Clinical Evaluation of Drug-Drug Interactions With Remdesivir

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Key Findings

- There were no clinically relevant effects of organic anion transporting polypeptide (OATP)1B1/1B3 inhibition or cytochrome P450 3A4 (CYP3A4) induction on plasma pharmacokinetics (PK) of remdesivir (RDV) and its metabolites
- RDV is not an inhibitor of CYP3A4 or OATP1B1/1B3

Conclusion

RDV has low potential for drug-drug interactions (DDIs)

References: **1.** Veklury® (remdesivir) injection, for intravenous use [package insert]. Gilead Sciences, Inc.; 2023. **2.** Beigel JH, et al. *N Engl J Med*. 2020;383(19):1813-1826. **3.** Spinner CD, et al. *JAMA*. 2020;324(11):1048-1057. **4.** Gottlieb RL, et al. *N Engl J Med*. 2022;386(4):305-315. **5.** Humeniuk R, et al. *Clin Pharmacokinet*. 2021;60(5):569-583. **6.** Pitts J, et al. *Antimicrob Agents Chemother*. 2022;66(6):e00222-22. **7.** US Food and Drug Administration. Clinical drug interaction studies — cytochrome P450 enzyme- and transporter-mediated drug interactions: guidance for industry. Accessed October 2, 2023. https://www.fda.gov/media/134581/download. **8.** Ader F, et al. *Lancet Infect Dis*. 2022;22(2):209-221.

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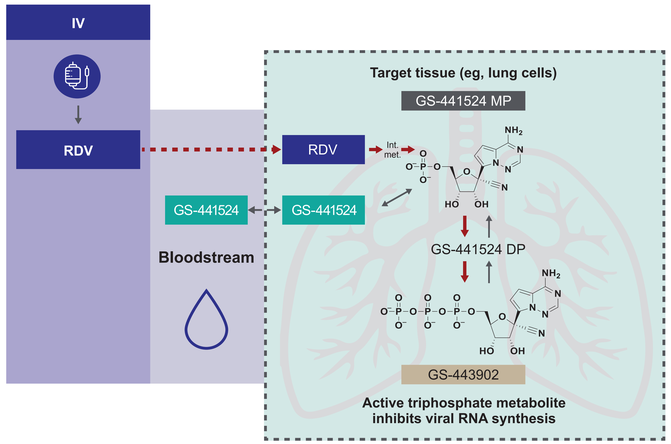
Introduction

Figure 1. RDV Mechanism of Action



RDV, remdesivir; IV, intravenous; MP, monophosphate; int. met., intermediate metabolite (GS-704277); DP, diphosphate.
Dashed arrows represent distribution/membrane crossing.
Bold red arrows indicate the major pathway; solid gray arrows represent the minor pathways.

- RDV is a nucleotide analog prodrug approved to treat COVID-19 in both hospitalized and nonhospitalized adult and pediatric patients,[1] with clinical benefits reported in several clinical trials[2-4]
- Intracellular metabolism of RDV involves the sequential formation of the intermediate metabolite GS-704277 and the major metabolite GS-441524; GS-441524 monophosphate is metabolized into the active nucleoside triphosphate, GS-443902, which acts as a SARS-CoV-2 RNA-dependent RNA polymerase inhibitor[5,6] (**Figure 1**)
- Nonclinical studies have demonstrated that RDV is a substrate of OATP1B1/1B3, CYP3A4, and esterases and a weak inhibitor of OATP1B1/1B3 and CYP3A4[1,5]

Objectives

- To assess DDIs of RDV as a victim of OATP1B1/1B3 inhibition and CYP3A4 induction using cyclosporin A (CsA) and carbamazepine (CBZ), respectively
- To assess DDIs of RDV as an inhibitor of CYP3A4 and OATP transporters using midazolam (MDZ) and pitavastatin (PIT) as sensitive substrates, respectively

Methods

- Two independent, Phase 1, open-label, fixed-sequence studies (**Table 1**) were conducted in healthy participants aged 18 to 45 years; female participants could not be pregnant or lactating
- Treatment was administered in fixed sequences separated by washout periods

Table 1. Study Design

Study 1 (RDV as a DDI victim)									
Interaction tested	Coadministered drug	Treatment period							Prespecified no-effect bounds[a]
		Day 1	Days 2-4	Day 5	Days 6-8	Days 9-33	Day 34	Days 35-38	
OATP1B1/1B3 inhibition or CYP3A4 induction	CsA or CBZ (N = 9)	RDV 100 mg IV	Washout	CsA 400 mg PO + RDV 100 mg IV	Washout	CBZ 100 mg (Days 9-10), 200 mg (Days 11-12), and 300 mg (Days 13-33) PO BID	RDV 100 mg IV QD + CBZ 300 mg PO BID	CBZ 200 mg (Days 35-36) and 100 mg (Days 37-38) PO BID	70.0%-143.0%

Study 2 (RDV as a DDI perpetrator)							
Interaction tested	Coadministered drug	Treatment period					Prespecified no-effect bounds[a]
		Day 1	Day 2	Day 3	Day 4	Day 5	
CYP3A4 inhibition	MDZ (N = 19)	MDZ 2.5 mg PO	Washout	MDZ 2.5 mg PO + ODV[b] 500 mg PO	Washout	MDZ 2.5 mg PO + RDV 200 mg IV	80.0%-125.0%
		Day 1	Days 2-3	Day 4	Days 5-6	Day 7	
OATP1B1/1B3 inhibition	PIT (N = 20)	PIT 2 mg PO	Washout	PIT 2 mg PO + ODV[b] 500 mg PO	Washout	PIT 2 mg PO + RDV 200 mg IV	80.0%-125.0%

RDV, remdesivir; DDI, drug-drug interaction; OATP, organic anion transporting polypeptide; CYP3A4, cytochrome P450 3A4; CsA, cyclosporin A; CBZ, carbamazepine; IV, intravenous; PO, oral; BID, twice daily; QD, once daily; MDZ, midazolam; ODV, obeldesivir; PIT, pitavastatin; PK, pharmacokinetic.
[a]Prespecified bounds of 80.0% to 125.0% established per US Food and Drug Administration DDI guidance[7] and 70.0% to 143.0% bounds established in the context of clinical relevance or higher PK variability of the studied drug.
[b]ODV was assessed for DDIs in a separate study; findings are not described in this poster.

Results

Participant Demographics

- In Study 1, most participants were male (5 [55.6%]) and White (9 [100%]); the mean (standard deviation [SD]) age and body mass index (BMI) were 27 (8.3) years and 25.4 (2.7) kg/m^2, respectively
- In Study 2, most participants were male (28 [71.8%]) and White (28 [71.8%]); the mean (SD) age and BMI were 28 (7.0) years and 25.7 (2.6) kg/m^2, respectively

Safety

- No serious adverse events (Grade 4 adverse events, adverse events leading to study discontinuation, or deaths) were reported
- Most AEs were Grade 1 or 2 and were consistent with the known safety profiles of RDV and each perpetrator or probe substrate

RDV as Victim

Figure 2. RDV and CsA

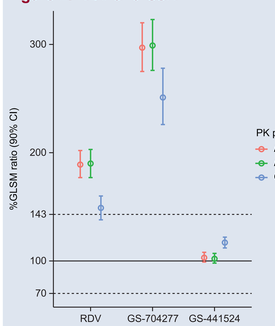
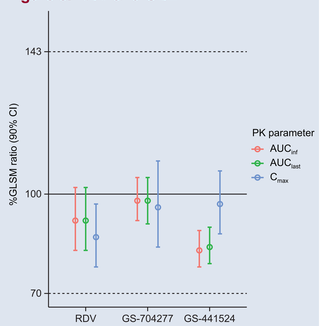


Figure 3. RDV and CBZ



- Coadministration of RDV and CsA resulted in increases in the AUC_{inf} and C_{max} for RDV and GS-704277; PK parameters for GS-441524 were within the no-effect bounds
- Increases in the exposure of RDV and its metabolite were within the range of exposures shown to be safe and well tolerated in the Phase 3 RDV studies and thus were not considered clinically relevant[8]
- Coadministration with CBZ resulted in geometric least squares mean (GLSM) ratios (90% confidence interval [CI]) for the AUC and C_{max} for RDV and its metabolites that were within the no-effect bounds

RDV as Perpetrator

Figure 4. RDV and MDZ

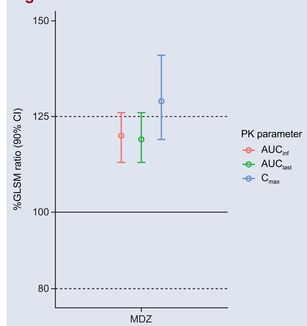
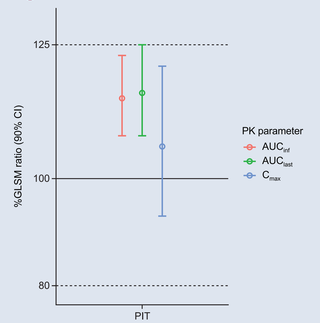


Figure 5. RDV and PIT



- Coadministration of RDV and MDZ increased the C_{max} of MDZ, while the GLSM ratio for the AUC was within the no-effect bounds
- Based on the observed change in the AUC, RDV is not a CYP3A4 inhibitor[7]
- Coadministration of RDV and PIT resulted in GLSM ratios for the AUC and C_{max} that were within the no-effect bounds

RDV, remdesivir; OATP, organic anion transporting polypeptide; CsA, cyclosporin A; GLSM, geometric least squares mean; CI, confidence interval; PK, pharmacokinetic; AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from dosing to last measurable concentration; C_{max}, maximum concentration observed; CYP3A4, cytochrome P450 3A4; CBZ, carbamazepine; MDZ, midazolam; PIT, pitavastatin; DDI, drug-drug interaction.
Dotted lines represent prespecified no-effect bounds; 80.0% to 125.0% bounds established per US Food and Drug Administration DDI guidance[7] and 70.0% to 143.0% bounds established in the context of clinical relevance or higher PK variability of the studied drug.

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