently similar between adults and younger pediatric patients

Table 2. GS-US-540-5823 (Submitted in the Sponsor's Initial Pediatric Study Plan)

Cohort	No.	Description	Dosing
1	12	Aged ≥12 y to <18 y and weight ≥40 kg	200 mg IV on day 1 followed by 100 mg IV once daily for up to 10 days[a]
2	12	Aged ≥28 days to <18 y and weight ≥20 kg to <40 kg	5 mg/kg IV on day 1 followed by 2.5 mg/kg IV once daily for up to 10 days[a]
3	12	Aged ≥28 days to <18 y and weight ≥12 kg to <20 kg	
4	12	Aged ≥28 days to <18 y and weight ≥3 kg to <12 kg	
5[b]	4	Aged ≥14 days to <28 days, gestational age >37 wks, and weight at screening ≥2.5 kg	
6[b]	[d,e]	Aged 0 days to <14 days, gestational age >37 wks, and birth weight ≥2.5 kg	Dose, TBD; duration is for up to 10 days[a]
7[c]	[d,e]	Aged 0 days to <56 days, gestational age ≤37 weeks, and birth weight ≥1.5 kg	Dose, TBD; duration is for up to 10 days[a]
8	5[e]	Aged <12 years and weight ≥40 kg	200 mg IV on day 1 followed by 100 mg IV once daily for up to 10 days[a]

RDV, remdesivir; TBD, to be determined.
[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.

(including neonates), and response to antiviral treatment is expected to be similar, 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 New Drug Application (NDA), the initial indication for RDV did not include pediatric patients aged <12 years or weighing <40 kg. The FDA concluded that refinement of the PBPK model would require PK data from COVID-19–infected patients, which were not available at that time. In the interim, access to RDV for pediatric patients aged <12 years and weighing <40 kg was continued through EUA. Pharmacokinetic data from a dedicated pediatric trial would be essential to provide support for approval and an indication in pediatric patients aged <12 years of age or weighing <40 kg. Pediatric study GS-US-540-5823 (ClinicalTrials.gov Identifier: NCT04431453) was initiated in July 2020, that is, within 4 months after the onset of the pandemic (Table 2).[22] The available nonclinical data and the demonstrated benefit in adults with COVID-19 supported initiating the pediatric trial. The proposed pediatric development plan comprised a broad range of pediatric patients, including the following: (1) preterm neonates and infants aged 0 days to <56 days; (2) term neonates aged 0 days to <28 days; and (3) pediatric patients aged ≥28 days to <18 years. Patients in all age ranges were to be enrolled in parallel, except for preterm neonates and infants aged <56 days and a subset of term neonates.

GS-US-540-5823 is an ongoing Phase 2/3, single-arm, open-label study to investigate the safety, tolerability, PK, and efficacy of RDV in pediatric subjects from birth to <18 years of age who are hospitalized with laboratory-confirmed COVID-19 (Table 2).[22] The FDA's review of the PK and safety data from completed cohorts 1–4 and cohort 8 concluded that RDV and metabolite exposures in pediatric subjects are within the range of RDV exposures deemed safe and effective in adults at the approved dose(s). Further, the overall safety profile in the GS-US-540-5823 pediatric population is consistent with the known safety profile of RDV.[5]

As discussed above, at the time of the original NDA, popPK models of RDV, GS-441524, and GS-704277 incorporated PK data from 3 intensive PK studies in healthy adults (GS-US-399-1812, GS-US-399-1954, GS-US-399-5505).[3] In the recent pediatric supplemental NDA, the revised popPK models incorporated PK data from 3 healthy adult studies (GS-US-399-1812, GS-US-399-1954, GS-US-399-5505), GS-US-540-9012 in adult outpatients with COVID-19, and GS-US-540-5823 in hospitalized pediatric subjects with COVID-19. The revised popPK models provided data that helped meet the evidentiary standard to support approval of RDV dosing in pediatric patients aged ≥28 days and weighing at least 3 kg to <40 kg.[5] The efficacy of the RDV dose in pediatric patients aged ≥28 days and weighing at least 3 kg to <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[5]:

- Extrapolation of efficacy from adequate and well-controlled studies in adults (3 phase 3 RCTs in hospitalized adults of varying disease severity).
- Extrapolation of efficacy from an adequate and well-controlled phase 3 RCT in nonhospitalized adults and adolescents with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19, including hospitalization or death.

- PK data from pediatric patients enrolled in GS-US-540-5823, which was compared to the adult PK data.
- Safety and pharmacodynamic data from pediatric patients.

Conclusions

The April 25, 2022, expansion of the approved indication of RDV to include its use in pediatric patients aged ≥28 days and weighing at least 3 kg marked an important step toward addressing the needs of pediatric patients with COVID-19, including younger ages and lower weights.[5,6] The use of pediatric extrapolation, including leveraging data from the prior RDV development program, facilitated rapid initiation of COVID-19 phase 3 RCTs and helped expedite initiation of the registrational pediatric clinical trial. Close collaboration occurred between the FDA and the sponsor to reach agreement on the initial pediatric study plan and pediatric trial protocol as quickly as possible to avoid delays in the initiation of said trial. The pediatric clinical trial began within 4 months after the pandemic was declared and adult phase 3 RCTs initiated.

Despite numerous challenges of the ongoing COVID-19 pandemic, the marketing applications (original NDA 214787 and supplemental NDAs) submitted over the past 2 years have resulted in the first approved COVID-19 treatment for pediatric patients aged <12 years. Cohorts 5–7 from GS-US-540-5823 (Table 2) are ongoing to support labeling for pediatric patients aged <28 days and weighing <3 kg.[22] For pediatric patients aged <28 days and/or weighing <3 kg who are not eligible or able to participate in GS-US-540-5823, the sponsor will continue to support single-patient emergency investigational new drugs.[25]

Since the onset of the pandemic, the FDA has been committed to expediting the development and availability of potential COVID-19 treatments. The EUA for RDV, based on phase 3 clinical trial data, and subsequent revisions as additional data became available, has helped provide patients with timely access to new therapies where appropriate, while simultaneously supporting research to further evaluate safety and efficacy as development programs move toward marketing applications with the ultimate goal of FDA approval/licensure.[26,27]

While approval of the first COVID-19 treatment for pediatric patients aged <12 years of age is an important public health milestone, the only approved dosage formulation of RDV is IV and the logistical considerations associated with administering multiple-day infusion regimens, especially in nonhospitalized patients, are acknowledged. Continued therapeutic development, including of oral agents, is ongoing with the goal of providing additional approved treatment options for pediatric patients with COVID-19, including infants and neonates.

Acknowledgments

The data discussed in this article were submitted in the NDA and supplemental NDAs for remdesivir. The authors thank the patients who participated in these trials and their families. The authors acknowledge Manuela Grimstein and Yuching Yang for their contributions during drug development.

Author Contributions

All authors contributed extensively in the regulatory review, independent analysis of submitted data, and FDA approval of remdesivir. K.C.T., M.S., Y.B., and K.S. drafted the initial manuscript and reviewed and revised the manuscript. J.E., V.A., L.Y., J.A., E.H., and D.B. reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

Funding Information

This work did not receive any funding.

Data Availability Statement

Individual participant data that underlie the results reported in this article, after deidentification (text, tables).

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