Pharmacokinetics, Safety, and Tolerability of Obeldesivir (OBV; GS-5245) in Healthy Participants

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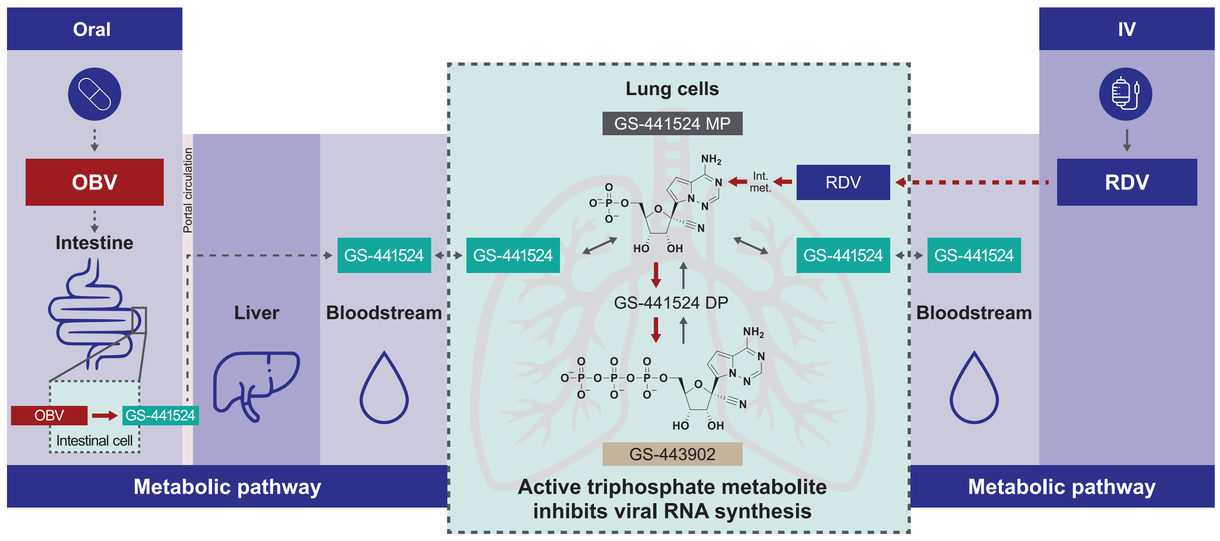
Introduction

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, has infected >750 million people worldwide, resulting in >6 million deaths as of 1 March 2023[1]
- Currently approved or authorised therapies for treating nonhospitalised individuals with COVID-19 are limited by efficacy, drug-drug interactions, or route of administration
- Remdesivir (RDV) is an intravenously (IV) administered COVID-19 treatment approved in nonhospitalised and hospitalised individuals,[2] with safety and efficacy demonstrated in numerous clinical trials[3-5]
- Obeldesivir (OBV), an oral inhibitor of the SARS-CoV-2 polymerase, is currently being evaluated in Phase 3 studies and has the potential to be a simple twice daily (BID) treatment regimen with limited drug-drug interactions

Figure 1. RDV and OBV Generate the Same Active Metabolite Through Different Metabolic Pathways



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

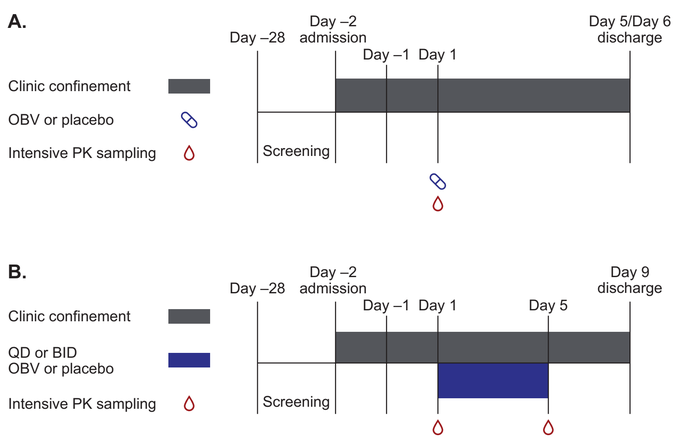
Objective

- To evaluate the pharmacokinetics (PK), safety, and tolerability of OBV in healthy participants

Methods

- This was a randomised, blinded, placebo-controlled, Phase 1 study in which fasted healthy participants were randomly assigned (3:1) to receive OBV or placebo in 4 single-dose cohorts (100 mg, 300 mg, 900 mg, and 1600 mg; **Figure 2A**) and 2 multiple-dose cohorts (500 mg BID and 900 mg once daily [QD] for 5 days; **Figure 2B**)
- The effect of food on GS-441524 plasma exposures was assessed (high-fat/high-calorie breakfast, 500 mg single dose; **Figure 2A**)
- GS-441524 plasma and urine concentrations and GS-443902 peripheral blood mononuclear cell (PBMC) concentrations were determined using fully validated liquid chromatography-tandem mass spectrometry methods[6]
- The Phase 3 dose was selected based on the totality of the data from the first-in-human study, plasma exposures associated with efficacy in SARS-CoV-2 animal models, and prior knowledge of active metabolite generation following RDV administration
- Safety assessments were conducted throughout the study

Figure 2. Schematic for (A) Single-dose and (B) Multiple-dose Cohorts



OBV, obeldesivir; PK, pharmacokinetic; QD, once daily; BID, twice daily.

Results

Table 1. Baseline Characteristics of Trial Participants

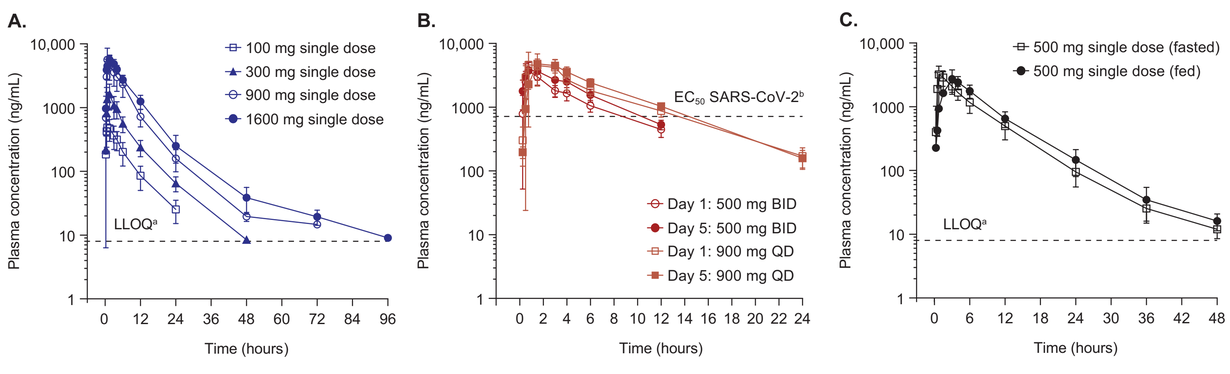
	Single-dose cohorts					Multiple-dose cohorts			Food-effect cohorts		
	100 mg (n = 6)	300 mg (n = 6)	900 mg (n = 6)	1600 mg (n = 6)	Pooled placebo (n = 8)	500 mg BID (n = 6)	900 mg QD (n = 6)	Pooled placebo (n = 4)	Fasted 500 mg (n = 11)	Fed 500 mg (n = 11)	Total (n = 70)
Age, mean (SD; years)	32 (9.7)	30 (8.7)	35 (6.0)	34 (7.5)	32 (8.5)	33 (7.7)	32 (7.7)	29 (5.3)	33 (8.9)	33 (6.9)	32 (7.5)
Sex, n (%)											
Female	2 (33.3)	1 (16.7)	3 (50.0)	2 (33.3)	5 (62.5)	2 (33.3)	4 (66.7)	2 (50.0)	6 (54.5)	6 (54.5)	33 (47.1)
Race, n (%)											
American Indian or Alaska Native	0	0	0	0	1 (12.5)	0	1 (16.7)	0	0	0	2 (2.9)
Asian	0	1 (16.7)	0	0	0	0	0	1 (25.0)	2 (18.2)	2 (18.2)	6 (8.6)
Black	1 (16.7)	3 (50.0)	2 (33.3)	5 (83.3)	4 (50.0)	2 (33.3)	2 (33.3)	1 (25.0)	7 (63.6)	4 (36.4)	31 (44.3)
White	5 (83.3)	2 (33.3)	4 (66.7)	1 (16.7)	2 (25.0)	4 (66.7)	3 (50.0)	1 (25.0)	2 (18.2)	5 (45.5)	29 (41.4)
Other	0	0	0	0	1 (12.5)	0	0	1 (25.0)	0	0	2 (2.9)
Weight, mean (SD; kg)	75.7 (11.6)	73.9 (13.6)	75.9 (12.1)	79.6 (14.1)	73.1 (13.6)	77.3 (12.0)	73.2 (11.1)	80.9 (8.3)	74.0 (11.1)	72.2 (14.0)	75.0 (11.9)

BID, twice daily; QD, once daily; SD, standard deviation.

Plasma PK

- Maximum observed concentrations of GS-441524 in plasma were achieved shortly after drug administration (time to maximum observed concentration, ~0.75 hours) and remained detectable for 24 to 96 hours postdose; OBV levels were undetectable or transient (**Figure 3** and **Table 2**)
- GS-441524 exhibited linear and dose-proportional PK in the 100 to 900 mg range; less than dose-proportional increases were observed at the 1600 mg dose; terminal plasma elimination half-life was 6 to 7 hours across the 100 to 900 mg single-dose cohorts

Figure 3. Plasma Concentration-time Profiles of the GS-441524 Metabolite in Healthy Participants Receiving OBV in (A) Single-dose Cohorts, (B) Multiple-dose Cohorts, and (C) Food-effect Cohorts



OBV, obeldesivir; LLOQ, lower limit of quantification; EC_{50}, half-maximal effective concentration; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BID, twice daily; QD, once daily.
[a]The LLOQ for GS-441524 was 8 ng/mL.
[b]The EC_{50} for GS-441524 in normal human bronchial epithelial cells was 714 ng/mL.

Plasma PK (cont.)

- Multiple-dose PK were consistent with single-dose PK (**Table 2**)
- Accumulation was ~12% after QD dosing and ~35% after BID dosing; steady state was reached on Day 4 of dosing

Table 2. Mean (%CV) GS-441524 Plasma PK Parameters in Healthy Participants Following a Single Dose of OBV

	Single-dose cohorts				Multiple-dose cohorts			
PK parameter[a]	100 mg (n = 6)	300 mg (n = 6)	900 mg (n = 6)	1600 mg (n = 6)	Day 1: 500 mg BID (n = 8)	Day 5: 500 mg BID (n = 8)	Day 1: 900 mg QD (n = 8)	Day 5: 900 mg QD (n = 8)
C_{max} (ng/mL)	570 (30.5)	1830 (32.6)	5940 (44.6)	7170 (26.7)	3820 (32.7)	4620 (18.2)	6230 (14.5)	5180 (19.6)
T_{max} (h)	0.75 (0.50-0.75)	0.78 (0.50-1.50)	0.75 (0.75-1.50)	1.50 (0.75-1.53)	0.75 (0.75-1.50)	0.75 (0.50-1.50)	0.75 (0.75-1.50)	1.5 (1.5-3.0)
$t_{1/2}$ (h)	5.85 (5.57-6.26)	6.10 (4.86-6.93)	7.36 (6.89-7.81)	15.70 (14.1-17.6)	–	–	–	–
$AUC_{inf/tau}$ (h•ng/mL)[b]	3700 (34.7)	10,400 (21.4)	34,600 (34.7)	48,300 (22.4)	15,900 (18.2)	21,500 (19.3)	32,000 (11.6)	35,700 (11.6)
AUC_{0-24} (h•ng/mL)	–	–	–	–	~31,800[c]	~43,000[c]	–	–

%CV, percentage coefficient of variation; PK, pharmacokinetic; OBV, obeldesivir; BID, twice daily; QD, once daily; C_{max}, maximum observed concentration; T_{max}, time to maximum observed concentration; $t_{1/2}$, terminal elimination half-life; AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours; Q1, Quartile 1; Q3, Quartile 3; AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; AUC_{0-12}, area under the concentration-time curve from 0 to 12 hours; AUC_{tau}, area under the concentration-time curve at steady state over the dosing interval.
[a]Data are presented as mean (%CV), with the exception of T_{max} and $t_{1/2}$, which are presented as median (Q1-Q3).
[b]AUC_{inf} is reported for single-dose cohorts. On Day 1, AUC_{0-12} and AUC_{0-24} are reported for BID and QD dosing, respectively; on Day 5, AUC_{tau} is reported.
[c]BID dosing AUC_{0-24} was calculated as 2 × AUC_{0-12} and does not account for the expected additional accumulation on Day 1; Day 1 AUC_{0-12} = 15,900 (18.2); Day 5 AUC_{0-12} = 21,500 (19.3).

Intracellular PK

- Dose-proportional increases in the intracellular concentrations of the active metabolite (GS-443902) were observed in PBMCs; substantial accumulation was observed after repeat dosing (6-fold for BID and 3-fold for QD)
- OBV resulted in sufficient plasma concentrations of GS-441524 expected for efficacy
- At the selected Phase 3 dosing regimen of 350 mg BID for 5 days, exposures of GS-443902 are likely to exceed those observed with the approved IV RDV dosing regimen

Urine PK

- Approximately 40% to 45% of the OBV dose was recovered as GS-441524 in urine over the first 24 hours postdose; OBV was not detectable in urine
- GS-441524 metabolite renal clearance was approximately 150 to 180 mL/min across all single-dose cohorts
  - These values are consistent with historical data describing the urine PK of GS-441524 after IV RDV

Food-effect Study

- Administration of OBV with a high-fat meal decreased the rate (time to maximum observed concentration increased from 0.75 to 3.0 hours) but not the extent of absorption; therefore, OBV can be given without regard to food (**Table 3**)

Table 3. GS-441524 Plasma PK Parameters in Fasted Versus Fed Healthy Participants Receiving a Single Dose of OBV

PK parameter[a]	Fasted 500 mg (n = 11)	Fed 500 mg (n = 11)	GLSM ratio (90% CI)[b]
C_{max} (ng/mL)	3600 (33.3)	3430 (35.3)	0.94 (0.73-1.21)
T_{max} (h)	0.75 (0.75-1.50)	3.0 (3.0-4.1)	–
AUC_{last} (h•ng/mL)	20,700 (18.0)	23,000 (13.5)	1.13 (0.99-1.29)
AUC_{inf} (h•ng/mL)	20,900 (17.9)	23,100 (13.4)	1.13 (0.99-1.29)
AUC_{extrap} (%)	0.60 (46.7)	0.60 (45.1)	–
$t_{1/2}$ (h)	6.3 (5.5-7.1)	6.2 (4.7-6.5)	–

PK, pharmacokinetic; OBV, obeldesivir; GLSM, geometric least-squares mean; CI, confidence interval; C_{max}, maximum observed concentration; T_{max}, time to maximum observed concentration; AUC_{last}, area under the concentration-time curve from dosing to last measurable concentration; AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; AUC_{extrap}, area under the concentration-time curve extrapolated as a percentage of the total; $t_{1/2}$, terminal elimination half-life; %CV, percentage coefficient of variation; Q1, Quartile 1; Q3, Quartile 3; AUC_{0-24}, area under the concentration-time curve from 0 to 24 hours.
[a]Data are presented as mean (%CV), with the exception of T_{max} and $t_{1/2}$, which are presented as median (Q1-Q3).
[b]The no-effect bounds were defined by 2-sided 90% CIs (calculated for the ratios of GLSM of fasted vs fed cohorts) falling within [0.70 to 1.43] for AUC_{0-24} and AUC_{inf} and [0.60 to 1.67] for C_{max}.

Safety

- Safety data are summarised below (**Table 4**)
  - Of the 14 AEs reported, 13 were Grade 1 and 1 was Grade 2
  - There were 3 study drug–related AEs, all of which were headaches: 2 of 58 (3.4%) in participants who received OBV and 1 of 12 (8.3%) in the pooled placebo group

Table 4. Summary of AEs

	Single-dose cohorts					Multiple-dose cohorts			Food-effect cohorts		
n (%)	100 mg (n = 6)	300 mg (n = 6)	900 mg (n = 6)	1600 mg (n = 6)	Pooled placebo (n = 8)	500 mg BID (n = 6)	900 mg QD (n = 6)	Pooled placebo (n = 4)	Fasted 500 mg (n = 11)	Fed 500 mg (n = 11)	Total (n = 70)
AE	1 (16.7)	0	0	2 (33.3)	2 (25.0)	2 (33.3)	1 (16.7)	2 (50.0)	3 (27.3)	1 (9.1)	14 (20.0)
Grade ≥3 AE	0	0	0	0	0	0	0	0	0	0	0
AE related to study drug	0	0	0	0	0	1 (16.7)	0	1 (25.0)	1 (9.1)	0	3 (4.3)

AE, adverse event; BID, twice daily; QD, once daily.

- The most common laboratory abnormality in both the OBV and placebo groups was a Grade 2 creatinine clearance decrease, which occurred in 18 of 58 (31%) and 3 of 12 (25%) participants, respectively
- Only 1 participant experienced a Grade ≥3 laboratory abnormality
  - A participant in the 300 mg single-dose OBV cohort had Grade 3 elevated lipase on Day 3 that was transient and returned to normal on Day 5; the participant also had a pre-dose Grade 1 lipase elevation

Conclusions

- **Linear and dose-proportional GS-441524 plasma PK were observed across the 100 to 900 mg OBV doses**
- **Target therapeutic exposures of plasma GS-441524 and the active intracellular metabolite GS-443902 were achieved and exceeded in the multiple-dose cohorts**
- **Administration of OBV was safe and well tolerated**
- **Results of this Phase 1 study support further clinical evaluation of 350 mg OBV BID, which is being assessed in two Phase 3 clinical trials (ClinicalTrials.gov Identifiers: NCT05603143 and NCT05715528)**

References: **1.** World Health Organization. WHO coronavirus (COVID-19) dashboard. Accessed 1 March 2023. https://covid19.who.int. **2.** Veklury® (remdesivir) injection, for intravenous use [package insert]. Gilead Sciences, Inc.; 2022. **3.** Beigel JH, et al. *N Engl J Med*. 2020;383(19):1813-1826. **4.** Spinner CD, et al. *JAMA*. 2020;324(11):1048-1057. **5.** Gottlieb RL, et al. *N Engl J Med*. 2022;386(4):305-315. **6.** Humeniuk R, et al. *Clin Pharmacokinet*. 2021;60(5):569-583.

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