Efficacy in Multiple SARS-CoV-2 Animal Models Supports Phase 3 Dose Selection for Obeldesivir

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Key Finding

— Obeldesivir (ODV) is a potent inhibitor of SARS-CoV-2 replication, with efficacy observed in 3 different nonclinical animal models of SARS-CoV-2 infection

Conclusion

In humans, the Phase 3 dosing regimen of ODV 350 mg twice daily (BID) is expected to provide GS-441524 plasma exposures within the range observed for doses exhibiting potent antiviral efficacy in nonclinical species

References: **1.** Humeniuk R, et al. *Clin Pharmacokinet.* 2021;60(5):569-583. **2.** Anoshchenko O, et al. Presented at: 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 15-18, 2023; Copenhagen, Denmark. Poster P2620. **3.** Martinez DR, et al. *bioRxiv*. Preprint posted online June 28, 2023. doi:10.1101/2023.06.27.546784. **4.** Mackman R, et al. *J Med Chem.* 2023;66(17):11701-11717.

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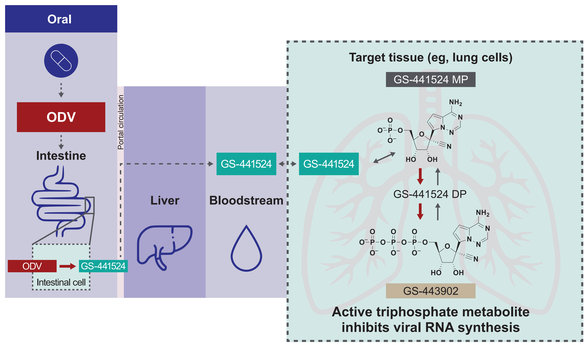
Introduction

Figure 1. Metabolic Activation Pathway of ODV



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

— ODV is an oral prodrug that is converted to GS-441524 in the intestine (**Figure 1**)[1,2]

— GS-441524 is intracellularly metabolized to GS-443902, an active nucleoside triphosphate that inhibits the SARS-CoV-2 RNA-dependent RNA polymerase

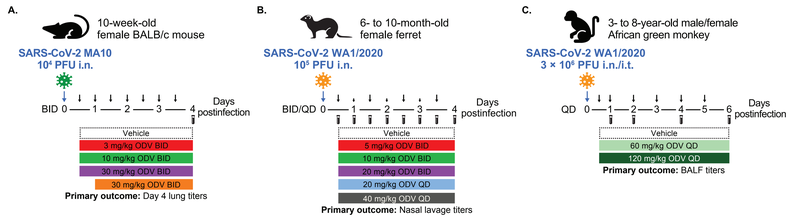
— ODV is currently being evaluated in Phase 3 studies as a simple BID treatment regimen with limited drug-drug interactions

Objective

— To determine plasma exposures of GS-441524 obtained after oral ODV administration that yield efficacy in multiple nonclinical SARS-CoV-2 animal models, thereby informing clinical dose selection of ODV for the treatment of COVID-19

Methods

Figure 2. Study Designs for Orally Administered ODV in Nonclinical (A) Mouse, (B) Ferret, and (C) African Green Monkey Models of SARS-CoV-2 Infection



ODV, obeldesivir; SARS-CoV-2 MA10, mouse-adapted SARS-CoV-2 virus; SARS-CoV-2 WA1/2020, viral strain recovered from a patient who returned to Washington from China in January 2020; PFU, plaque-forming unit; i.n., intranasally; i.t., intratracheal; BID, twice daily; QD, once daily; BALF, bronchoalveolar lavage fluid.
Black arrows denote dosing. Test tubes denote sampling.

— In vitro potency against SARS-CoV-2 and cytotoxicity for ODV were determined in the human lung carcinoma line A549-hACE2

— Efficacy of ODV against SARS-CoV-2 was evaluated in multiple nonclinical species; infectious viral titers were determined from lung tissue, bronchoalveolar lavage fluid (BALF), or nasal washes by plaque assay (**Figure 2**)

  • An unpaired 2-tailed t-test and a 2-way analysis of variance with Bonferroni correction were utilized to assess the significance of efficacy in the mouse model and the African green monkey model, respectively

— Human GS-441524 plasma concentrations were determined using fully validated liquid chromatography-tandem mass spectrometry methods from a randomized, blinded, placebo-controlled, Phase 1 study in which healthy participants were randomly assigned to receive ODV or placebo in single-dose cohorts (100 mg, 300 mg, 900 mg, or 1600 mg) or multiple-dose cohorts (500 mg BID or 900 mg once daily [QD]) under fasted conditions for 5 days[1]

Results

Table 1. Potency and Cytotoxicity of ODV and GS-441524 Against SARS-CoV-2 in a Human Lung Cell Line

Cells	ODV[a]		GS-441524[a]	
	EC_{50}, μM	CC_{50}, μM	EC_{50}, μM	CC_{50}, μM
A549-hACE2	1.27 ± 0.20	>50	2.10 ± 0.63	>50

ODV, obeldesivir; EC_{50}, half-maximal effective concentration; CC_{50}, half-maximal cytotoxic concentration; A549-hACE2, transformed human lung epithelial small-cell carcinoma cells overexpressing human angiotensin-converting enzyme 2; SD, standard deviation.
[a]The data comparing EC_{50} and CC_{50} between ODV and GS-441524 represent the mean ± SD of ≥2 independent experiments performed in duplicate.

— ODV is a potent inhibitor of SARS-CoV-2 in vitro, with a half-maximal effective concentration (EC_{50}) and a half-maximal cytotoxic concentration (CC_{50}) of 1.27 ± 0.20 μM and >50 μM, respectively, in A549-hACE2 cells (**Table 1**)

— GS-441524 exhibited an EC_{50} of 2.10 ± 0.63 μM and a CC_{50} of >50 μM against SARS-CoV-2 in A549-hACE2 cells

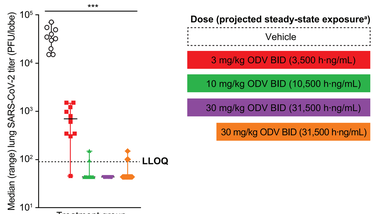
Table 2. GS-441524 Oral Bioavailability Following ODV or GS-441524 Dosing Across Multiple Species

Compound[a]	Mouse	Ferret[b]	Cynomolgus monkey	African green monkey
GS-441524, F (%)	33.3 ± 4.0	87.0	5.4 ± 2.5	10.0 ± 2.1
ODV, F (%)	40.5 ± 1.8	157	37.6 ± 18.7	31.3 ± 14.3

ODV, obeldesivir; F, bioavailability; SD, standard deviation; PK, pharmacokinetic.
[a]Data represent mean ± SD.
[b]Represents composite PK sampling for ferrets (n = 2); serial PK sampling is shown for all other nonclinical species.

— ODV showed 1.2- to 7-fold higher GS-441524 oral bioavailability across multiple animal models compared with parent GS-441524 (**Table 2**)

Figure 3. Efficacy of Oral ODV in a Mouse Model of SARS-CoV-2 Infection[3]

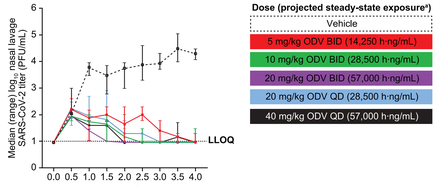


ODV, obeldesivir; PFU, plaque-forming unit; LLOQ, lower limit of quantification; BID, twice daily; AUC_{0-24h}, area under the concentration-time curve over 24 hours.
[a]Projected steady-state exposures for BID data were based on AUC_{0-24h}, which was calculated using composite sampling for 2 separate doses.
***P <0.001.

— ODV demonstrated dose-dependent efficacy in a mouse model of SARS-CoV-2 infection (**Figure 3**)

— Near-maximal efficacy was observed in mice treated orally with 10 mg/kg ODV BID when treatment was initiated 12 hours after infection

Figure 4. Efficacy of Oral ODV in an Upper Respiratory Tract Model of SARS-CoV-2 Infection in Ferrets

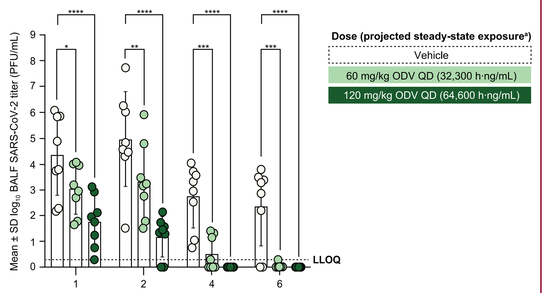


ODV, obeldesivir; PFU, plaque-forming unit; LLOQ, lower limit of quantification; BID, twice daily; QD, once daily; AUC_{0-24h}, area under the concentration-time curve over 24 hours.
[a]Projected steady-state exposures were derived following 1 or 2 doses. For BID data, exposures were based on AUC_{0-24h}, which was calculated using composite sampling for 2 separate doses.

— In ferrets treated 12 hours after infection with 20 mg/kg oral ODV QD, no detectable SARS-CoV-2 was observed by 3 days after infection (**Figure 4**)

— Maximal efficacy was observed in ferrets treated orally with 20 mg/kg ODV BID

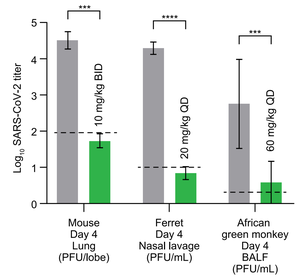
Figure 5. Efficacy of Oral ODV in an African Green Monkey Model of SARS-CoV-2 Infection[4]



ODV, obeldesivir; SD, standard deviation; BALF, bronchoalveolar lavage fluid; PFU, plaque-forming unit; LLOQ, lower limit of quantification; QD, once daily.
[a]Projected steady-state exposures were derived following a single dose.
*P <0.05; **P <0.01; ***P <0.001; ****P <0.0001.

— Both doses of oral ODV showed statistically significant reductions in infectious viral loads in BALF at all sampling days when compared with vehicle (**Figure 5**)

Figure 6. Efficacious Doses of ODV in Lung, Nasal Lavage, and BALF Samples From Nonclinical SARS-CoV-2 Infection Animal Models



ODV, obeldesivir; BALF, bronchoalveolar lavage fluid; BID, twice daily; QD, once daily; LLOQ, lower level of quantification; PFU, plaque-forming unit.
***P <0.001; ****P <0.0001.

Table 3. Comparison of Steady-state PK of Plasma GS-441524 Following Administration of Oral ODV in Nonclinical Species or Healthy Participants

GS-441524 plasma PK parameter	Mouse[a] 10 mg/kg BID[b]	Ferret[a] 20 mg/kg QD	African green monkey[a] 60 mg/kg QD	ODV[c] Phase 3 regimen 350 mg BID[d] (N = 6)
AUC_{0-24h}, h·ng/mL (mean [%CV])	10,500	28,500	32,300	30,100 (19.3)

PK, pharmacokinetic; ODV, obeldesivir; BID, twice daily; QD, once daily; AUC_{0-24h}, area under the concentration-time curve over 24 hours; %CV, % coefficient of variation; AUC_{tau}, area under the concentration-time curve during the dosing interval.
[a]Dose-proportional extrapolations from single-dose PK studies were performed in uninfected nonclinical animal models.
[b]For BID data, AUC_{0-24h} was calculated using composite sampling from 2 separate doses.
[c]Multiple-dose PK parameters following 500 mg BID oral administration of ODV to healthy participants for 5 days were scaled to 350 mg BID, as supported by dose-exposure proportionality in this range. $AUC_{tau,ss}$ for ODV in healthy human participants was calculated as $2 \times AUC_{0-12h}$.

— Phase 1 data suggest that 350 mg ODV BID should result in plasma exposure (AUC_{0-24h}) of GS-441524 within the range shown to be efficacious in nonclinical species[2] (**Figure 6**; **Table 3**)

— Mean concentrations of GS-441524 at 350 mg ODV BID were above the EC_{50} observed against SARS-CoV-2 in A549-hACE2 cells

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