

Physiologically-Based Pharmacokinetic Modeling of Remdesivir and Its Metabolites to Support Dose Selection for the Treatment of Pediatric Patients With COVID-19

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Severe coronavirus disease 2019 (COVID-19) disease, including multisystem inflammatory syndrome, has been reported in children. This report summarizes development of a remdesivir physiologically-based pharmacokinetic (PBPK) model that accurately describes observed adult remdesivir and metabolites exposure and predicts pediatric remdesivir and metabolites exposure. The adult PBPK model was applied to predict pediatric remdesivir and metabolites steady-state exposures using the Pediatric Population Model in SimCYP and incorporated the relevant physiologic and mechanistic information. Model development was based on adult phase I exposure data in healthy volunteers who were administered a 200-mg loading dose of remdesivir intravenous (IV) over 0.5 hours on Day 1, then 100-mg daily maintenance doses of IV over 0.5 hours starting on Day 2 and continuing through Days 5 or 10. Simulations indicated that use of the adult therapeutic remdesivir dosage regimen (200-mg loading dose on Day 1 then 100-mg daily maintenance dose starting on Day 2) in pediatric patients ≥ 40 kg and a weight-based remdesivir dosage regimen (5-mg/kg loading dose on Day 1 then 2.5-mg/kg daily maintenance dose starting on Day 2) in pediatric patients weighing 2.5 to < 40 kg is predicted to maintain therapeutic exposures of remdesivir and its metabolites. The comprehensive PBPK model described in this report supported remdesivir dosing in planned pediatric clinical studies and dosing in the emergency use authorization and pediatric compassionate use programs that were initiated to support remdesivir as a treatment option during the pandemic.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Severe coronavirus disease 2019 (COVID-19) disease, including multisystem inflammatory syndrome, has been reported in children. Remdesivir dosing regimen specific to pediatric patients is required.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study addressed what the optimal weight-based remdesivir dosing regimen is for treatment of pediatric patients with COVID-19 infection.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Physiologically-based pharmacokinetic modeling indicated that use of the adult dosage regimen in pediatric

patients ≥ 40 kg and a weight-based regimen in pediatric patients weighing 2.5 to < 40 kg is predicted to maintain exposures of remdesivir and metabolites generally within the expected adults steady-state exposure range following an adult therapeutic dosage regimen.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The recommended remdesivir weight-based dosing regimens are expected to provide safe and efficacious exposures of remdesivir and metabolites in pediatric patients with COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO)

on March 11, 2020.^{1,2} As of December 2020, there have been over 67 million infections worldwide with greater than 890,000 deaths.³ The incidence of SARS CoV-2 infection in children is unknown; however, the proportion of COVID-19 diagnoses in

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children appears to be much lower than adults. In the United States, only 1.7% of laboratory-confirmed Centers for Disease Control and Prevention (CDC)-reported COVID-19 cases were in individuals < 18 years of age.⁴ Although severe disease and fatalities have been reported, generally the disease course appears to be milder in children with fewer showing symptoms of fever, cough, or shortness of breath compared with adults.^{4,5} A higher likelihood of intensive care unit admission and disease severity has been noted in children < 1 year of age.⁶⁻⁸ Recent reports from Europe and North America show clusters of children presenting with features of multisystem inflammation, with the majority having cardiac and gastrointestinal system involvement and some displaying features of Kawasaki's disease and/or toxic shock syndrome associated with recent SARS CoV-2 infection.⁹⁻¹³ In response, the WHO developed a preliminary case definition and case report form for multisystem inflammatory syndrome in children.^{7,11,14} Treatment of multisystem inflammatory syndrome in children includes supportive therapy for pneumonia, respiratory failure, and sepsis, as well as immune modulators such as intravenous immunoglobulin and corticosteroids.^{11,12,13,15}

Remdesivir (GS-5734, Veklury), a monophosphoramidate prodrug that potently inhibits SARS-CoV-2 RNA polymerases *in vitro*, is being investigated for the treatment of COVID-19. Remdesivir has been granted approvals in several countries for use in treatment of adults and pediatric patients ≥ 12 years old and weighing ≥ 40 kg requiring hospitalization for COVID-19.¹⁶⁻¹⁸ The pediatric dosing strategy for remdesivir was supported by physiologically-based pharmacokinetic (PBPK) modeling. Generally, in pediatric drug development, pharmacokinetic and pharmacodynamic (PK/PD) modeling and simulation are a vital first step in defining risk:benefit of a new medication. These models minimize the need for unnecessary clinical trials while maximizing the use of available data by exploring PK, efficacy, and safety under various physiological conditions, bridging gaps from adults, if any, and aiding in efficient trial design.¹⁹⁻²² Pediatric doses have traditionally been scaled from adult doses using the two most common methods for translating adult to pediatric PK: PBPK modeling and allometric scaling (including population PK-based approaches).^{23,24} PBPK models provide more reliable predictions of plasma drug concentrations as they account for enzyme ontogeny and age-related changes in organ development and function.^{19,25} Allometric scaling does not incorporate drug-specific disposition mechanisms but instead simply extrapolates exposure based on body size and a fixed exponent (generally 0.75), potentially leading to large overpredictions of metabolic plasma clearance in very young children as their enzymes are immature.^{19,26} This report summarizes selection of an optimal weight-based remdesivir dosing regimen, informed by a PBPK model, for treatment of COVID-19-infected pediatric patients as young as full-term neonates born of adequate weight (> 2.5 kg).

METHODS

Remdesivir elimination

The PK properties of remdesivir have been described elsewhere (R. Humeniuk, A. Mathias, B.J. Kirby, J.D. Lutz, H. Cao, A. Osinusi, *et al.*,

unpublished data).²⁷ *In vitro* assessments suggest that remdesivir is primarily metabolized (~ 80% of total metabolism) in the liver by carboxylesterase 1 (CES1), and to a lesser extent (~ 10% of total metabolism each), by cathepsin A (CatA) and cytochrome P450 3A4 (CYP3A4). Approximately 10% of remdesivir clearance is via renal excretion of unchanged drug (R. Humeniuk, A. Mathias, B.J. Kirby, J.D. Lutz, H. Cao, A. Osinusi, *et al.* unpublished data).

Figure 1 depicts the intracellular metabolic pathway of remdesivir. Briefly, remdesivir is rapidly metabolized via esterase to an intermediate metabolite, GS-704277. Subsequent cleavage of the phosphoramidate bond results in the formation of the nucleoside analog monophosphate that is further phosphorylated to the pharmacologically active nucleoside triphosphate, GS-443902, which selectively inhibits viral RNA polymerases but not host RNA or DNA polymerases (data on file).²⁸⁻³⁰ It is believed that GS-443902 is also the species responsible for pharmacological activity *in vivo*, but this has not been conclusively shown, and a GS-443902 exposure-efficacy relationship has not been established. Because of this, it is assumed that remdesivir plasma exposure is a reasonable surrogate for the pharmacologically active species. Dephosphorylation of the nucleoside analog monophosphate (MP) results in the formation of the nucleoside analog, GS-441524, that is not efficiently rephosphorylated.³⁰ Remdesivir and its metabolites (GS-441524 and GS-704277) are detectable in plasma; however, GS-441524-MP and GS-443902 are not observable in the plasma (data on file).²⁷

Remdesivir model development and drug-dependent parameters

The remdesivir PBPK model was developed to describe the plasma concentration-time profile for remdesivir, GS-704277, and GS-441524 using the commercially available software, SimCYP (version 18, Certara USA, Princeton, NJ).³¹

The dose, physicochemical properties, and PK parameters that were used for the final remdesivir adult PBPK model are listed in **Table 1**. One limitation in the model and current understanding of remdesivir is that the PK of remdesivir and metabolites in patients with COVID-19 is currently unknown. Because of this, model development was based on the adult phase I exposure data in healthy volunteers ($N = 28$) who were administered a 200-mg loading dose of remdesivir intravenous (IV) over 0.5 hours on Day 1, then 100-mg daily maintenance doses of remdesivir IV over 0.5 hours starting on Day 2 and continuing through Days 5 or 10 (R. Humeniuk, A. Mathias, B.J. Kirby, J.D. Lutz, H. Cao, A. Osinusi, *et al.*, unpublished data). Observed, calculated, or assumed model parameters were incorporated as follows. (i) Physicochemical properties (molecular weight, octanol-to-water partition ratio, and acid dissociation constant) of remdesivir and metabolites were calculated based on chemical structure (ChemAxon, Budapest, Hungary). (ii) The fraction unbound in plasma values and blood/plasma ratio values used for remdesivir, GS-704277, and GS-441524 were from observed *in vitro* data. Full and minimal PBPK models were employed to predict distribution; estimation of tissue partition ratio scalars were required to accurately recover half-life. (iii) *In vitro* data indicate that ~ 80%, 10%, and 10% of remdesivir metabolism is via CES1, CatA, and CYP3A, respectively (R. Humeniuk, A. Mathias, B.J. Kirby, J.D. Lutz, H. Cao, A. Osinusi, *et al.*, unpublished data). The intrinsic clearance for these pathways was proportionally scaled to recover observed remdesivir area under the concentration-time curve (AUC). (iv) Unlike with CES1, the ontogenic functions (i.e., age-dependent expression levels relative to adults) of CatA and specific phosphoramidases or nucleotidases are not well established, and SimCYP does not provide tissue-specific expression levels for these enzymes. Furthermore, the enzymes responsible for intracellular phosphoramidate cleavage and phosphorylation (**Figure 1**) are currently unknown. With these limitations, these metabolic processes were incorporated into the PBPK model as nonspecific esterase processes (i.e., the "User ES" option in SimCYP) that are scaled by organ size, but without ontogenic changes, when performing the

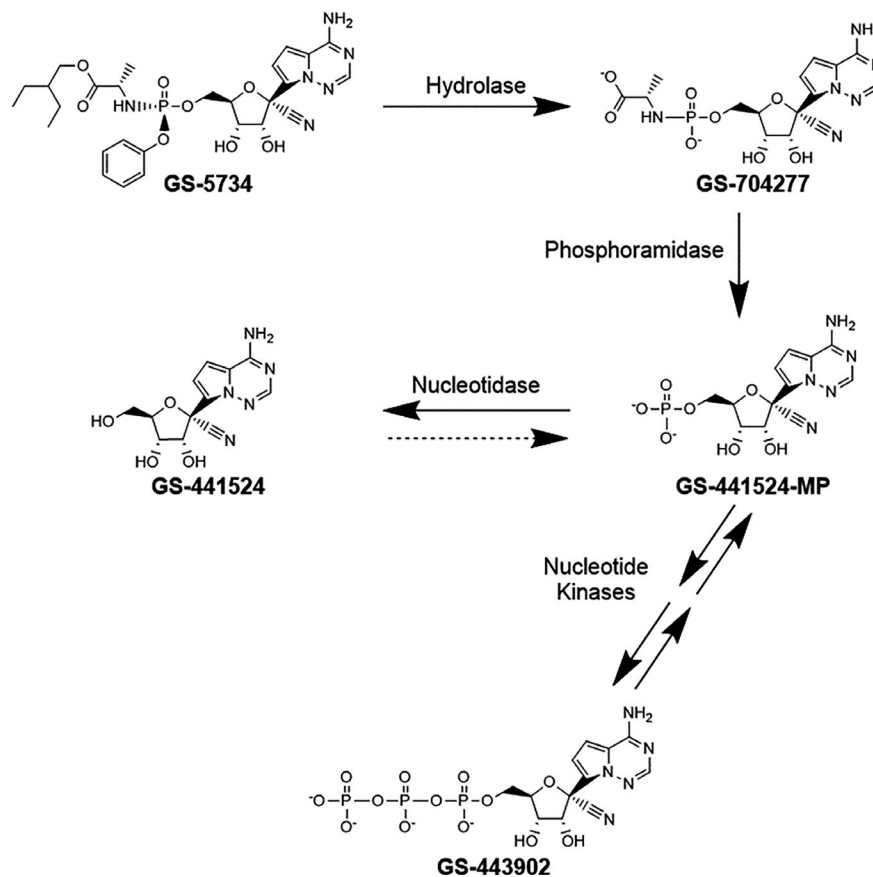


Figure 1 Proposed intracellular metabolic pathway of remdesivir (GS-5734).

pediatric exposure predictions. (v) Remdesivir is transported by organic anion transporting polypeptide 1B1 (OATP1B1) and P-glycoprotein (P-gp). As remdesivir exhibits moderate-to-high hepatic extraction due to high hydrolase activity, changes in the activity of OATP1B1 or P-gp (e.g., after coadministration with a transporter modulator or age-dependent changes in transporter expression) after IV administration of remdesivir are not expected to result in significant changes in remdesivir exposure. As such, OATP1B1 or P-gp transport of remdesivir was not incorporated into the PBPK model, and the omission of these mechanisms are not expected to materially affect predicted pediatric remdesivir exposure. (vi) Remdesivir, GS-704277, and GS-441524 undergo renal elimination (8.7%, 4.3%, and 35.4% of remdesivir dose, respectively) and observed *in vivo* renal clearance values were incorporated into the model.²⁷ Additional human hepatocyte clearance of GS-441524 was estimated to accurately recover GS-441524 AUC.

Adult PBPK dose prediction. The SimCYP default “Healthy Volunteers” population model was used for simulating adult phase I remdesivir and metabolites exposure. Ten trials of $N = 28$ patients per trial (default age range of 20–50 years and equal proportion of males and females) were simulated to match the observed phase I study. The adult observed and PBPK predicted remdesivir and metabolites plasma concentration vs. time profiles are depicted in **Figure 2**. The developed PBPK model adequately captures the plasma concentration data observed in the adult healthy volunteer population ($N = 28$). All median observed/predicted AUC over the dosing interval (AUC_{τ}), maximum plasma drug concentration (C_{\max}), and trough plasma drug concentration (C_{τ}) (only measurable for GS-441524) ratios were within the range of 0.70–1.10 (**Supplementary Section 2**). Adult PK after daily IV

remdesivir maintenance dosing through Day 10 were not predicted in the final simulations because preliminary modeling confirmed that steady state for remdesivir and metabolites is reached by Day 5. Overall, the developed remdesivir PBPK model accurately describes observed adult remdesivir and metabolites exposure, providing increased confidence that this model will accurately predict pediatric remdesivir and metabolites exposure.

Pediatric PBPK dose prediction. The adult PBPK model was applied to predict pediatric remdesivir and metabolites maintenance dose steady-state exposure after IV administration of a remdesivir loading dose on Day 1, then a daily maintenance dose using the default Pediatric Population Model in SimCYP. This population model accounts for age-dependent changes in organ volume/size, enzyme expression, plasma protein binding, blood cell distribution, and organ blood flow.^{32,33}

For these predictions, a large simulated pediatric population was generated ($N \approx 13,000$; 0 to < 18 years; equal proportion of males and females) in SimCYP. The data set is evenly distributed by body weight (17 individuals per 0.1 kg bin; 2.5–80.1 kg range; 776 total bins).

Development of an optimal weight-based dosing regimen for remdesivir administration to pediatric patients. To construct a weight-based dosing regimen for pediatric patients, a single IV remdesivir loading dose was administered on Day 1 and then daily IV remdesivir maintenance doses were administered on Days 2 through 5. Various weight-based dose reduction strategies were explored. Ultimately, a regimen was selected that yielded an optimal maintenance of remdesivir and metabolites exposure (AUC_{τ} and C_{\max}) within a target adult exposure range for each analyte.

Table 1 Physicochemical and pharmacokinetic parameters

	Remdesivir	GS-704277	GS-441524	References
Dose used for adult PBPK model development	200 mg IV over 0.5 h on Day 1, then 100 mg IV over 0.5 h on Days 2–5 or 2–10, lyophilized formulation	—	—	32
MW	602.6	442.3	291.3	Calculated from Structure (ChemAxon)
LogP	2.01	−2.31	−1.88	
pKa (all weak acid)	10.23	3.27 2.36	12.13	
B/P Ratio	0.76	0.56	1.19	Data on file ³²
$f_{u,p}$	0.12	0.99	0.98	
Distribution Model	Full PBPK	Minimal	Minimal	—
K_p Scalar (Method 2)	0.56	3.30	12.1	Model estimated from <i>in vivo</i> data
SAC k_{in}/k_{out} (/h)	—	0.36/1.10	0.21/0.38	
CES1 S9 CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$) ^a	203	—	—	
CatA S9 CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$) ^a	22	—	—	
CYP3A HLM CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$)	69	—	—	
Generic HEP Esterase S9 CL_{int} ($\mu\text{L}/\text{min}/\text{mg}$) ^b	—	9.7	—	
Generic HEP CL_{int} ($\mu\text{L}/\text{min}/10^6$ cells)	—	—	0.45	
CL_r (L/h)	5.71	9.74	9.85	Observed ^{31,32}

Physicochemical and pharmacokinetic parameters used for development of the remdesivir, GS-704277, and GS-441524 metabolite PBPK model in adult healthy volunteers.

B/P, blood to plasma; CES1, carboxylesterase 1; CL_{int} , intrinsic clearance; CL_r , renal clearance; CYP3A, cytochrome P450 3A; $f_{u,p}$, fraction unbound in plasma; h, hour; HEP, hepatocyte; HLM, human liver microsome; K_p , plasma:tissue partition ratio; LogP, water:octanol partition ratio; min, minute; MW, molecular weight; PBPK, physiologically-based pharmacokinetic; pKa, acid dissociation constant; SAC, Single Adjusting Compartment; S9, subcellular liver fraction 9; —, not applicable.

^aCES1 and CatA mediate the hydrolysis of remdesivir and this same clearance was set as the formation clearance of GS-704277. ^bAn unidentified phosphoramidase mediates the biotransformation of GS-704277 and this same clearance was set as the formation clearance of GS-441524.

For remdesivir and metabolites, the target AUC_{τ} and C_{max} range was based on a representative range of observed exposures in adult healthy volunteers after administration of the therapeutic dosage regimen (R. Humeniuk, A. Mathias, B.J. Kirby, J.D. Lutz, H. Cao, A. Osinusi, *et al.*, unpublished data). Additionally, metabolite exposure was not to exceed exposures observed historically in healthy adult volunteers who received 150 mg remdesivir IV for 14 days.²⁷

Comparison of pediatric exposure predicted by PBPK and Allometry. Allometric scaling was performed (body weight exponent = 0.75) to predict pediatric Day 5 AUC_{τ} of remdesivir, GS-704277, and GS-441524. These exposures were directly compared with those predicted by PBPK to evaluate whether PBPK will yield similar results to more traditional methodologies for pediatric exposure prediction.

RESULTS

For patients weighing ≥ 40 kg, preliminary predictions indicated that the adult dosage regimen was considered appropriate, and as such, a loading dose of 200 mg remdesivir IV infused over 0.5 hours on Day 1, followed by daily 100-mg doses of remdesivir IV infused over 0.5 hours for 5 days was simulated for the final predictions. For patients weighing 2.5 to < 40 kg, preliminary predictions indicated that a weight-based regimen consisting of 5 mg/kg remdesivir IV infused over 0.5 hours on Day 1, then daily 2.5 mg/kg remdesivir IV infused over 0.5 hours for 5 days was simulated for the final predictions.

Model-predicted pediatric Day 5 AUC_{τ} and C_{max} of remdesivir, GS-704277, and GS-441524 are compared with adult exposures and presented in **Figure 3**, respectively. Under the proposed pediatric dosing regimen, the steady-state maintenance dose AUC_{τ} and C_{max} values for remdesivir, GS-441524, and GS-704277 were generally within the adult steady-state exposure range following the adult therapeutic dosage regimen (gray lines). Pediatric exposure after daily IV remdesivir maintenance dosing through Day 10 were not predicted in the final simulations because preliminary modeling confirmed that steady state for remdesivir and metabolites is reached by Day 5.

In the adult phase I program, daily 150 mg remdesivir IV administration over 1 hour for 14 days was generally well tolerated²⁷ and the maximum observed adult steady-state exposure (AUC_{τ} and C_{max}) of remdesivir, GS-704277, and GS-441524 in this study was considered as the upper limit of exposure to be targeted for pediatric dose selection (blue lines). Simulations indicate that the proposed pediatric dosage regimen is predicted to maintain remdesivir and metabolites exposures during maintenance dosing under this maximum steady-state exposure observed in the phase I adult program.

Comparison of pediatric exposure predicted by PBPK and allometry

To provide increased confidence in the pediatric PK predictions, the PBPK predicted remdesivir, GS-704277, and GS-441524 AUC_{τ}

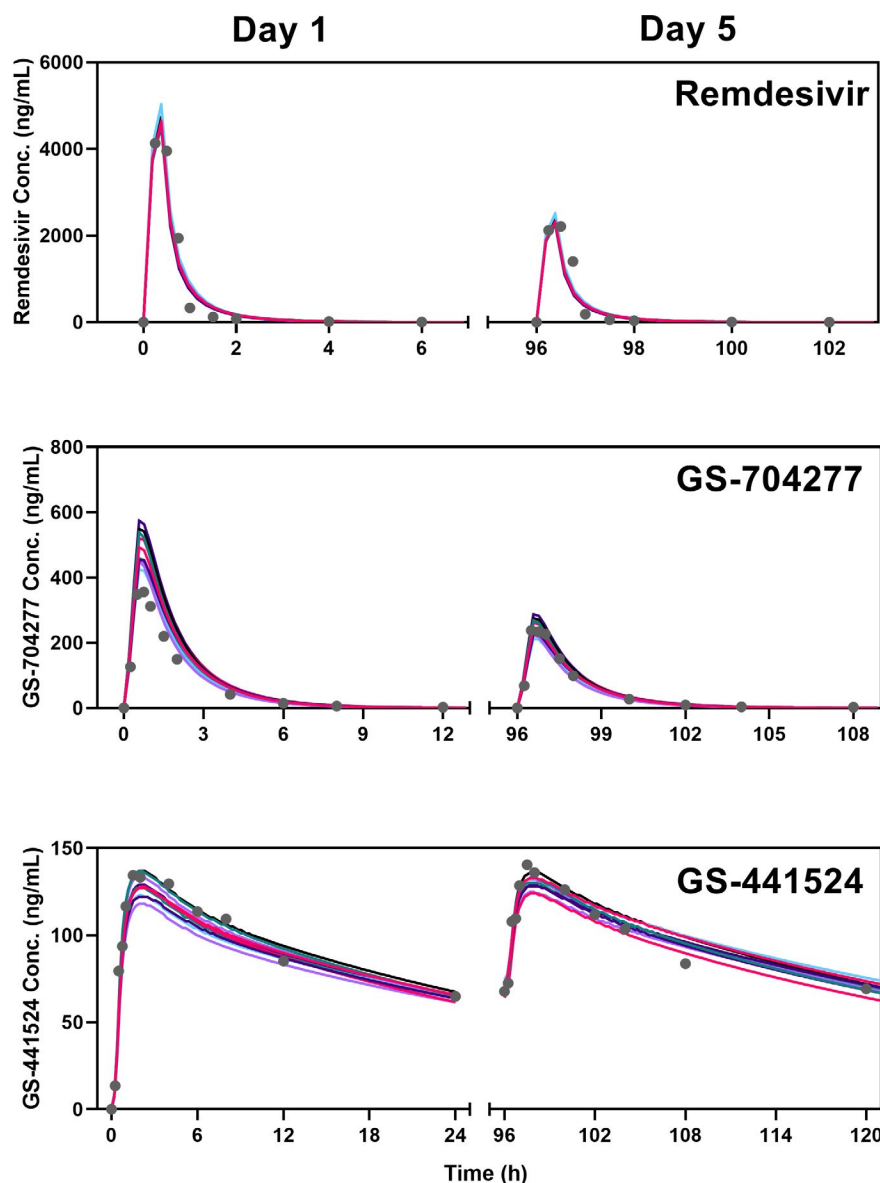


Figure 2 Observed and predicted remdesivir, GS-704277, and GS-441524 Day 1 and 5 plasma concentration vs. time after intravenous administration of a single dose of 200 mg remdesivir over 0.5 hours on Day 1, then daily 100 mg remdesivir over 0.5 hours on Days 2–5 to adult healthy volunteers. Gray dots: observed phase I mean plasma concentration profiles. The PK on Day 5 of Cohort 1 ($N = 8$) and Day 10 of Cohort 2 ($N = 20$) were combined for analysis. Colored lines: 10 simulated trial median predicted plasma concentrations of $N = 28$ healthy volunteers per trial. Conc., concentration; PK, pharmacokinetics.

were directly compared with those predicted using simple allometry. Simple allometry and PBPK model predicted Day 5 AUC_{τ} of remdesivir, GS-704277, and GS-441524 after IV administration of a loading dose (200 mg or 5 mg/kg) of remdesivir on Day 1 then a daily maintenance dose (100 mg or 2.5 mg/kg) of remdesivir on Days 2–5 to pediatric patients are shown in **Figure 4**.

The SimCYP Pediatric Population model incorporates a form of allometric scaling in that it predicts decreasing organ size (and hence, hepatic or renal clearance) as a function of decreasing weight/age based on observed pediatric demographic data.³³ As such, the finding that both methodologies predict similarly increased remdesivir, GS-704277, and GS-441524 AUC_{τ} with decreased body weight in children > 20 kg is expected. In children < 20 kg, there is a notable

deviation between PBPK and allometry predictions with greater separation at lower weights. This deviation is likely explained by two key additional factors that are accounted for by PBPK modeling, but not allometry: enzyme ontogeny in very young children (< 2 years) and changes in metabolite formation clearance.

DISCUSSION

As the COVID-19 epidemic is spreading rapidly, pediatric cases are gradually increasing with reports of children requiring hospitalization and intensive care.^{11,14,34} Most studies investigating therapeutics for treatment of COVID-19 have been conducted in adults.³⁵ Remdesivir is currently being investigated for the treatment of COVID-19 in adults and there are minimal data that support exposure and

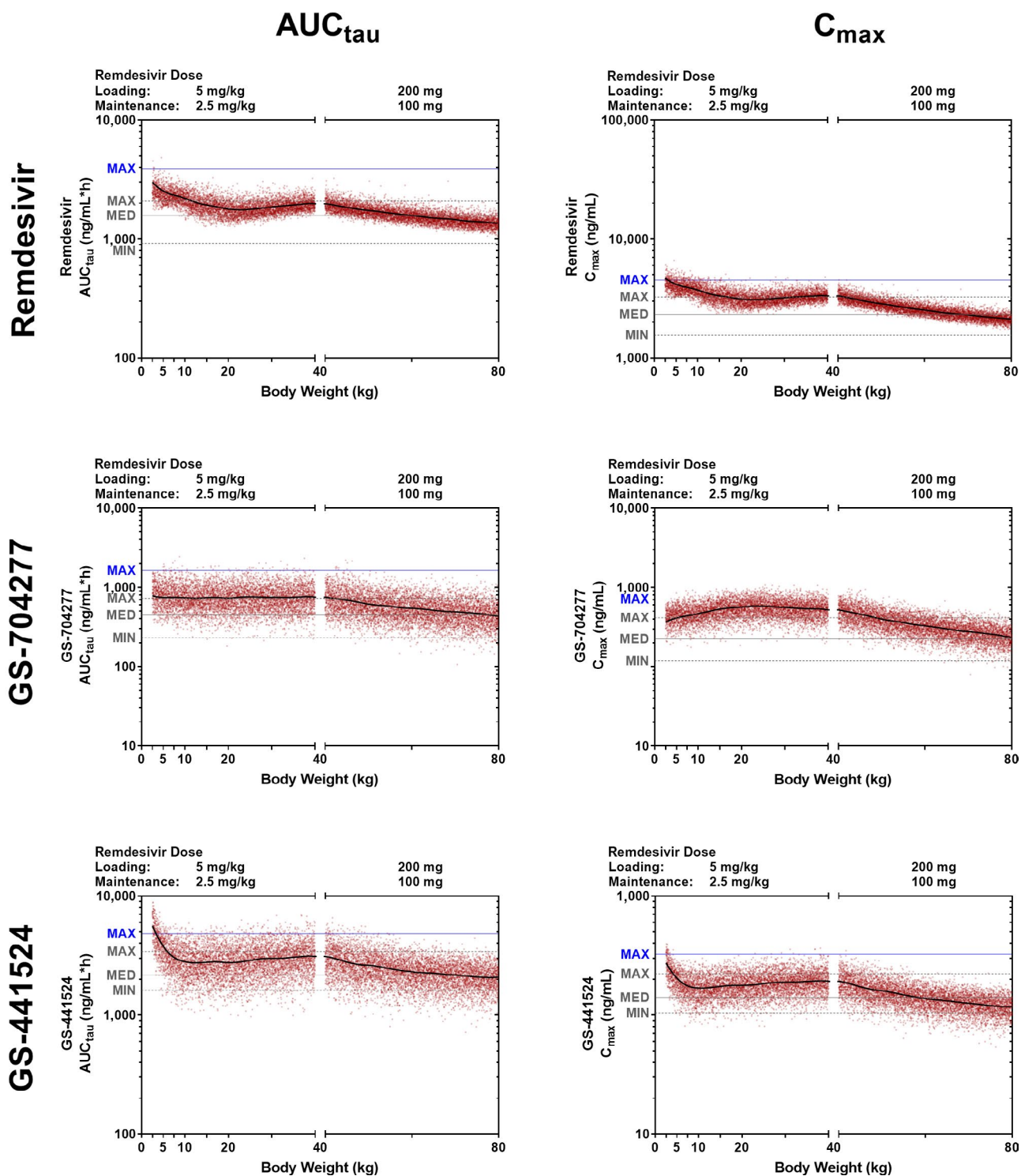


Figure 3 Predicted remdesivir Day 5 AUC_{τ} and C_{\max} after intravenous administration of a loading dose (200 mg or 5 mg/kg) of remdesivir over 0.5 hours on Day 1 then a daily maintenance dose (100 mg or 2.5 mg/kg) of remdesivir over 0.5 hours on Days 2–5 to pediatric patients. The simulated remdesivir dosage regimen for pediatric patients, ≥ 40 kg, was a single remdesivir 200-mg loading dose on Day 1 followed by four once-daily 100-mg maintenance doses. The simulated remdesivir dosage regimen for pediatric patients, < 40 kg, was a single remdesivir 5 mg/kg loading dose on Day 1 followed by four once-daily 2.5-mg/kg maintenance doses. The adult observed exposures are from the remdesivir phase I program in adult healthy volunteers.^{31,32} Blue line: MAX observed AUC_{τ} or C_{\max} after 14 daily doses of 150 mg remdesivir IV over 1 hour.³¹ Gray lines: MIN, MED, and MAX observed AUC_{τ} or C_{\max} from after a single loading dose of 200 mg remdesivir IV over 0.5 hours on Day 1 then daily doses of 200 mg remdesivir IV over 0.5 hours.³² Red dots: AUC_{τ} or C_{\max} values predicted across the weight range (2.5–80 kg) based on the remdesivir, GS-704277, and GS-441524 PBPK model. Black line: LOWESS smoother line of predicted AUC_{τ} or C_{\max} across the weight range. AUC_{τ} , area under the concentration-time curve over the dosing interval; C_{\max} , maximum plasma drug concentration; h, hour; IV, intravenous; MAX, maximum; MED, median; MIN, minimum.

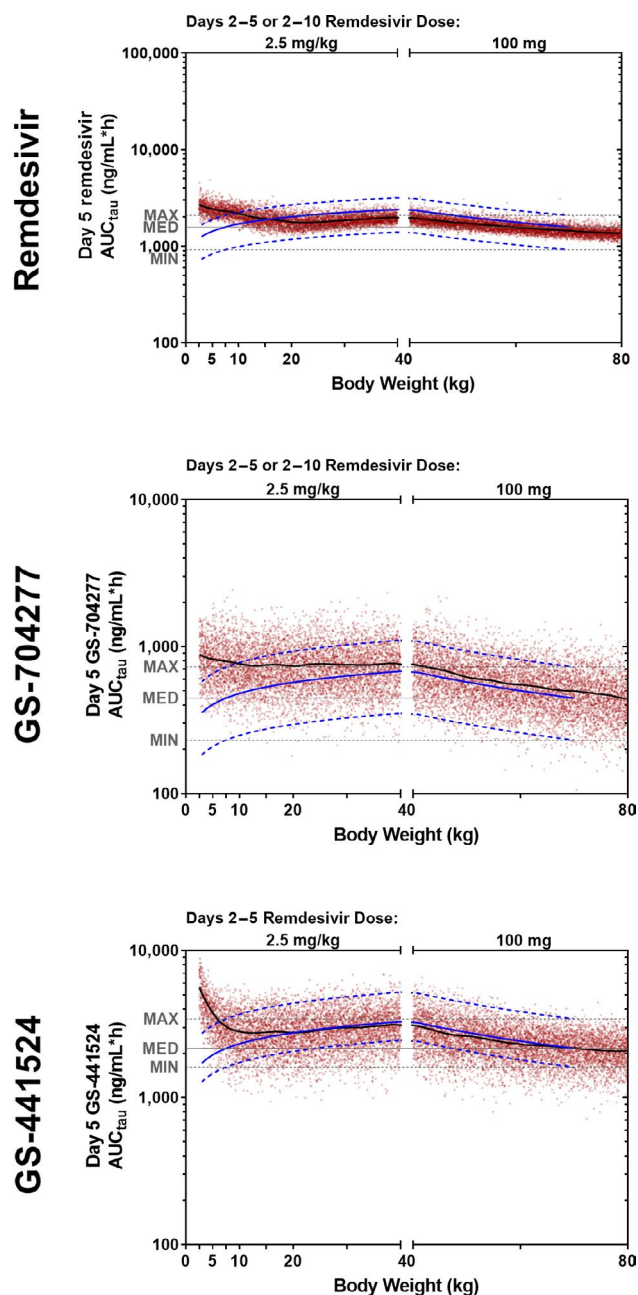


Figure 4 Comparison Between remdesivir, GS-704277, and GS-441524 Day 5 AUC_{τ} after intravenous administration of a loading dose (200 mg or 5 mg/kg) of remdesivir on Day 1 then a daily maintenance dose (100 mg or 2.5 mg/kg) on Days 2–5 to pediatric patients predicted by PBPK and allometry. The simulated remdesivir dosage regimen for pediatric patients, ≥ 40 kg, was a single remdesivir 200-mg loading dose on Day 1 followed by four once-daily 100-mg maintenance doses. The simulated remdesivir dosage regimen for pediatric patients, < 40 kg, was a single remdesivir 5 mg/kg loading dose on Day 1 followed by four once-daily 2.5-mg/kg maintenance doses. The adult observed exposures are from the remdesivir phase I program in adult healthy volunteers.^{31,32} Gray lines: MIN, MED, and MAX observed AUC_{τ} from after a single loading dose of 200 mg remdesivir IV over 0.5 hours on Day 1 then daily doses of 200 mg remdesivir IV over 0.5 hours.³¹ Blue lines: minimum (dashed), median (solid) and maximum (dashed) AUC_{τ} values predicted across the weight range (3–70 kg) based on simple allometry (exponent of 0.75 on clearance normalized to 70 kg body weight). Red dots: AUC_{τ} values predicted across the weight range (2.5–80 kg) based on the remdesivir, GS-704277, and GS-441524 PBPK model. Black line: LOWESS smoother line of predicted AUC_{τ} or C_{\max} across the weight range. AUC_{τ} , area under the concentration-time curve over the dosing interval; C_{\max} , maximum plasma drug concentration; h, hour; IV, intravenous; MAX, maximum; MED, median; MIN, minimum; PBPK, physiologically-based pharmacokinetic.

scaling (including population PK-based approaches).^{25,36} In this manuscript, we describe remdesivir dose selection in pediatric patients informed by a PBPK model. This model was developed to simulate adult exposure of remdesivir and its circulating metabolites, GS-704277 and GS-441524, and applied to predict pediatric patient steady-state exposure based on age-dependent physiologic changes (e.g., organ volume/function and blood flow). Simulations indicated that the use of the adult dosage regimen in pediatric participants ≥ 40 kg and a weight-based remdesivir dosage regimen in pediatric patients weighing 2.5 to < 40 kg is predicted to maintain remdesivir, GS-704277, and GS-441524 exposures generally within the expected adult steady-state exposure range following the adult dosage regimen.

In a recent publication, Maharaj *et al.* used allometric scaling to define a pediatric remdesivir dose regimen that may provide pediatric AUC_{τ} values that are bioequivalent to adult. Dose extrapolations for remdesivir were performed assuming the presence of dose-proportional PK in both children and adults, and PK simulations were computed after single remdesivir doses.³⁸ In our report, we compared pediatric AUC_{τ} predicted by both PBPK and allometry. We observed that there were two clinically relevant factors that caused notable deviations in predicted AUC_{τ} in children < 20 kg with greater separation between the methods at lower weights: enzyme ontogeny in very young children and changes in metabolite formation clearance. Both factors are easily accounted for by PBPK, but not by simple allometry. In all comparisons, PBPK tends to predict higher exposures in lower weight / younger children than simple allometry. Thus, PBPK represents a more conservative prediction with respect to safety.

As mentioned above, 77 pediatric patients < 18 years who received remdesivir through a compassionate use program were dosed according to our model-informed regimen. The preliminary clinical data and outcomes from these subjects support the

exposure–response in pediatrics. The urgency of this pandemic and the need for providing remdesivir as a treatment option in pediatrics necessitates the use of PK modeling and simulation techniques to support safe and effective pediatric dosing recommendations.

The herein described PBPK model-selected dose regimen of remdesivir has been administered to pediatric patients (birth to 18 years of age) with severe COVID-19 under Gilead’s compassionate use program. Furthermore, a single-arm phase II/III clinical trial is planned that will evaluate the safety, tolerability, PK, and efficacy of this remdesivir regimen in treating ~ 50 pediatric patients with moderate-to-severe COVID-19, including newborns through adolescents.^{36,37}

Generally, dose selection in the pediatric population is derived from adult PK data via two approaches, PBPK and allometric

efficacy and tolerability of this dosing algorithm in this population. Additionally, with the limited current knowledge regarding emerging SARS CoV-2 resistance during treatment, conservative predictions using our PBPK modeling are necessary for the treatment of COVID-19 in children.

The ontogenic profile of CES1 has been well established using both immunoblot and proteomic methodologies on large libraries of adult and pediatric liver tissue.^{39,40} Overall, the profile is similar to that observed with other phase I drug metabolizing enzymes, where expression is low at birth but quickly rises to approximate adult levels by 2 years of age.⁴¹ Specifically, CES1 expression in neonates is roughly 20% that of adults and reaches 50% of adult levels (i.e., AGE50) by ~ 7 months of age. The exact source for the CES1 ontogenic profile used in SimCYP v.18 was unclear to the authors at the time of this publication, but a very similar profile was observed using proteomic evaluation of $N = 171$ liver tissue samples and incorporated into a PBPK model for oseltamivir (SimCYP v.15).³⁹ Reasonably accurate predictions of oseltamivir neonatal exposure parameters (< 2.1-fold from observed) were obtained with this model, suggesting the appropriateness of this profile for pediatric exposure prediction of CES1-dependent remdesivir clearance.

Key study limitations

Data on ontogenic changes of hydrolytic enzymes other than CES1 are sparse, and hence, it is currently unclear if CatA and phosphoramidase ontogeny could play a significant role in determining the exposure of remdesivir and metabolites in very young children. To test this, a sensitivity analysis of CatA and phosphoramidase ontogeny was conducted (**Supplementary Section 2**). This analysis demonstrated that the application of an identical ontogeny profile to that of CES1 to CatA and phosphoramidase increases GS-704277, but not remdesivir or GS-441524, AUC_{tau} and C_{max} in children < 5 kg (**Figure S4**) to a greater extent than that which would be predicted without these ontogeny profiles (**Figure 3**). Given the lack of information on CatA and phosphoramidase ontogeny, it is unclear if these predictions would bear out *in vivo*, and if so, result in decreased tolerability in these children after administration of the proposed pediatric dose regimen. The use of proteomic quantification to elucidate ontogenic expression is a promising methodology⁴¹ that should be applied to better understand less-common drug metabolizing enzymes (e.g., CatA) and inform prediction of pediatric remdesivir PK.

Next, although disease presentation appears to be milder in children, the proposed pediatric dosing regimens assume that the exposure–response (safety and efficacy) relationship in pediatric patients will be similar to that of adults or can be reasonably extrapolated from adults. If data emerging in children during the pandemic suggest that this assumption is inaccurate, then additional clinical trials examining a different (alternate) target remdesivir exposure may need to be conducted.

Finally, this analysis is limited by the lack of available observed pediatric remdesivir PK data, and so the predictive performance of the PBPK model cannot be confirmed at this time. Qualification of PBPK model performance is a critical

component of model development.^{42,43} A pediatric study to evaluate the safety, efficacy, and PK of the PBPK model-selected remdesivir dose regimen is planned and data from this study will be integral to ultimate model qualification.^{36,37}

CONCLUSIONS

This report provides strong evidence that the defined remdesivir weight-based dosing regimen will provide safe and efficacious remdesivir, GS-704277, and GS-441524 exposures in pediatric patients with COVID-19. Briefly, a PBPK model was developed that accurately captures observed adult healthy volunteer remdesivir, GS-704277, and GS-441524 PK. Using this model, the pediatric exposures of remdesivir and metabolites were predicted and compared with observed exposures from the adult phase I program.^{30,31} Simulations indicated that:

1. For pediatric patients ≥ 40 kg, the adult remdesivir dose can be administered.
2. For pediatric patients weighing 2.5 to < 40 kg, a weight-based remdesivir dosage regimen (5 mg/kg IV infusion over 0.5 hours on Day 1 then 2.5 mg/kg IV infusion over 0.5 hours daily starting on Day 2 through up to Day 10) can be administered.

These regimens are predicted to maintain remdesivir, GS-704277, and GS-441524 exposures generally within the range of those observed historically and considered to be well tolerated.

AUTHOR CONTRIBUTIONS

J.D.L., A.M., B.J.K., P.G., C.P., and S.R. wrote the manuscript. J.D.L., A.M., and B.J.K. designed the research. J.D.L. analyzed the data.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

All authors are current or former employees of Gilead Sciences and own stocks/shares in Gilead Sciences.

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