Obeldesivir Clinical Dose Projection for Marburg Virus Infection Postexposure Prophylaxis

P-1166

Jack Chang*, Eric Salgado*, Darius Babusis, Meghan Vermillion, Santosh Davies, Roy Bannister, Yoshihiko Murata, Luzelena Caro

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

*Co-first authors

Conclusions

- Based on the totality of preclinical and clinical data, an obeldesivir dose was selected that is anticipated to meet the efficacy target for Marburg virus postexposure prophylaxis with a low rate of treatment-emergent laboratory abnormalities related to serum creatinine
  - A Phase 2 study has been initiated in Rwanda in adults who have been exposed to Marburg virus (ClinicalTrials.gov Identifier: NCT06682234); no participants had been dosed as of September 2025

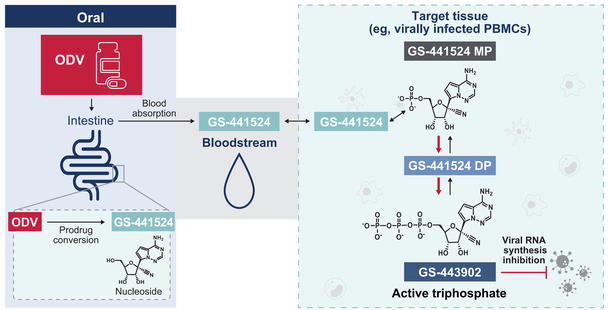
Plain Language Summary

- Marburg virus disease is a serious infection with no approved treatments and a high chance of death
- A new antiviral drug called obeldesivir has been tested in animals for preventing death from diseases caused by filoviruses, such as Marburg virus disease
  - Researchers used this information to select the most effective dose that works best to prevent the disease
- Obeldesivir has also been tested in humans for other diseases
  - Researchers used this information to select a safe and effective dose of obeldesivir for preventing Marburg virus disease
- Using both the animal and human study results, researchers selected an obeldesivir dose expected to be safe and effective for adults with normal or slightly reduced kidney function
  - This dose may be tested in upcoming human studies to see if it can prevent Marburg virus disease

Introduction

- Marburg virus (MARV) disease is a rapidly progressive hemorrhagic disease, with fatality rates of up to 90%, and for which there is no licensed vaccine or approved therapeutic for prevention or treatment[1]
- Obeldesivir (ODV) is an orally administered ester prodrug of the parent nucleoside GS-441524
  - ODV is extensively hydrolyzed to GS-441524, which then undergoes intracellular metabolism to form the active nucleoside triphosphate GS-443902 (**Figure 1**)
- ODV has broad preclinical antiviral activity against SARS-CoV-2, respiratory syncytial virus, and filoviruses, such as MARV[1-5]
  - In vivo, ODV has demonstrated antiviral activity against MARV; in nonhuman primates (NHPs), it showed efficacy as a postexposure prophylaxis (PEP) agent, with 10 days of dosing (100 mg/kg/d) providing an 80% survival benefit and reducing plasma viremia following lethal MARV challenge[3]
- The pharmacokinetics (PK) and safety of ODV have been well characterized with low doses and/or short dosing durations in Phase 1 studies (1600 mg single dose, 900 mg once daily × 5 days, or 350 mg twice daily × 10 days) and a Phase 3 COVID-19 program (350 mg twice daily × 5 days)
- A logistic regression PK/pharmacodynamics (PD) model found a relationship between plasma GS-441524 exposure and asymptomatic creatinine clearance (CrCL) treatment-emergent laboratory abnormalities (TELAs)[6]
- While asymptomatic CrCL TELAs have been observed in ODV clinical studies, the incidence of events in patients with COVID-19 was comparable for those receiving ODV and placebo[7-9]

Figure 1. Metabolic Activation Pathway of ODV



Red, bold arrows indicate the major pathway. Bidirectional arrows represent reactions that can occur in either direction.
DP, diphosphate; MP, monophosphate; ODV, obeldesivir; PBMC, peripheral blood mononuclear cell.

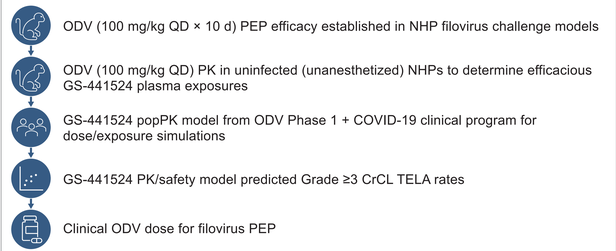
Objective

- To identify the optimal ODV dosing regimen for MARV PEP based on the totality of preclinical and clinical safety, efficacy, and PK data

Methods

- The dose-selection strategy for the safe and efficacious ODV dosing regimen for MARV PEP is summarized in **Figure 2**
- Data from uninfected NHP single-dose PK studies of ODV 100 mg/kg were used to simulate multidose PK projections and estimate the efficacious exposure of GS-441524
- A population PK (popPK) model for GS-441524, incorporating plasma concentration data from 5 completed Phase 1 studies (first-in-human, renal impairment, Japanese bridging, and drug-drug interaction [2 studies]) and 2 pivotal Phase 3 studies (ClinicalTrials.gov Identifiers: NCT05603143 [BIRCH; N = 468] and NCT05715528 [OAKTREE; N = 2011]),[7-11] was used to evaluate the clinical PK for different ODV dosing regimens
- The popPK[12] and logistic regression PK/PD[6] models were used to predict efficacious and safe exposures as a part of the dose-selection program for MARV PEP
- To balance efficacy and safety, we selected a dosing regimen that would achieve the NHP efficacy target while maintaining acceptable Grade ≥3 CrCL TELA rates
  - The projected area under the concentration-time curve across the entire duration of treatment (AUC_{total}), derived from the popPK model, was used in the logistic regression model to predict the percentage of adults with Grade ≥3 CrCL TELAs for all regimens
    - AUC_{total} was the PK parameter that was most predictive for Grade ≥3 asymptomatic CrCL TELAs (P <0.0005)[6]
    - Efficacy and safety of the selected ODV regimen were evaluated on both Day 1 and Day 10 to ensure adequate coverage for MARV disease prevention and acceptable safety
- Exposures for adults (aged >16 years; body weight >40 kg) with normal renal function (estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73 m^2) and those with mild renal impairment (eGFR 60 to <90 mL/min/1.73 m^2) were evaluated

Figure 2. Selection of MARV PEP Dosing Regimen Based on GS-441524 Exposures



CrCL, creatinine clearance; MARV, Marburg virus; NHP, nonhuman primate; ODV, obeldesivir; PEP, postexposure prophylaxis; PK, pharmacokinetics; popPK, population pharmacokinetic; QD, once daily; TELA, treatment-emergent laboratory abnormality.

Results

- A dose was selected that achieved the NHP efficacy target on Day 1 and Day 10 of ODV treatment while maintaining a low rate of Grade ≥3 CrCL TELAs; the projected incidence of Grade ≥3 CrCL TELAs was 5.8% in participants with normal renal function and 9.1% in participants with mild renal impairment (**Table 1**)

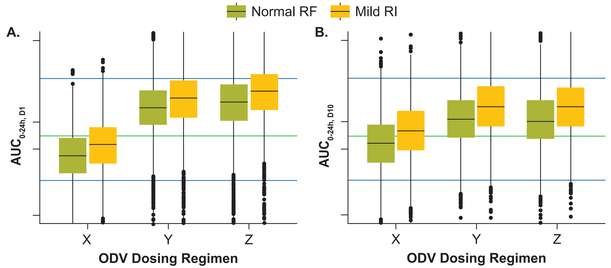
Table 1. Projected Incidence of Grade ≥3 CrCL TELAs

ODV Dosing Regimen	Projected Incidence, % (95% CI)	
	Normal RF (eGFR ≥90 mL/min/1.73 m^2)	Mild RI (eGFR 60 to <90 mL/min/1.73 m^2)
Dose X	2.3 (1.3-4.4)	3.5 (1.8-6.2)
Dose Y	5.8 (2.9-10.7)	9.1 (4.2-16.6)
Dose Z	5.5 (2.8-10.2)	8.6 (3.9-15.8)

CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; ODV, obeldesivir; RF, renal function; RI, renal impairment; TELA, treatment-emergent laboratory abnormality.

- The predicted clinical PK exposures indicate that the selected dose is expected to meet the NHP PK efficacy target in >75% of participants with normal renal function and mild renal impairment on Day 1 (**Figure 3A**)
- From Days 2 through 10, the selected dose is anticipated to sustain exposures above the efficacy target in >75% of the population (**Figure 3B**)

Figure 3. Predicted GS-441524 (A) $AUC_{0\text{-}24h}$ at Day 1 and (B) $AUC_{0\text{-}24h}$ at Day 10 for Simulated Populations (Aged >16 Years/Body Weight >40 kg) With Normal RF or Mild RI



Blue lines represent the 5th and 95th percentile Day 1 AUC_{24h} observed in the Phase 3 COVID-19 study; green line represents the efficacy exposure target in NHPs.
$AUC_{0\text{-}24h}$, area under the concentration-time curve from time 0 to 24 hours; D, Day; NHP, nonhuman primate; ODV, obeldesivir; RF, renal function; RI, renal impairment.

Limitations

- Participants with moderate and severe renal impairment were excluded from the target population of the predicted dose due to anticipated high rates of predicted Grade ≥3 CrCL TELAs at the projected efficacious MARV PEP dose
- Because the analysis was primarily based on safety results from ≤5 days of ODV administration, these findings provide limited confidence in predicting Grade ≥3 TELA rates for ODV administration >5 days
- The relationship between ODV exposures and CrCL TELAs may be confounded by kidney function and the presence of COVID-19; 2 of the studies included in the PK/TELA regression included participants with COVID-19

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Correspondence: Jack Chang, jack.chang19@gilead.com; 333 Lakeside Dr, Foster City, CA 94404, USA

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