P0474

Impact of Multiple-dose Remdesivir, a COVID-19 Antiviral, on Cytochrome P450 3A4 Activity: A Clinical Drug-Drug Interaction Study With Midazolam

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Conclusions

- Multiple-dose remdesivir did not result in clinically relevant cytochrome P450 3A4 induction as there was no decrease in plasma exposures of the probe substrate midazolam
- Increases, rather than decreases, in midazolam exposures were observed, showing weak cytochrome P450 3A4 inhibition by remdesivir
  - These results were consistent with a previous clinical drug-drug interaction study, which demonstrated that remdesivir is not a clinically relevant inhibitor of cytochrome P450 3A4[1]
- Multiple doses of remdesivir administered alone or in combination with midazolam were safe and well tolerated in healthy participants
- The clinical regimen of ≤10 days of remdesivir has been demonstrated to be safe and effective for the treatment of COVID-19
- These data, together with those of previous studies (GS-US-611-6409 and GS-US-540-9013), demonstrate that there are no clinically relevant drug-drug interactions with remdesivir

Plain Language Summary

Drug-drug interactions occur when the activity of one drug alters the activity of another drug. Due to the prevalence of COVID-19, there is a need for safe and effective treatments that are compatible with other medications a patient may be taking. Remdesivir is an antiviral drug administered intravenously that is approved for the treatment of COVID-19. A previous study showed that drug-drug interactions are unlikely when a single dose of remdesivir is administered with the probe drug midazolam.[1] Midazolam was studied because both remdesivir and midazolam interact with cytochrome P450 3A4, a liver enzyme that is important for metabolising drugs. Repeated dosing of drugs can increase the activity of liver enzymes, thereby contributing to drug-drug interactions. Therefore, in this study, drug-drug interactions with midazolam were investigated following multiple doses of remdesivir. The exposure of midazolam was not meaningfully different when it was administered alone or after multiple doses of remdesivir. Overall, these data indicate that remdesivir is safe to take with other medications that are metabolised by cytochrome P450 3A4.

Introduction

- The sustained impact of COVID-19 on public health highlights the need for antiviral treatments with low drug-drug interaction (DDI) potential[2]
- Remdesivir (RDV) is an intravenous (IV) nucleotide prodrug approved for the treatment of COVID-19 in hospitalised and nonhospitalised adult and paediatric patients[3]
- In vitro studies showed that RDV is a weak inhibitor of the drug-metabolising enzyme cytochrome P450 3A4 (CYP3A4)[4]
- Similarly, in vitro studies did not show induction of CYP3A4 by RDV; however, the concentrations of RDV tested could not reach the maximum ranges specified by European Medicines Agency DDI guidelines due to solubility limitations[5]
- In a previous Phase 1 DDI study, no clinically relevant CYP3A4 inhibition was observed when single-dose RDV was coadministered with midazolam (MDZ), a CYP3A4 probe substrate[1]

Objective

- To evaluate the induction potential of the 10-day clinical regimen of RDV on CYP3A4 activity through the probe substrate MDZ

Methods

Table 1. Study Design

Interaction Tested	Coadministered Drug	Treatment Period				Prespecified No-effect Bounds (%)[d]
		Day 1[a]	Day 2[b]	Days 3-10[b]	Day 11[b,c]	
CYP3A4 induction	MDZ (N = 14)	PO MDZ 2.5 mg	IV RDV 200 mg	IV RDV 100 mg once daily	PO MDZ 2.5 mg + IV RDV 100 mg	70-143

[a]All PO MDZ doses were delivered under fasted conditions.
[b]All IV RDV doses were administered as 30-minute infusions without regard to food, except on Day 11, when RDV and MDZ were administered under fasted conditions.
[c]On Day 11, PO MDZ was administered at the end of RDV infusion.
[d]Prespecified bounds of 70% to 143% were supported by previous Gilead studies with MDZ.
CYP3A4, cytochrome P450 3A4; IV, intravenous; MDZ, midazolam; PO, oral; RDV, remdesivir.

- This was a Phase 1, fixed-sequence study (**Table 1**) conducted in healthy male and nonpregnant/nonbreastfeeding female participants aged 18 to 45 years who had a body mass index of ≥19.0 and ≤30.0 kg/m^2
- To maximise induction potential, daily doses of IV RDV were administered for 10 consecutive days prior to MDZ coadministration[5]
- On Days 1 and 11, blood samples were collected for pharmacokinetic (PK) analysis until 24 hours post dose, with samples quantified for MDZ and its metabolite (1'-hydroxymidazolam [1'-OH-MDZ])
- Plasma concentrations of MDZ and 1'-OH-MDZ were measured by validated liquid chromatography-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}]) of MDZ and 1'-OH-MDZ were estimated by noncompartmental analysis and compared between treatments (test [Day 11] vs reference [Day 1]) using a mixed-effects model with geometric least squares mean (GLSM) and 2-sided 90% CIs with prespecified no-effect bounds (70%-143%)
- The molar ratio of MDZ to 1'-OH-MDZ plasma concentrations, with or without RDV coadministration (Day 11 vs Day 1), was assessed
- Safety was monitored throughout the study

Results

Table 2. Participant Demographics

Characteristic	Total (N = 14)
Age, y, median (Q1, Q3)	35 (33, 38)
Sex at birth, n (%)	
Female	7 (50)
Male	7 (50)
Race, n (%)	
Black	3 (21)
White	11 (79)
Ethnicity, n (%)	
Hispanic or Latino	14 (100)
BMI, kg/m^2, median (Q1, Q3)	28.1 (22.5, 30.5)

BMI, body mass index; Q1, first quartile; Q3, third quartile.

Participants

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

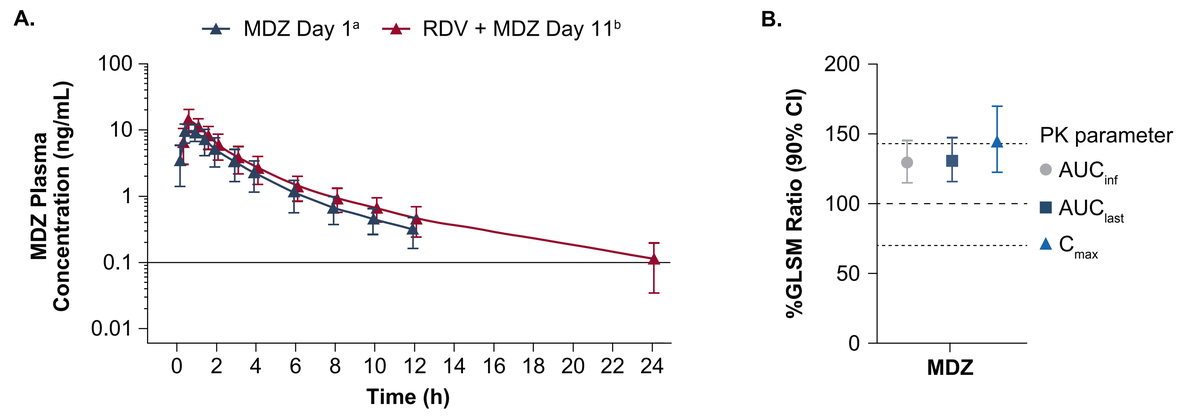
PK of MDZ and 1'OH-MDZ

- There was a marginal increase in MDZ plasma concentrations following multiple-dose RDV + MDZ (Day 11) compared to MDZ alone (Day 1; **Figure 1A**)
- Following multiple-dose RDV, coadministration of RDV with MDZ resulted in 30%, 31%, and 45% increases in the AUC_{inf}, AUC_{last}, and C_{max} of MDZ, respectively, compared to MDZ alone (**Figure 1B**)
  - For MDZ AUC_{inf} and AUC_{last}, the %GLSM ratios and lower 90% CIs were within the no-effect bounds, whereas the upper 90% CIs slightly exceeded the bounds
  - For MDZ C_{max}, the %GLSM ratio and upper 90% CI slightly exceeded the no-effect bounds
  - The increases in MDZ AUC_{inf}, AUC_{last}, and C_{max} were consistent with observations from a previous RDV DDI study (GS-US-611-6409) that specifically evaluated the CYP3A4 inhibition potential of RDV under the worst-case scenario; results from the study demonstrated that the increase in MDZ exposure was not clinically relevant, and thus, RDV is not a clinically relevant inhibitor of CYP3A4[1]
- There was a marginal increase in plasma concentrations of 1'-OH-MDZ following multiple-dose RDV + MDZ (Day 11) compared to MDZ alone (Day 1; **Figure 2A**)
- Following multiple-dose RDV, coadministration of RDV with MDZ resulted in 24%, 23%, and 45% increases in the AUC_{inf}, AUC_{last}, and C_{max} of 1'-OH-MDZ, respectively, compared to MDZ alone (**Figure 2B**)
  - For 1'-OH-MDZ AUC_{inf} and AUC_{last}, the %GLSM ratios and 90% CIs were within the no-effect bounds
  - For 1'-OH-MDZ C_{max}, the %GLSM ratio and lower 90% CI were within the no-effect bounds, whereas the upper 90% CI slightly exceeded the bounds
- No significant differences in plasma MDZ to 1'-OH-MDZ molar concentration ratios for Day 11 versus Day 1 were observed, supporting the conclusion that minor elevations in plasma 1'-OH-MDZ were not due to changes in CYP3A4 metabolism

Safety

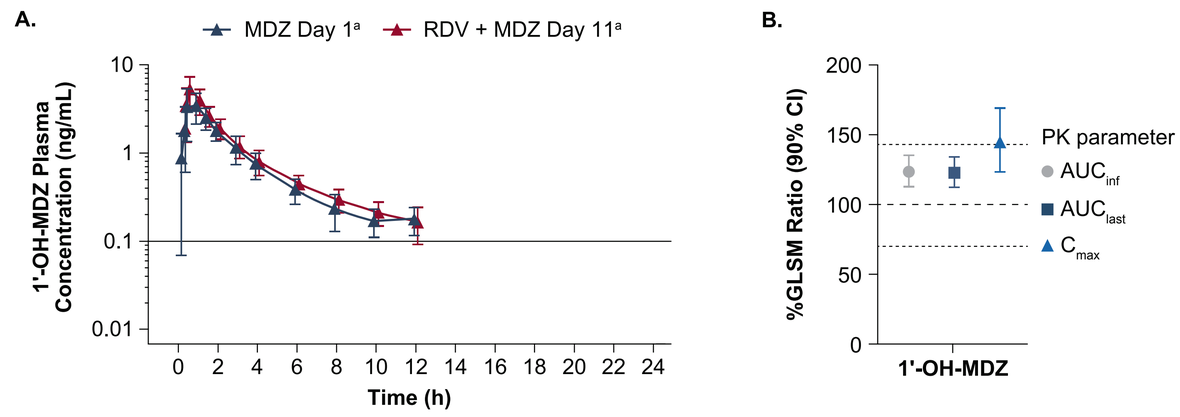
- Remdesivir was safe and well tolerated among healthy participants
  - Overall, 1 (7%) Grade 2 adverse event (AE) of an increase in hepatic enzymes was reported; this was considered treatment related by the investigator and resolved after study treatment was completed
    - All other AEs were Grade 1, without clinically significant laboratory abnormalities
  - There were no clinically significant changes in vital signs or physical examination findings

Figure 1. Effects of Multiple-dose RDV on the (A) Mean ± SD Plasma Concentrations of MDZ and (B) Plasma PK Parameters of MDZ



[a]On Day 1 (MDZ alone), plasma PK samples for all participants at the 24-hour collection time point were below the limit of quantification (<0.1 ng/mL).
[b]On Day 11 (RDV + MDZ), plasma PK samples collected at 24 hours post MDZ dose for 7 of 14 participants were below the limit of quantification (<0.1 ng/mL).
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 observed concentration; GLSM, geometric least squares mean; MDZ, midazolam; PK, pharmacokinetic; RDV, remdesivir.

Figure 2. Effects of Multiple-dose RDV on the (A) Mean ± SD Plasma Concentrations of 1'-OH-MDZ and (B) Plasma PK Parameters of 1'-OH-MDZ



[a]On Days 1 and 11, all plasma PK samples collected at 24 hours post MDZ dose were below the limit of quantification (<0.1 ng/mL).
1'-OH-MDZ, 1'-hydroxymidazolam; 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 observed concentration; GLSM, geometric least squares mean; MDZ, midazolam; PK, pharmacokinetic; RDV, remdesivir.

References: **1.** Peng CC, et al. *Open Forum Infect Dis*. 2023;10:ofad500.607. **2.** World Health Organization. WHO COVID-19 dashboard. Accessed 15 February 2024. https://data.who.int/dashboards/covid19/cases. **3.** Veklury® (remdesivir) for injection, for intravenous use [package insert]. Gilead Sciences, Inc.; 2024. **4.** Humeniuk R, et al. *Clin Pharmacokinet*. 2021;60:569-83. **5.** European Medicines Agency. Guideline on the investigation of drug interactions - revision 1. Accessed 21 February 2023. https://www.ema.europa.eu/en/investigation-drug-interactions-scientific-guideline.

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

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Disclosure: **JC**, **NS**, **MA**, **SD**, **SC**, **KG**, **RHH**, and **AK** are stockholders and employees of Gilead Sciences, Inc.

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