Pharmacokinetics Inform Remdesivir Dosing for Patients With Severe Renal Impairment

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Introduction

- Patients requiring treatment for coronavirus disease 2019 (COVID-19) resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have preexisting renal impairment (RI) or experience acute kidney injury because of the infection[1]
- Chronic kidney disease has been reported as one of the most prevalent risk factors for severe COVID-19[2]
  - Despite this, antiviral treatment options for patients with severely impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) or kidney failure (eGFR <15 mL/min/1.73 m^2) are limited
- Remdesivir (RDV) is a broad-spectrum antiviral approved for the treatment of COVID-19 in patients who are hospitalized, or those who are not hospitalized and are at risk for progression to severe disease[3]
- Physiologic changes in RI, such as impaired excretion and altered protein binding, can affect concentrations of drugs dominated by renal clearance (CL), which may result in toxicity[1]
- When RDV was initially approved for the treatment of COVID-19, it was not recommended for use in patients with severely impaired renal function because the pharmacokinetics (PK) of RDV, its metabolites, and its sulfobutylether-β-cyclodextrin sodium (SBECD) excipient had not been evaluated in patients with RI[4]
- RDV is primarily eliminated via carboxylesterase 1 enzymatic cleavage; renal elimination represents a primary and secondary elimination pathway for its metabolites GS-441524 and GS-704277, respectively. The excipient SBECD is also renally eliminated[5]
- Following intravenous (IV) administration, RDV is rapidly distributed into cells and tissues and simultaneously metabolized into GS-704277 in plasma[6]
- Intracellularly, RDV is converted to the pharmacologically active nucleotide triphosphate metabolite, GS-443902, or the inactive nucleoside, GS-441524. Only the GS-441524 is subsequently detectable in plasma[6]
- **As RDV is the primary source of the active metabolite (GS-443902) at the site of action (lung epithelium), RDV levels are used as a surrogate for efficacious exposures[6]**
- **The safety of higher exposures to GS-441524 and SBECD was evaluated in REDPINE, a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in hospitalized participants with COVID-19 and severely impaired renal function, including those with end-stage kidney disease on dialysis**

Objectives

- To evaluate the PK disposition of RDV and its metabolites (GS-441524 and GS-704277) in participants with COVID-19 and severely impaired renal function using population PK (PopPK) modeling
- To assess the need for RDV dose adjustments in participants with impaired renal function

Methods

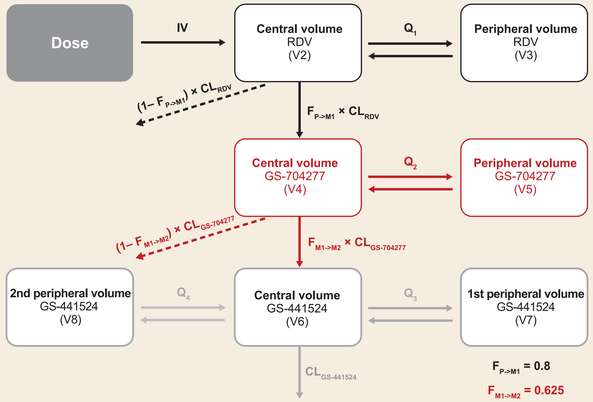
- PK samples for RDV, GS-441524, and GS-704277 were collected in the following studies:
  - In REDPINE (GS-US-540-5912), eligible participants (hospitalized with confirmed SARS-CoV-2, ≥12 years of age, O_2 saturation ≤94% on room air or requiring O_2 supplementation, and eGFR <30 mL/min/1.73 m^2) were randomized 2:1 to IV RDV (200 mg on Day 1 followed by 100 mg daily up to Day 5) or placebo (saline) to match
  - Phase 1 study in non–COVID-19–infected individuals with impaired renal function (GS-US-540-9015, ranging from mild RI [60-90 mL/min/1.73 m^2] to kidney failure on dialysis)
- PopPK model(s) for RDV, GS-704277, and GS-441524 have been developed previously and refined using concentration-time data from the REDPINE and GS-US-540-9015 studies.[7] The full list of studies included in the PopPK analysis is shown in **Table 1**
  - The development of the PopPK model(s) was performed sequentially, starting with the parent RDV data, then moving on to GS-704277 data, and ending with GS-441524 data
  - Each model was informed by the post hoc PopPK parameters from the previous model(s)
  - Upon IV administration of RDV, plasma concentrations of RDV, GS-704277, and GS-441524 were best described in adults by sequential 2-compartment models for RDV and GS-704277 and by a 3-compartment model for GS-441524 with first-order elimination in healthy volunteers (**Figure 1**)
  - The effect of body weight on the PK of RDV and its metabolites was explained with fixed allometry by setting CL-related body weight exponents to 0.75 and volume of distribution–related body weight exponents to 1.0
- Model-based inferences were carried out via forest plots to illustrate the effect of the different demographic factors and other variables of interest (intrinsic and extrinsic factors) in the exposure of RDV and its metabolites[8]
- SBECD PK were analyzed using a liquid chromatography-tandem mass spectrometry method in GS-US-540-9015 in non–COVID-19 participants who received a 100 mg dose of RDV (containing 3000 mg SBECD)

Table 1. Studies Included in the PopPK Analysis

Study	Summary	Participants with evaluable PK (n)
Phase 3		
GS-US-540-5912 (REDPINE)	Efficacy and safety of RDV in participants hospitalized for COVID-19 with severely reduced kidney function	90
GS-US-540-9012 (PINETREE)	Efficacy and safety of RDV for COVID-19 in an outpatient setting	148
CO-US-540-5844 (REMDACTA)	Efficacy and safety of RDV plus tocilizumab compared with RDV plus placebo in hospitalized patients with severe COVID-19 pneumonia	289
Phase 1		
GS-US-399-1812	Safety, tolerability, and PK of RDV and its metabolites following a single dose in healthy adult participants	96
GS-US-399-1954	Safety, tolerability, and PK of RDV and its metabolites following multiple doses in healthy adult participants	24
GS-US-399-5505	Safety, tolerability, and PK of RDV in healthy adult participants	28
GS-US-540-9015	A single-dose study in non–COVID-19 participants with RI	84

PopPK, population pharmacokinetics; PK, pharmacokinetics; RDV, remdesivir; COVID-19, coronavirus disease 2019; RI, renal impairment.

Figure 1. PopPK Model Schematic for RDV, GS-704277, and GS-441524



PopPK, population pharmacokinetics; RDV, remdesivir; IV, intravenous; V, volume of distribution; Q_n, intercompartment clearance for RDV; $F_{P->M1}$, fraction of RDV metabolized to GS-704277; CL_{RDV}, clearance for RDV; Q_n, intercompartment clearance for GS-704277; $F_{M1->M2}$, fraction of GS-704277 metabolized to GS-441524; $CL_{GS-704277}$, clearance for GS-704277; Q_n, second intercompartment clearance for GS-441524; Q_n, first intercompartment clearance for GS-441524; $CL_{GS-441524}$, clearance for GS-441524.

Results

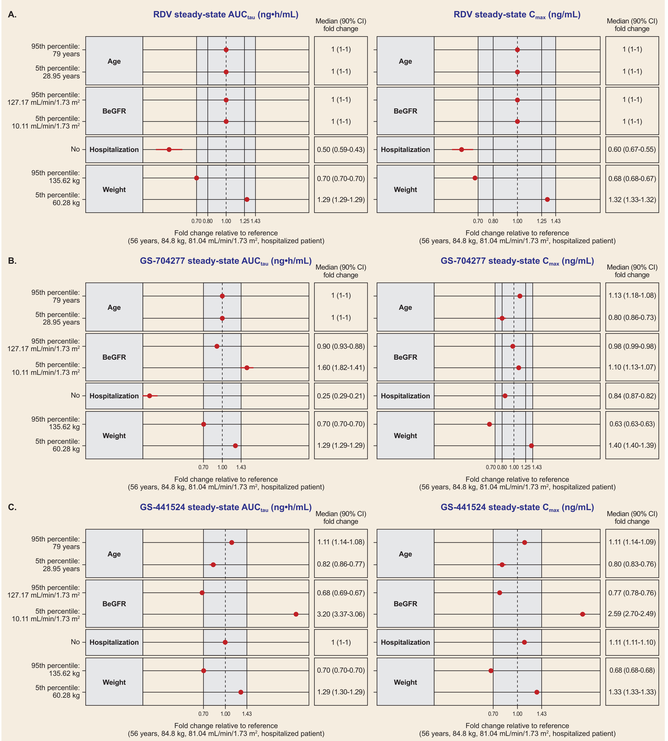
Impact of Statistically Significant Covariates on RDV, GS-704277, and GS-441524 Exposure

- **In the population analysis including participants across the full spectrum of eGFR, baseline eGFR did not impact RDV disposition but did impact the plasma exposure (area under the concentration-time curve over the dosing interval [AUC_{tau}]) of metabolites; median change (90% confidence interval) was 220% (206%-237%) for GS-441524 at eGFR = 10.11 mL/min/1.73 m^2 and 60% (41%-82%) for GS-704277 at eGFR = 10.11 mL/min/1.73 m^2 (Figure 2)**
- The effect of hospitalization was identified as having a statistically significant impact on RDV and GS-704277 exposures
  - The decrease in AUC_{tau}, median change (90% confidence interval) in nonhospitalized participants compared with hospitalized participants was 50% (43%-59%) for RDV and 25% (21%-29%) for GS-704277 (**Figure 2**)
- Age was found to affect GS-441524 and GS-704277 exposures; however, this needs to be carefully considered as eGFR and age are correlated

Evaluation of the Impact of Baseline eGFR on RDV Metabolites in Hospitalized Populations With COVID-19

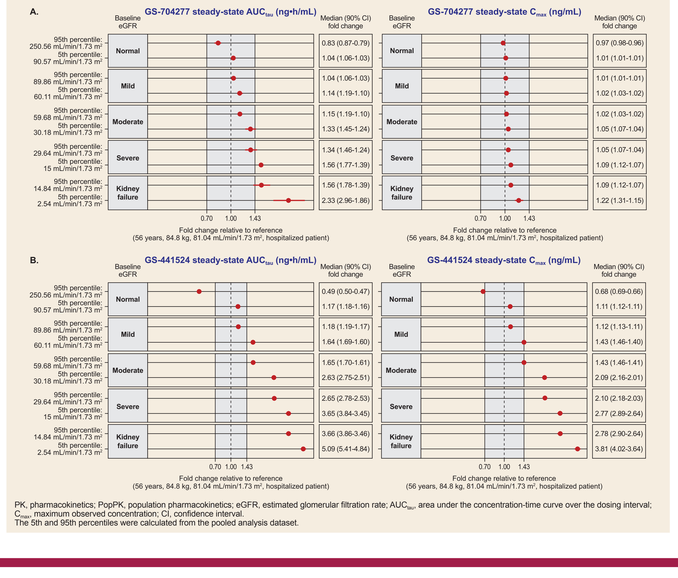
- Baseline eGFR was highly correlated with increasing GS-441524 and, to a lesser degree, GS-704277 exposures; in those with kidney failure (5th percentile eGFR of 2.54 mL/min/1.73 m^2), median GS-704277 and GS-441524 AUC_{tau} increased up to 2-fold and 5-fold, respectively (**Figure 3**)
- **The increased PK exposures for GS-704277 and GS-441524 were not associated with new safety signals in REDPINE (RDV, n = 163; placebo, n = 80)**

Figure 2. Forest Plots Generated Using PK Parameter Uncertainty (Bootstraps) From Final PopPK Models for (A) RDV, (B) GS-704277, and (C) GS-441524 Steady-state AUC_{tau} and C_{max}



PK, pharmacokinetics; PopPK, population pharmacokinetics; RDV, remdesivir; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max}, maximum observed concentration; CI, confidence interval; BeGFR, baseline estimated glomerular filtration rate.
The 5th and 95th percentiles were calculated from the pooled analysis dataset.

Figure 3. Forest Plots Generated Using PK Parameter Uncertainty (Bootstraps) From Final PopPK Models to Compare the Effects of Baseline eGFR on (A) GS-704277 and (B) GS-441524 Steady-state AUC_{tau} and C_{max} in Hospitalized Participants



PK, pharmacokinetics; PopPK, population pharmacokinetics; eGFR, estimated glomerular filtration rate; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max}, maximum observed concentration; CI, confidence interval.
The 5th and 95th percentiles were calculated from the pooled analysis dataset.

PK of SBECD in Participants With RI

- SBECD PK were characterized by a short terminal elimination half-life ($t_{1/2}$; 1.6 hours in normal renal function to 5.7 hours in severe RI) and plasma CL (7.9 to 9.5 L/h in normal renal function; **Table 2**)
  - An analysis of SBECD in severe RI (REDPINE) is ongoing, but accumulation is not expected based on its observed short plasma $t_{1/2}$

Table 2. GM (%CV)[a] SBECD Plasma PK Parameters in Adult Participants Following IV Administration of a Single 100 mg RDV Dose

Geometric mean (%CV)	Mild RI (n = 10)	Mild RI healthy-matched control (n = 7)	Moderate RI (n = 10)	Moderate RI healthy-matched control (n = 9)	Simulated severe RI[b] (n = 20)
C_{max}, µg/mL	247 (87.1)	156 (32.1)	217 (28.4)	204 (22.2)	231 (16.2)
AUC_{0-4h}, h•µg/mL	345 (18.4)	235 (25.6)	447 (27.6)	315 (25.8)	503 (17.4)
AUC_{inf}, h•µg/mL	396 (22.3)	316 (16.9)	808 (42.0)	380 (33.1)	1273 (21.2)
$t_{1/2}$, h[a]	0.95 (0.83, 1.74)	1.65 (1.61, 1.87)	3.80 (2.48, 4.54)	1.60 (1.36, 1.79)	5.67 (3.97, 7.37)
V_z, L	12.8 (38.0)	24.1 (24.4)	17.8 (19.2)	17.9 (16.9)	19.3 (23.9)
CL, L/h	7.6 (19.6)	9.5 (18.4)	3.7 (41.7)	7.9 (28.8)	2.4 (19.1)

GM, geometric mean; %CV, percentage coefficient of variation; SBECD, sulfobutylether-β-cyclodextrin sodium; PK, pharmacokinetics; IV, intravenous; RDV, remdesivir; RI, renal impairment; C_{max}, maximum observed concentration; AUC_{0-4h}, partial area under the concentration-time curve from time 0 hours to time 4 hours; AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; $t_{1/2}$, terminal elimination half-life; NA, not appropriate to calculate; V_z, volume of distribution of terminal phase; CL, clearance; Q1, quartile 1; Q3, quartile 3.
[a]Data are presented as GM (%CV), with the exception of $t_{1/2}$, which are presented as median (Q1, Q3).
[b]Simulated 100 mg dose–normalized values based on a population PK model built on GS-US-540-9015 mild, moderate, and severe RI cohorts and healthy matched controls.

Steady-state Exposures in REDPINE Study Participants

- PopPK-estimated exposures and basic demographic information for participants with PK samples collected in the REDPINE study are summarized in **Table 3**

Table 3. PopPK-estimated Plasma Steady-state Exposures to RDV and Metabolites (GS-704277 and GS-441524)

Characteristic	GM (%CV)
Number of participants	90[a] (severe RI; kidney failure)
eGFR, mL/min/1.73 m^2, median (min, max)	14.7 (2.5, 41.7)[b]
Body weight, kg	79.0 (43.0, 148.0)
RDV AUC_{tau}, ng•h/mL	2950 (63.1) (3250 [68.5]; 2670 [56.8])
RDV C_{max}, ng/mL	3850 (56.3) (4170 [58.9]; 3570 [53.8])
GS-704277 AUC_{tau}, ng•h/mL	1550 (57.5) (1480 [55.1]; 1660 [55.6])
GS-704277 C_{max}, ng/mL	378 (67.0) (397 [73.3]; 370 [59.2])
GS-441524 AUC_{tau}, ng•h/mL	15,400 (44.6) (11,600 [38.3]; 20,200 [28.0])
GS-441524 C_{max}, ng/mL	703 (41.5) (548 [36.7]; 893 [28.1])
GS-441524 C_{tau}, ng/mL	377 (40.3) (321 [38.7]; 440 [35.3])

PopPK, population pharmacokinetics; RDV, remdesivir; GM, geometric mean; %CV, percentage coefficient of variation; RI, renal impairment; eGFR, estimated glomerular filtration rate; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max}, maximum observed concentration; PK, pharmacokinetics;
[a]Among REDPINE participants with available PK data, 47.8% (43/90) had severe RI (eGFR, 15-29 mL/min/1.73 m^2) and 51.1% (46/90) had kidney failure (eGFR, <15 mL/min/1.73 m^2); 45.6% (41/90) needed renal replacement therapy; 5.6% (5/90) received intermittent hemodialysis.
[b]Protocol enrollment criterion was baseline eGFR <30 mL/min/1.73 m^2 for REDPINE.

Conclusion

- Given the observed PK measures and the absence of any new safety signals associated with increased GS-441524 metabolite and SBECD levels in the REDPINE study, no dose adjustment is recommended for RDV in COVID-19 patients with eGFR <30 mL/min/1.73 m^2, regardless of the need for dialysis

Disclosures: RH, SR, HZ, YK, JL, RHH, AO, SG, AR-G, and HW are stockholders and employees of Gilead Sciences, Inc. RD is a paid consultant for Gilead Sciences, Inc. ICS is an employee of Certara, Inc. RR is an employee of New Zealand Clinical Research and conducted the trial for Gilead Sciences, Inc., as a primary investigator. MS has received research funding from Gilead Sciences, Inc., EMD Serono, AbbVie, and Angion; and has served as a scientific advisory board member for Travere, Novartis, and Mallinckrodt.

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