Drug-Drug Interaction Profiling of Obeldesivir, a Promising Oral Treatment for COVID-19

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Key Findings

— Obeldesivir (ODV) is not a clinically relevant inhibitor of cytochrome P450 3A4 (CYP3A4), P-glycoprotein (P-gp), organic anion transporting polypeptide (OATP)1B1/1B3, or organic cation transporter 1 (OCT1)

— There were no clinically relevant effects of P-gp inhibition or increased gastric pH on the plasma pharmacokinetics (PKs) of GS-441524

Conclusion

ODV is a promising oral treatment for COVID-19 with low potential for drug-drug interactions (DDIs)

References: 1. Humeniuk R, et al. *Clin Pharmacokinet*. 2021;60(5):569-583. **2.** 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.

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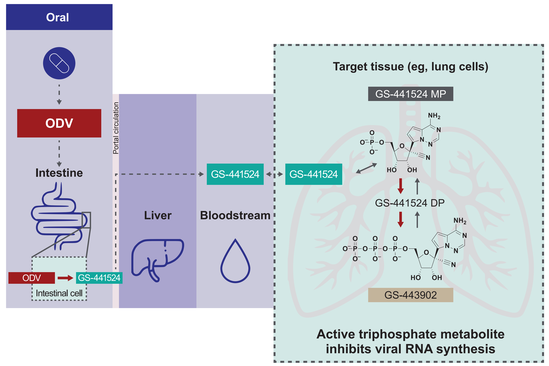
Introduction

— Availability of a highly effective oral treatment with a high barrier to resistance, minimal DDIs, and a reduced pill burden has the potential to address a critical public health need in the ongoing fight against COVID-19

— ODV is currently under investigation for the treatment of COVID-19 in Phase 3 studies (ClinicalTrials.gov Identifiers: NCT05715528, NCT05603143)

Figure 1. ODV Mechanism of Action



ODV, obeldesivir; MP, monophosphate; DP, diphosphate.
Dashed arrows represent distribution/membrane crossing.
Bold red arrows indicate the major pathway; solid gray arrows represent the minor pathways.

— ODV is an oral GS-441524 prodrug, which is metabolized to GS-443902, an active nucleoside triphosphate that selectively inhibits viral RNA-dependent RNA polymerase activity[1] (**Figure 1**)

— This clinical study was conducted to evaluate DDI liabilities identified during in vitro screening

Objectives

— To assess DDIs of ODV as a victim of P-gp inhibition and gastric acid suppression using ritonavir (RTV) and famotidine (FAM), respectively

— To assess DDIs of ODV as a perpetrator of CYP3A4, P-gp, OATP1B1/1B3, and OCT1 using midazolam (MDZ), dabigatran (DAB), pitavastatin (PIT), and metformin (MET), respectively, as sensitive substrate probes

Methods

— This was a Phase 1, open-label, multicenter, multicohort study with fixed or crossover treatment sequences (**Table 1**)

Table 1. Study Design

ODV as a DDI victim

Cohort	Interaction tested	Coadministered drug	Treatment period					Prespecified no-effect bounds[a]
			Day 1	Days 2-3	Days 4-5	Day 6	Days 7-8	
A	P-gp inhibition	RTV (N = 15)	ODV 350 mg	Washout	RTV 100 mg BID	RTV 100 mg BID + ODV 350 mg	RTV 100 mg BID	70.0%-143.0%
			Day 1		Days 2-3		Day 4	
B	Gastric acid suppression	FAM (N = 15)	ODV 350 mg		Washout		FAM 40 mg, followed by ODV 350 mg 2 hours later	70.0%-143.0%

ODV as a DDI perpetrator

Cohort	Interaction tested	Coadministered drug	Treatment period			Prespecified no-effect bounds[a]
			Day 1	Day 2	Day 3	
C	CYP3A4 inhibition	MDZ (N = 19)	MDZ 2.5 mg	Washout	MDZ 2.5 mg + ODV 500 mg	80.0%-125.0%
			Day 1	Days 2-7	Day 8	
D	P-gp inhibition	DAB[b] (N = 24)	DAB 150 mg	Washout	DAB 150 mg + ODV 500 mg	70.0%-143.0%
			Day 1	Days 2-3	Day 4	
E	OATP1B1/1B3 inhibition	PIT (N = 22)	PIT 2 mg	Washout	PIT 2 mg + ODV 500 mg	80.0%-125.0%
			Day 1	Days 2-7	Day 8	
F	OCT1 inhibition	MET[b] (N = 14)	MET 850 mg	Washout	MET 850 mg + ODV 500 mg	80.0%-125.0%

ODV, obeldesivir; DDI, drug-drug interaction; P-gp, P-glycoprotein; RTV, ritonavir; BID, twice daily; FAM, famotidine; CYP3A4, cytochrome P450 3A4; MDZ, midazolam; DAB, dabigatran; OATP, organic anion transporting polypeptide; PIT, pitavastatin; OCT1, organic cation transporter 1; MET, metformin; PK, pharmacokinetic.
[a]Prespecified bounds of 80.0% to 125.0% established per US Food and Drug Administration DDI guidance[2] and 70.0% to 143.0% bounds established in the context of clinical relevance or higher PK variability of the studied drug.
[b]DAB and MET were administered in a randomized sequence of treatment.

— The study was conducted in healthy male and nonpregnant, nonlactating female participants aged 18 to 45 years

— All study drugs were administered orally under fasted conditions at approximately the same time of the morning on dosing days

— PK samples were taken ≤5 minutes predose and at multiple time points up to 72 hours postdose

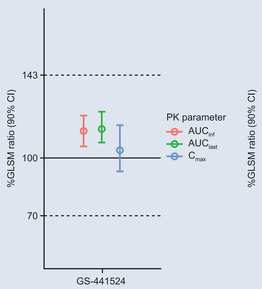
— PK samples were quantified via liquid chromatography-tandem mass spectrometry

— Plasma PK parameters were estimated by noncompartmental analysis using Phoenix WinNonlin™ (version 8.4.0); test and reference treatments were compared using the ratios of geometric least squares means (GLSMs) with 2-sided 90% confidence intervals (CIs)

Results

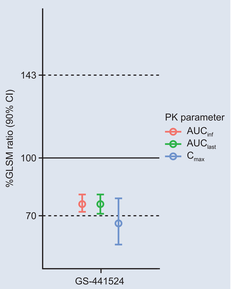
ODV as Victim

Cohort A: ODV and RTV



GS-441524 plasma PK parameters were within the no-effect bounds

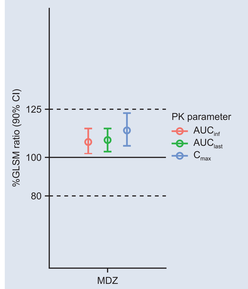
Cohort B: ODV and FAM



GS-441524 AUC was within the no-effect bounds; the decrease in C_{max} was not considered to be clinically relevant

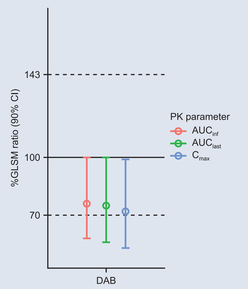
ODV as Perpetrator

Cohort C: ODV and MDZ



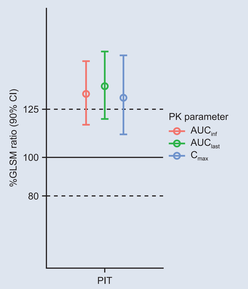
MDZ plasma PK parameters were within the no-effect bounds

Cohort D: ODV and DAB



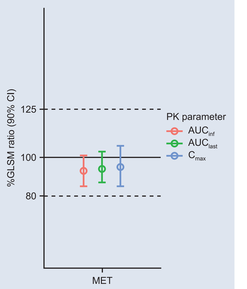
Decreases in the AUC and C_{max} of DAB were not considered to be clinically relevant

Cohort E: ODV and PIT



Increases in the AUC and C_{max} of PIT were not considered to be clinically relevant

Cohort F: ODV and MET



MET plasma PK parameters were within the no-effect bounds

ODV, obeldesivir; RTV, ritonavir; 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; FAM, famotidine; MDZ, midazolam; DAB, dabigatran; PIT, pitavastatin; MET, metformin; 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[2] and 70.0% to 143.0% bounds established in the context of clinical relevance or higher PK variability of the studied drug.

— Based on these findings, ODV is administered in the Phase 3 trials with no restrictions in regard to medications that are victims or perpetrators of CYP3A4, OATP1B1/1B3, or OCT1

Safety

— No serious adverse events, study drug–related discontinuations, or deaths were reported

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