Clinical Evaluation of Drug-Drug Interactions With Obeldesivir, a Promising Oral Antiviral Treatment

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Conclusions

- Obeldesivir resulted in <25% change in the plasma pharmacokinetics of caffeine; thus, per US Food and Drug Administration (FDA) guidance, obeldesivir is not a cytochrome P450 1A2 inhibitor
- Multiple-dose administration of obeldesivir resulted in <20% change in the plasma pharmacokinetics of midazolam; thus, per FDA guidance, obeldesivir is not a cytochrome P450 3A4 inducer
- Cyclosporin A, a breast cancer resistance protein inhibitor, did not meaningfully affect the plasma pharmacokinetics of the obeldesivir metabolite, GS-441524
- Obeldesivir is a promising oral antiviral with a low potential for drug-drug interactions

Plain Language Summary

Obeldesivir is broadly active orally administered antiviral drug. Previous studies have shown that a single dose of obeldesivir does not interact with midazolam, a drug that affects cytochrome P450 enzymes. Cytochrome P450 enzymes are a family of enzymes that are important for drug metabolism. Here, we show that when obeldesivir is taken along with drugs that are substrates for cytochrome P450 1A2 (caffeine) or cytochrome P450 3A4 (midazolam), the concentration of caffeine or midazolam in the plasma is not affected in a clinically meaningful manner. Additionally, we showed that when obeldesivir is taken with cyclosporin A, concentrations of the metabolite, GS-441524, are not meaningfully affected. This is important because cyclosporin A is an inhibitor of breast cancer resistance protein, a protein shown to transport obeldesivir and/or GS-441524 in vitro. Overall, this study demonstrates that obeldesivir is safe to take with other medications that are substrates of cytochrome P450 1A2 or cytochrome P450 3A4 or are inhibitors of breast cancer resistance protein.

Introduction

- Obeldesivir (ODV) is an oral nucleoside prodrug with broad antiviral activity[1]
- Phase 1, single-dose clinical trials have shown that ODV is not a clinically relevant inhibitor of cytochrome P450 3A4 (CYP3A4), P-glycoprotein (P-gp), organic anion transporting polypeptide 1B1/1B3, or organic cation transporter[2]
- Furthermore, there were no clinically relevant effects of P-gp inhibition or increased gastric pH on the plasma pharmacokinetics (PK) of the ODV metabolite, GS-441524[2]
- In vitro, GS-441524 was identified as a weak cytochrome P450 1A2 (CYP1A2) substrate, ODV showed low to no liability as a CYP3A4 inducer, and ODV and/or GS-441524[3] were identified as substrates of breast cancer resistance protein (BCRP)

Objective

- To assess the potential of ODV as an inhibitor of CYP1A2, an inducer of CYP3A4, or a victim of BCRP inhibition in healthy participants

Methods

Table 1. Study Design

Interaction Tested	Coadministred Drug	Treatment Period						Prespecified No-effect Bounds (%)[a]
ODV as a perpetrator								
		Day 1		Days 2-3		Day 4[b]		
CYP1A2 inhibition	CAF (N = 17)	CAF 200 mg		Washout		CAF 200 mg + ODV 500 mg		80-125
		Day 1	Day 2	Days 3-6	Day 7	Days 8-11	Day 12	
CYP3A4 induction	MDZ[c] (N = 19)	MDZ 2.5 mg (single dose)	Washout	ODV 350 mg BID	MDZ 2.5 mg (single dose) + ODV 350 mg BID	ODV 350 mg BID	MDZ 2.5 mg (single dose) + ODV 350 mg BID	80-125
ODV as a victim								
		Day 1		Days 2-3		Day 4[d]		
BCRP inhibition	CsA (N = 15)	ODV 350 mg		Washout		ODV 350 mg + CsA 400 mg		70-143

[a]Prespecified bounds of 80% to 125% were established per US Food and Drug Administration DDI guidance.[4] Prespecified bounds of 70% to 143% were supported by previous Gilead studies.
[b]On Day 4, a single dose of CAF was administered 15 minutes before a single dose of ODV. All CAF administrations were under fasted conditions.
[c]On Days 7 and 12, a single dose of MDZ was administered simultaneously with ODV in the morning under fasted conditions. On Days 3 to 6 and 8 to 11, ODV 350 mg was administered orally BID without regard to food, except for the morning dose of Day 3, which was administered under fasted conditions.
[d]On Day 4, a single dose of CsA was administered in the morning, 45 minutes before a single dose of ODV. All ODV administrations were under fasted conditions.
BCRP, breast cancer resistance protein; BID, twice daily; CAF, caffeine; CsA, cyclosporin A; CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; DDI, drug-drug interaction; MDZ, midazolam; ODV, obeldesivir.

- This was a Phase 1, open-label, fixed-sequence crossover study (**Table 1**)
  - Study participants were healthy males or nonpregnant, nonlactating females aged 18 to 45 years
- PK samples were taken ≤5 minutes before administration and at multiple time points up to 72 hours post dose (for those receiving caffeine [CAF] ± ODV and ODV ± cyclosporin A [CsA]) or up to 24 hours post dose (for those receiving midazolam [MDZ] ± ODV)
- Plasma concentrations of probe substrates were measured using validated liquid chromatography-tandem mass spectrometry methods
- PK parameters (area under the concentration-time curve extrapolated to infinite time [AUC_{inf}], area under the concentration-time curve from dosing to last measurable concentration [AUC_{last}], and maximum observed concentration [C_{max}]) were estimated by noncompartmental analysis (Phoenix WinNonlin™, Version 8.2), and reference treatments were compared using a mixed-effects model with point estimates for geometric least squares means (GLSMs) and 2-sided 90% CIs
- Safety was assessed by adverse events (AEs) and clinical laboratory abnormalities

Results

Participants

Table 2. Participant Demographics

Characteristic	CAF ± ODV (N = 17)	MDZ ± ODV (N = 19)	ODV ± CsA (N = 15)
Age, years, mean (range)	32 (19-45)	33 (24-43)	32 (24-40)
Weight, kg, mean (range)	70 (56-81)	69 (55-79)	71 (44-86)
Sex at birth, n (%)			
Female	11 (65)	8 (42)	9 (60)
Male	6 (35)	11 (58)	6 (40)
Race, n (%)			
Black	4 (24)	4 (21)	1 (7)
White	12 (71)	14 (74)	11 (73)
Other	1 (6)	1 (5)	3 (20)
Ethnicity, n (%)			
Hispanic or Latino	9 (53)	11 (58)	8 (53)
Not Hispanic or Latino	8 (47)	8 (42)	7 (47)

CAF, caffeine; CsA, cyclosporin A; MDZ, midazolam; ODV, obeldesivir.

- Baseline participant demographics are shown in **Table 2**

Safety

Table 3. TEAEs and TEAEs by Preferred Term[a] Occurring in ≥2 Participants

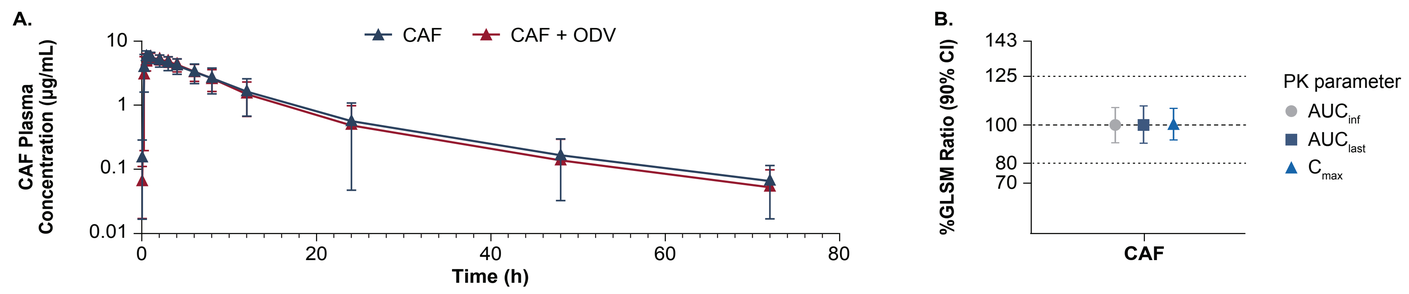
TEAE, n (%)	CAF ± ODV[b] (N = 17)	MDZ ± ODV (N = 19)	ODV ± CsA (N = 15)
Any TEAE	10 (59)	13 (68)	12 (80)
Serious TEAE	0	0	1 (7)
Grade ≥3 TEAE	0	0	0
TEAE leading to study discontinuation	0	0	0
TEAE in ≥2 participants			
Nausea	7 (41)	0	7 (47)
Hot flush	8 (47)	0	4 (27)
Somnolence	0	10 (53)	0
Headache	5 (29)	2 (11)	2 (13)
Flushing	0	0	4 (27)
Vomiting	4 (24)	0	0
Abdominal discomfort	0	1 (5)	2 (13)
Dizziness	0	1 (5)	2 (13)
Abdominal distension	0	1 (5)	1 (7)
Chills	2 (12)	0	0
Paraesthesia	0	2 (11)	0

[a]TEAEs were coded using the *Medical Dictionary for Regulatory Activities*, Version 26.1.
[b]Participants in this cohort received CAF and ODV as indicated in the study design during Days 1 to 4. This was followed by a second dosing period, which consisted of a washout period (Days 5-6), ODV 350 mg (Day 7), another washout period (Days 8-9), and ODV 350 mg and CsA 400 mg (Day 10). Due to a PK sampling error in the second period, these data were not included in PK analyses, and Cohort 3 (ODV ± CsA) was enrolled. Many of the TEAEs reported in Cohort 1 (CAF ± ODV) were attributed to CsA.
CAF, caffeine; CsA, cyclosporin A; MDZ, midazolam; ODV, obeldesivir; PK, pharmacokinetic; TEAE, treatment-emergent adverse event.

- ODV as a single dose or twice daily (BID) up to 10 days, alone or in combination with probe drugs (CAF, MDZ, or CsA), was generally safe and well tolerated
- One participant experienced a serious AE of spontaneous abortion, which was not considered related to the study drug (**Table 3**)
- Overall, 2/51 (4%) participants had Grade 1 AEs considered related to the study drug and attributed to ODV (abdominal discomfort and abdominal distension)
- No Grade ≥3 AEs, AEs leading to discontinuation, or deaths were reported
- All laboratory abnormalities were Grade 1 or 2 in severity; none were considered clinically significant

ODV as a Perpetrator

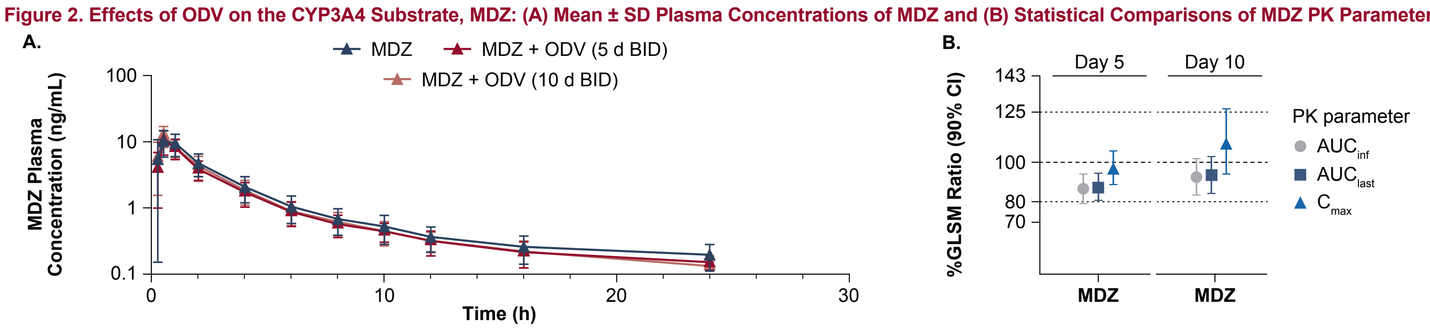
Figure 1. Effects of ODV on the CYP1A2 Substrate, CAF: (A) Mean ± SD Plasma Concentrations of CAF and (B) Statistical Comparisons of CAF PK Parameters



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; CAF, caffeine; C_{max}, maximum observed concentration; CYP1A2, cytochrome P450 1A2; GLSM, geometric least squares mean; ODV, obeldesivir; PK, pharmacokinetic.

- The overall CAF PK profile appeared similar when CAF was coadministered with ODV versus when CAF was administered alone (**Figure 1A**), with comparable AUC_{inf}, AUC_{last}, and C_{max} (**Figure 1B**)
- Coadministration of CAF with ODV resulted in %GLSM ratio 90% CIs that were within the no-effect bounds of 80% to 125% for all CAF PK parameters (**Figure 1B**)

Figure 2. Effects of ODV on the CYP3A4 Substrate, MDZ: (A) Mean ± SD Plasma Concentrations of MDZ and (B) Statistical Comparisons of MDZ PK Parameters

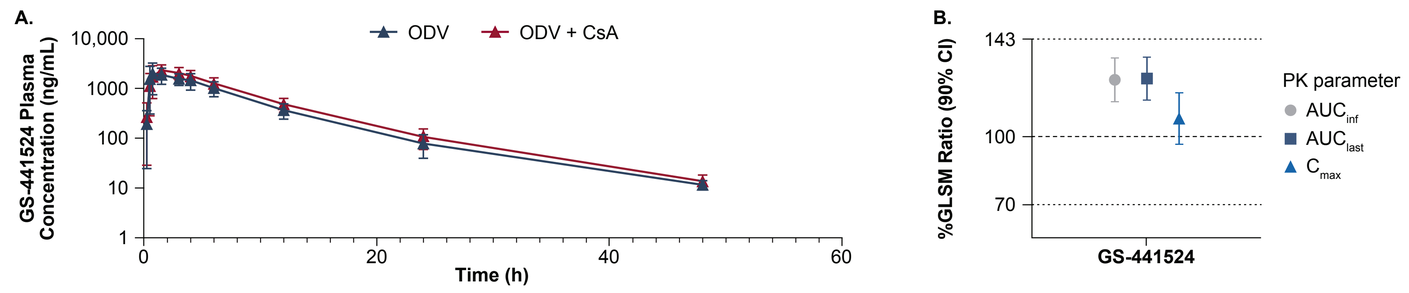


AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from dosing to last measurable concentration; BID, twice daily; C_{max}, maximum observed concentration; CYP3A4, cytochrome P450 3A4; GLSM, geometric least squares mean; MDZ, midazolam; ODV, obeldesivir; PK, pharmacokinetic.

- The overall MDZ PK profile appeared similar when MDZ was coadministered with ODV versus when MDZ was administered alone (**Figure 2A**), with comparable AUC_{inf}, AUC_{last}, and C_{max} (**Figure 2B**)
- Coadministration of MDZ with ODV after 5 or 10 days of ODV BID resulted in %GLSM ratios that were within the no-effect bounds of 80% to 125% for all MDZ PK parameters (**Figure 2B**)

ODV as a Victim

Figure 3. Effects of BCRP Inhibition by CsA on the ODV Metabolite, GS-441524: (A) Mean ± SD Plasma Concentrations of GS-441524 and (B) Statistical Comparisons of GS-441524 PK Parameters



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; BCRP, breast cancer resistance protein; C_{max}, maximum observed concentration; CsA, cyclosporin A; GLSM, geometric least squares mean; ODV, obeldesivir; PK, pharmacokinetic.

- The overall GS-441524 PK profile appeared similar when ODV was coadministered with CsA versus when ODV was administered alone (**Figure 3A**), with a comparable C_{max} (**Figure 3B**)
- Coadministration of ODV with CsA resulted in AUC_{inf} and AUC_{last} %GLSM ratios that only increased by ~25% and were not likely to be clinically relevant (**Figure 3B**)

References: **1.** Cross RW, et al. *Science*. 2024;383(6688):eadk6176. **2.** Amini E, et al. *Open Forum Infect Dis*. 2023;10:ofad500.574. **3.** Wang AQ, et al. *Front Pharmacol*. 2022;13:918083. **4.** US Food and Drug Administration. Clinical drug interaction studies — cytochrome P450 enzyme- and transporter-mediated drug interactions: guidance for industry. Accessed 2 October 2023. https://www.fda.gov/media/134581/download.

Acknowledgements: This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Laura Watts, PhD, of Lumanity Communications Inc., and were funded by Gilead Sciences, Inc.

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Disclosures: **C-CP**, **CS**, **SD**, **DX**, **XW**, **AL**, and **JL** are stockholders and employees of Gilead Sciences, Inc. **RH** was a stockholder and employee of Gilead Sciences, Inc., at the time of the study.

34th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 27-30 April 2024; Barcelona, Spain