

Participant-Level Meta-Analysis of Obeldesivir Clinical Safety and Pharmacokinetic Data

Vincent Chang, Eric Salgado, Elham Amini, Luzelena Caro, Xiaoning Wang

Gilead Sciences, Inc., Foster City, CA, USA

Copies of this poster obtained through QR (Quick Response) code are for personal use only and may not be reproduced without written permission of the authors.



Conclusions

- Clinical data, as well as modelling and simulation, were utilised to perform a participant-level meta-analysis of obeldesivir exposures relative to various safety endpoints
 - Logistic regression was considered an appropriate approach given the limited collection of laboratory tests during clinical trial conduct
- Statistically significant relationships with pharmacokinetic exposures were found only for Grade ≥ 3 asymptomatic treatment-emergent laboratory abnormalities of creatinine clearance
 - The relative contributions of obeldesivir treatment, SARS-CoV-2 infection, and renal impairment to asymptomatic treatment-emergent laboratory abnormalities of creatinine clearance remain unclear
- Establishing a pharmacokinetics/safety relationship could inform the dose selection of obeldesivir for further clinical development and future indications

Plain Language Summary

- Obeldesivir is an oral medication that is being studied for the treatment of different viral respiratory diseases, including COVID-19 and respiratory syncytial virus disease
- This study analysed data from previous clinical studies in order to understand the relationship between the amount of obeldesivir in the body and various safety endpoints
- We found that, while people were more likely to have temporary reduction of kidney function with higher amounts of obeldesivir in the body, other safety metrics were not impacted

Introduction

- Obeldesivir (ODV) is an oral prodrug of the circulating metabolite GS-441524 with antiviral activity against a broad spectrum of RNA viruses, including SARS-CoV-2 and other emerging viruses^{1,3}
- Renal impairment can increase systemic exposures of GS-441524, which is predominantly eliminated renally,⁴ and SARS-CoV-2 infection can impact renal function^{5,6}
- Data from 4 studies (three Phase 1 trials in healthy volunteers and one Phase 3 trial in participants with COVID-19), which evaluated the pharmacokinetics (PK), safety, and tolerability of ODV,^{4,7,8} were used in this PK/safety analysis

Objective

- To characterise the relationship between GS-441524 plasma PK exposures and various safety endpoints using clinical data from studies conducted in healthy volunteers and participants with COVID-19

Results

- The incidence rate of observed safety endpoints of interest is summarised in **Table 1**

Table 1. Summary of Observed Safety Endpoints of Interest

Safety Endpoint, n (%)	Phase 3 ^a		Phase 1 ^b
	ODV (n = 229)	Placebo (n = 226)	ODV (n = 103)
Grade ≥ 2 CrCL decrease	44 (19)	47 (21)	21 (20)
Grade ≥ 3 CrCL decrease	10 (4)	4 (2)	0
Grade ≥ 2 SCr increase	9 (4)	9 (4)	1 (1)
Grade ≥ 3 SCr increase	3 (1)	1 (<1)	0
Grade ≥ 2 diarrhoea	10 (4)	5 (2)	0

^aPhase 3 data were from high-risk, nonhospitalised participants with COVID-19 from study GS-US-611-6273.
^bPhase 1 data were pooled from healthy volunteers from studies GS-US-611-6248, GS-US-611-6469, and GS-US-611-6472.
CrCL, creatinine clearance; ODV, obeldesivir; SCr, serum creatinine.

- GS-441524 plasma PK metrics for each study and dose are summarised in **Table 2**

Table 2. Summary of PopPK-Estimated GS-441524 Plasma PK Metrics by Study and Dose

Dose	n	AUC _{0-24h} (μM ^h)	C _{max} (μM)		AUC _{0-24h} (μM ^h) ^a		C _{trough} (μM)	
			Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
GS-US-611-6248 (Phase 1 study in healthy volunteers)								
100 mg SAD	6	11.7 (10.6-17.9)	1.8 (1.6-2.5)	NA	10.7 (9.6-16.4)	0 (0-0)	NA	NA
300 mg SAD	6	32.8 (27.8-43.7)	5.6 (4.2-6.7)	NA	30.5 (26.8-41.3)	0 (0-0.1)	NA	NA
500 mg SAD	22	70.9 (47.8-81.2)	9.1 (5.0-13.4)	NA	67.0 (45.5-75.8)	0.1 (0.1-0.2)	NA	NA
500 mg MAD	6	676.6 (534.5-800.0)	12.2 (8.0-13.9)	14.4 (9.8-16.0)	121.1 (94.1-144.0)	139.9 (111.0-165.8)	1.5 (1.3-2.0)	2.1 (1.8-2.8)
900 mg SAD	6	108.2 (75.8-154.2)	16.8 (12.6-23.8)	NA	102.0 (71.0-146.7)	0.2 (0.1-0.4)	NA	NA
900 mg MAD	6	554.2 (497.5-621.1)	15.9 (14.8-18.7)	16.3 (15.5-19.2)	106.6 (96.8-120.4)	112.4 (100.5-125.7)	NA	NA
1600 mg SAD	6	193.2 (121.2-213.1)	24.9 (16.9-30.3)	NA	174.6 (115.3-192.1)	0.4 (0.1-0.5)	NA	NA
GS-US-611-6273 (Phase 3 study in high-risk, nonhospitalised participants with COVID-19)								
350 mg BID	230	638.1 (322.0-1322.7)	11.3 (3.4-17.1)	11.8 (6.5-19.5)	126.2 (59.6-218.8)	126.1 (7.2-289.3)	2.8 (1.3-5.4)	3.8 (1.7-11.0)
GS-US-611-6469 (Phase 1 study in healthy volunteers)								
350 mg BID	19	443.2 (307.9-636.2)	7.8 (5.2-10.0)	9.2 (6.2-12.0)	78.8 (55.7-108.7)	91.1 (63.4-134.1)	1.2 (0.8-2.2)	1.3 (0.9-2.6)
350 mg single dose	17	101.6 (70.8-139.6)	7.6 (6.3-9.7)	NA	40.6 (28.5-55.7)	NA	NA	NA
GS-US-611-6472 (Phase 1 study in healthy volunteers with normal or impaired renal function)								
175 mg single dose (normal renal function)	8	28.2 (23.7-40.1)	4.8 (3.1-6.1)	NA	26.6 (22.0-37.0)	0.1 (0.1-0.2)	NA	NA
175 mg single dose (renal impairment)	8	73.1 (27.4-135.1)	4.4 (3.3-7.1)	NA	51.3 (24.0-90.2)	1.0 (0.1-2.6)	NA	NA
350 mg single dose (normal renal function)	11	44.7 (29.9-72.3)	7.2 (3.6-11.9)	NA	43.2 (28.4-67.4)	0.1 (0-0.2)	NA	NA
350 mg single dose (renal impairment)	23	65.4 (45.0-120.7)	7.9 (4.6-13.7)	NA	58.0 (41.2-95.3)	0.2 (0.1-0.8)	NA	NA

Data are presented as median (95% prediction interval).
^aThe dosing interval for AUC_{0-24h} calculations was 0 to 24 hours after the first dose of ODV.
AUC_{0-24h}, area under the concentration-time curve across the entire duration of treatment; AUC_{0-24h}, area under the concentration-time curve within a dosing interval; BID, twice daily; C_{max}, maximum observed concentration; C_{trough}, minimum observed concentration; NA, not applicable; ODV, obeldesivir; PK, pharmacokinetic; popPK, population pharmacokinetic; SAD, single ascending dose.

Methods

- Available data from 332 participants who received ODV and 226 participants who received placebo from three Phase 1 trials in healthy volunteers and one Phase 3 trial in participants with COVID-19 were evaluated in this safety analysis^{1,7,8}
- Logistic regression models were used to determine the correlation between various PK metrics and the incidence of adverse events and asymptomatic treatment-emergent laboratory abnormalities (TELAs) of interest
- Participant-level GS-441524 plasma PK metrics were extracted from a previously developed population PK model (Poster IV-002)⁹
 - Exposure measures of interest were maximum observed concentration (C_{max}) at Days 1 and 5, area under the concentration-time curve within a dosing interval (AUC_{0-24h}) at Days 1 and 5, and cumulative area under the concentration-time curve across the entire duration of treatment (AUC_{cumulative}) to determine whether early exposure, steady-state exposure, or overall exposure, respectively, correlated with the incidence of safety endpoints
- The safety endpoints of interest included Grade ≥ 2 creatinine clearance (CrCL) TELAs, Grade ≥ 3 CrCL TELAs, Grade ≥ 2 serum creatinine (SCr) TELAs, Grade ≥ 3 SCr TELAs, and Grade ≥ 2 diarrhoea
- Logistic regression, data manipulation, and visualisation were performed in R v4.2.14 (The R Foundation)

- The odds ratios (ORs) and corresponding 95% CIs estimated from the logistic regression models are listed in **Table 3**

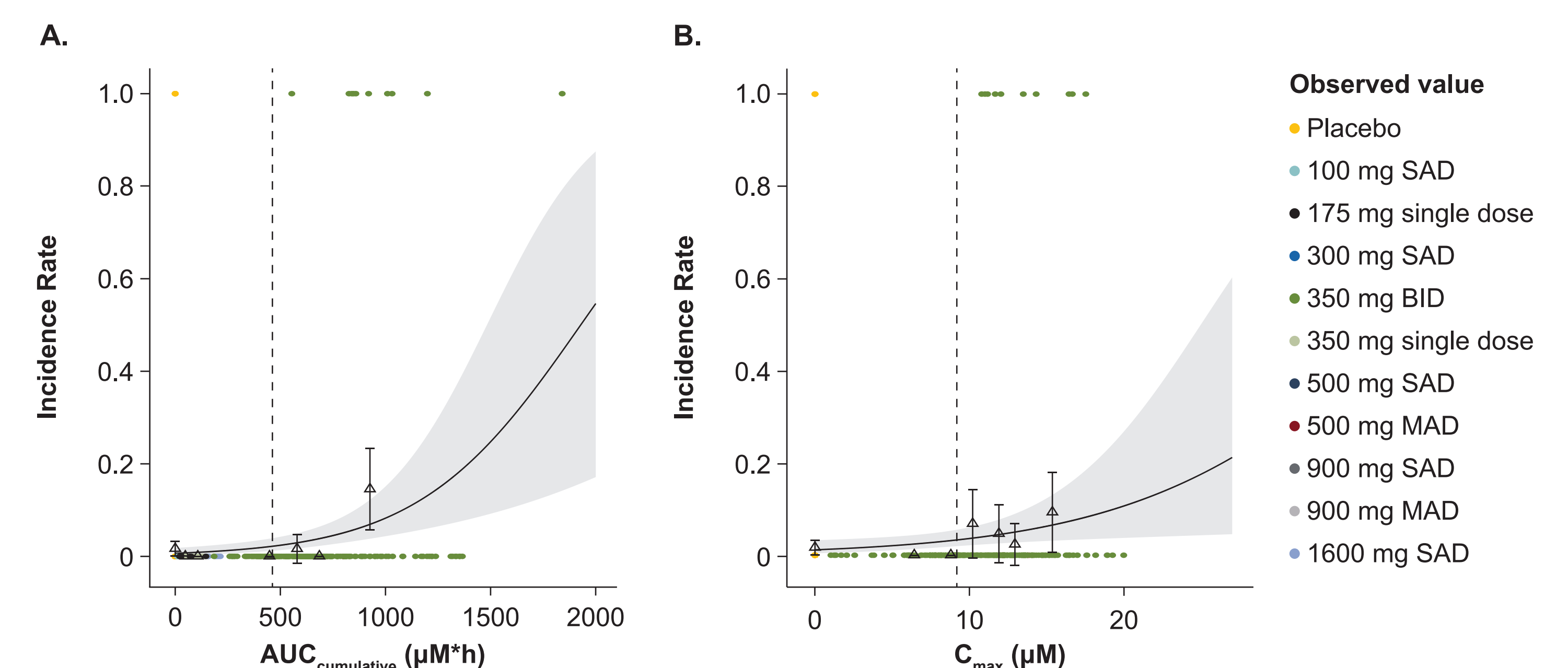
Table 3. Estimated ORs of Safety Endpoints by Exposure Measures

	Grade ≥ 2 Diarrhoea	Grade ≥ 2 CrCL TELA	Grade ≥ 3 CrCL TELA	Grade ≥ 2 SCr TELA	Grade ≥ 3 SCr TELA
AUC _{0-24h} ^{a,b} at Day 1	1.15 (0.27-4.45)	1.56 (0.83-2.91)	5.11 (1.27-17.90)*	1.46 (0.42-4.46)	3.14 (0.35-1.78)
AUC _{0-24h} ^{a,b} at Day 5	0.93 (0.33-2.48)	1.04 (0.63-1.69)	4.95 (1.82-13.40)**	1.80 (0.66-4.48)	5.10 (0.64-33.70)
AUC _{cumulative} ^c	0.98 (0.87-1.11)	1.02 (0.96-1.08)	1.30 (1.14-1.48)***	1.04 (0.93-1.15)	1.12 (0.92-1.33)
C _{max} ^d at Day 1	0.97 (0.67-1.37)	0.99 (0.82-1.19)	1.78 (1.14-2.95)*	1.00 (0.64-1.47)	1.74 (0.76-4.64)
C _{max} ^d at Day 5	0.97 (0.69-1.34)	1.00 (0.85-1.20)	1.86 (1.21-2.97)**	1.10 (0.75-1.58)	1.86 (0.78-5.11)

Data are presented as OR (95% CI). * indicates $P < 0.05$, ** indicates $P < 0.01$, and *** indicates $P < 0.001$.
^aORs are for every 100-μM^h increase in AUC_{0-24h}.
^bThe dosing interval for AUC_{0-24h} calculations was 0 to 24 hours after the first dose of ODV.
^cORs are for every 100-μM^h increase in AUC_{cumulative}.
^dORs are for every 5-μM increase in C_{max}. Single-dose data were excluded from the C_{max} models due to underprediction of TELAs with ODV in the Phase 3 BIRCH study data; for these calculations, only multiple-dose data were included.
AUC_{0-24h}, area under the concentration-time curve across the entire duration of treatment; AUC_{cumulative}, area under the concentration-time curve within a dosing interval; C_{max}, maximum observed concentration; CrCL, creatinine clearance; ODV, obeldesivir; OR, odds ratio; SCr, serum creatinine; TELA, treatment-emergent laboratory abnormality.

- Figure 1** shows the relationship between AUC_{cumulative} and C_{max} and the observed and predicted incidence of Grade ≥ 3 CrCL TELAs

Figure 1. Observed and Predicted Incidence of Grade ≥ 3 CrCL TELAs by (A) AUC_{cumulative} and (B) C_{max} on Day 1^a



Black triangles indicate observed incidence rates, with vertical error bars representing the 95% CIs. Solid black lines indicate incidence rates as predicted by the logistic regression models, with the shaded areas representing the 95% CIs. Dashed black lines indicate median exposures for the proposed ODV dose for patients with COVID-19 (350 mg BID).
^aSingle-dose data were excluded from the C_{max} models due to underprediction of TELAs with ODV in the Phase 3 BIRCH study data; for these calculations, only multiple-dose data were included.
AUC_{0-24h}, area under the concentration-time curve across the entire duration of treatment; BID, twice daily; C_{max}, maximum observed concentration; CrCL, creatinine clearance; MAD, multiple ascending dose; ODV, obeldesivir; SAD, single ascending dose; TELA, treatment-emergent laboratory abnormality.

- The likelihood of Grade ≥ 3 CrCL TELAs was significantly higher for every 100-μM^h increase in AUC_{cumulative} (OR, 1.30; 95% CI, 1.14-1.48; $P < 0.001$; **Table 3; Figure 1A**)
- The likelihood of Grade ≥ 3 CrCL TELAs was significantly higher for every 5-μM increase in C_{max} at Day 1 (OR, 1.78; 95% CI, 1.14-2.95; $P < 0.05$; **Table 3; Figure 1B**)
- Remaining safety endpoints (Grade ≥ 2 CrCL TELAs, Grade ≥ 2 SCr TELAs, Grade ≥ 3 SCr TELAs, and Grade ≥ 2 diarrhoea) were not found to have statistically significant relationships with any of the PK parameters

Limitations

- There may have been a confounding effect of ODV treatment, COVID-19 disease, and renal impairment on CrCL TELAs that was not able to be detected with the current analysis
- Because logistic regression is a time-independent method, it is unknown if ODV had any time-dependent or first-dose effects that the AUC_{cumulative} relationship could not capture; therefore, this exposure-safety relationship may have been underestimated

References: 1. Mackman RL, et al. *J Med Chem*. 2023;66:11701-17. 2. Cross RW, et al. *Nat Med*. 2025;31:1303-11. 3. Pitts J, et al. *bioRxiv*. Preprint posted online 25 February 2025. doi:10.1101/2025.02.24.639976. 4. Anoshchenko O, et al. *Clin Pharmacol Ther*. 2024;116:1231-9. 5. Dellepiane S, et al. *Kidney Med*. 2021;3:877-9. 6. Fisher M, et al. *J Am Soc Nephrol*. 2020;31:2145-57. 7. Peng CC, et al. *Clin Pharmacol Ther*. 2025;117:1403-12. 8. Streinu-Cercel A, et al. *Open Forum Infect Dis*. 2025;12:ofae631.2182. 9. Salgado E, et al. Presented at: 33rd Meeting of the Population Approach Group Europe (PAGE); 4-6 June 2025; Thessaloniki, Greece. Poster IV-002.

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. The authors would like to thank Rob Hyland, Santosh Davies, Olivia Fu, Shuguang Chen, and Marni White for their contributions to this study.

Correspondence: Vincent Chang, vincent.chang2@gilead.com

Disclosure: VC, ES, EA, LC, and XW are stockholders and employees of Gilead Sciences, Inc.