Dose Selection of Obeldesivir for Clinical Evaluation in Treatment of Adult Participants With Respiratory Syncytial Virus Infection

P-1232

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Conclusions

- Pharmacokinetic, safety, and efficacy data from previous preclinical and clinical studies were used to select an appropriate dosing regimen of obeldesivir to be evaluated for the treatment of adults with respiratory syncytial virus infection
- The selected dosing regimen of 700 mg twice daily on Day 1 and 350 mg twice daily on Days 2 to 5 was predicted to exceed the pharmacokinetic efficacy target and result in an acceptable rate of asymptomatic Grade ≥3 creatinine clearance treatment-emergent laboratory abnormalities in participants with normal renal function or mild renal impairment

Plain Language Summary

- Obeldesivir is an oral medication that has been studied for the treatment of respiratory viruses
- This study used data from animal models as well as data from human clinical trials of obeldesivir, including its safety and efficacy in different patient populations, in order to determine the best dose to use in adults with respiratory syncytial virus infection
- The selected dose was expected to be safe and effective

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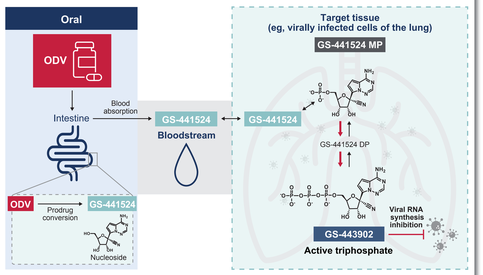
Introduction

- Obeldesivir (ODV) is an oral prodrug that is extensively hydrolyzed to the parent nucleoside, GS-441524, which is subsequently metabolized intracellularly to the active nucleoside triphosphate, GS-443902, an inhibitor of viral RNA-dependent RNA polymerases (**Figure 1**)[1,2]

Figure 1. Metabolic Activation Pathway of ODV



DP, diphosphate; MP, monophosphate; ODV, obeldesivir.

- ODV has been shown to be effective against respiratory syncytial virus (RSV), SARS-CoV-2, and filoviruses, both in vitro and in nonhuman primate studies[1,3-5]
- The pharmacokinetics (PK) and safety of ODV have been evaluated in a robust clinical program comprising five Phase 1 trials in healthy participants and two Phase 3 trials in participants with COVID-19[6-10] (**Table 1**)
- Asymptomatic creatinine clearance (CrCL) treatment-emergent laboratory abnormalities (TELAs) have been observed in previous ODV COVID-19 clinical studies; however, among participants with COVID-19, the rate of renal adverse events was similar between those receiving ODV and those receiving placebo[6,9,10]

Table 1. Summary of ODV Clinical Studies

Study	Phase (Population)	Participants, N	ODV Regimen	Relevant End Points
GS-US-611-6248[8]	Phase 1 (first-in-human)	70[a]	100-1600 mg single dose; 500 mg BID for 5 days; 900 mg QD for 5 days; 500 mg single dose (fasted or fed)	PK, safety
GS-US-611-6409[7]	Phase 1 (DDI)	111[a]	350 or 500 mg[c]	PK, safety
GS-US-611-6469[7]	Phase 1 (DDI)	51[a]	350 or 500 mg[c]	PK, safety
GS-US-611-6586[8]	Phase 1 (Japanese)	40[a]	350 mg single dose	PK, safety
GS-US-611-6472 (EUCT number 2023-504780-17-00)	Phase 1 (RI)	56[a]	175 or 350 mg single dose	PK, safety
OAKTREE (ClinicalTrials.gov Identifier: NCT05715528)[6]	Phase 3 (COVID-19)	1955[d]	350 mg BID for 5 days	Efficacy, PK, safety
BIRCH (ClinicalTrials.gov Identifier: NCT05603143)[10]	Phase 3 (COVID-19)	465[d]	350 mg BID for 5 days	Efficacy, PK, safety

[a]All-enrolled analysis set; healthy participants without COVID-19.
[b]ODV dosing regimens varied from 1 to 4 days based on the DDI tested.
[c]ODV dosing regimens varied from 1 to 8 days based on the DDI tested.
[d]Full analysis set and safety analysis set (all enrolled participants who received ≥1 dose of study drug).
BID, twice daily; DDI, drug-drug interaction; EUCT, European Union clinical trials; ODV, obeldesivir; PK, pharmacokinetics; QD, once daily; RI, renal impairment.

Objective

- To describe the methodology whereby the appropriate dosing regimen of ODV was selected for a Phase 2 study in nonhospitalized adults with acute RSV infection, leveraging PK, safety, and efficacy data from prior preclinical and clinical studies

Methods

- The strategy used to select the clinical ODV dosing regimen for RSV treatment is shown in **Figure 2**

Figure 2. Selection of an RSV ODV Dosing Regimen in Humans Based on GS-441524 Exposures

AGM, African green monkey; CrCL, creatinine clearance; ODV, obeldesivir; PK, pharmacokinetic(s); popPK, population pharmacokinetic; QD, once daily; RSV, respiratory syncytial virus; TELA, treatment-emergent laboratory abnormality.

- The RSV clinical efficacy target was based on preclinical PK and efficacy studies in African green monkeys (AGMs) wherein oral ODV administered at 30 and 90 mg/kg once daily (QD) for 6 days resulted in significant viral reductions in both the upper and lower respiratory tracts[4]
- The clinical efficacy targets for GS-441524 plasma exposures were estimated by extrapolating AGM single-dose PK data to multiple-dose PK projections using nonparametric superposition in Phoenix WinNonlin®
- The clinical safety target was based on maintaining rates of Grade ≥3 CrCL TELAs within an acceptable limit for an adult population with RSV infection and accounted for asymptomatic renal function laboratory abnormalities that can be confounded by ODV treatment, COVID-19, RSV, and preexisting renal impairment[11,12]
- A population PK (popPK) model for GS-441524, incorporating plasma concentration data from healthy volunteers and participants with COVID-19 from the studies listed in **Table 1**, was used to evaluate the clinical PK for different RSV ODV dosing regimens[13,14]
  - Estimated glomerular filtration rate (eGFR) and COVID-19 status were identified as the most impactful intrinsic factors affecting GS-441524 PK[14]
  - Simulations were conducted for adults (aged >18 years) with normal renal function (eGFR ≥90 mL/min/1.73 m^2) or mild renal impairment (eGFR 60-89 mL/min/1.73 m^2) using demographic data from the National Health and Nutrition Examination Survey database
  - It was assumed that populations with RSV disease and/or comorbidities had a 25% increase in GS-441524 PK exposures compared with healthy participants based on prior knowledge of GS-441524 exposures in patients with COVID-19 versus healthy participants
- To ensure safe GS-441524 exposures, a logistic regression PK/safety model utilizing the popPK estimates and the observed Grade ≥3 asymptomatic CrCL TELA rates was developed[13]
  - The PK/safety model was used to predict the rate of Grade ≥3 CrCL TELAs across different potential ODV dosing regimens
- Several dosing regimens were then evaluated to determine which would achieve the AGM efficacy target while maintaining acceptable CrCL TELA rates in participants with RSV

Results

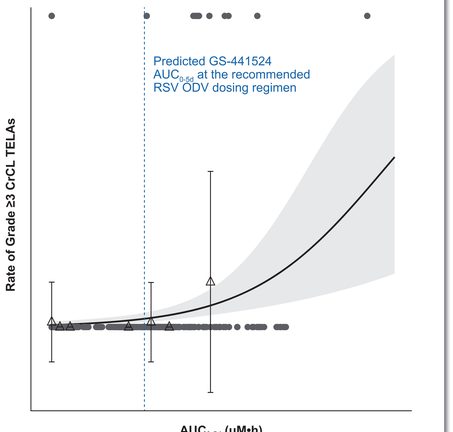
- The predicted plasma exposure for various RSV ODV dosing regimens (data not shown) suggested that a regimen of 700 mg twice daily (BID) on Day 1 + 350 mg BID on Days 2 to 5 would meet both the safety and efficacy bounds
- The predicted PK for the proposed RSV ODV dosing regimen in adults suggested that GS-441524 maximum observed concentration and area under the curve (AUC) from time 0 to 12 hours would be highest on Day 1 (**Table 2**)
  - These exposures are below those observed in a prior Phase 1 study wherein participants received a wide range of ODV dosing regimens, including 900 mg QD for 5 days or 500 mg BID for 5 days[6]
- Based on the ODV PK/safety analysis, the predicted rate of Grade ≥3 CrCL TELAs corresponding to the AUC from Day 0 to 5 at the proposed RSV ODV dosing regimen was low and did not exceed the established safety bound (**Figure 3**)[13]
- Insights from the preclinical efficacy and PK studies, combined with the clinical safety studies, informed the PK exposure bounds needed for an appropriate RSV ODV dosing regimen (**Figure 4**)
- The PK and safety estimated for various dosing regimens, together with these bounds, facilitated an informed dosing regimen selection, with GS-441524 exposures anticipated to exceed the preclinical ODV RSV efficacy bound, while remaining within the bounds to result in a favorable benefit-risk profile, including the estimated rates of Grade ≥3 CrCL TELAs

Table 2. Estimated Mean Plasma Exposures of GS-441524 Following the Proposed RSV ODV Dosing Regimen (700 mg BID on Day 1 + 350 mg BID on Days 2-5) in Adults

PK Parameter	Day 1	Day 5
C_{max}, μg/mL	4.76	2.54
$AUC_{0\text{-}12h}$, h•μg/mL	20.41	13.68

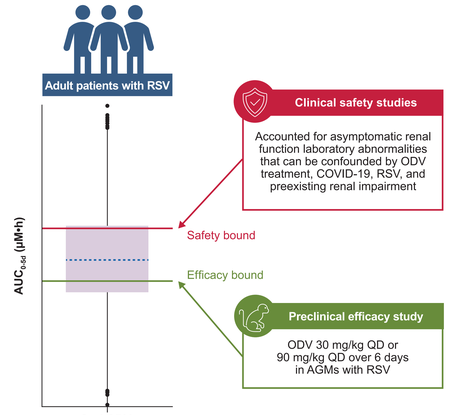
$AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0 to 12 hours; BID, twice daily; C_{max}, maximum observed concentration; ODV, obeldesivir; PK, pharmacokinetic; RSV, respiratory syncytial virus.

Figure 3. PK/Safety Model of Grade ≥3 CrCL TELAs Versus GS-441524 Exposure



The dashed blue line represents the predicted GS-441524 $AUC_{0\text{-}5d}$ for adults with normal renal function at the recommended RSV ODV dosing regimen (700 mg BID on Day 1 + 350 mg BID on Days 2-5). Dots represent observed clinical exposures with and without reversible Grade ≥3 asymptomatic CrCL TELAs. Triangles indicate observed incidence rates, with vertical error bars representing the 95% CIs. The solid black line indicates the incidence rate as predicted by a logistic regression model, with the shaded area representing the 95% CI.
$AUC_{0\text{-}5d}$, area under the concentration-time curve from Day 0 to 5; BID, twice daily; CrCL, creatinine clearance; ODV, obeldesivir; PK, pharmacokinetic; RSV, respiratory syncytial virus; TELA, treatment-emergent laboratory abnormality.

Figure 4. The Proposed ODV Dosing Regimen for Adults With RSV Meets GS-441524 Exposure Safety and Efficacy Bounds



AGM, African green monkey; $AUC_{0\text{-}5d}$, area under the concentration-time curve from Day 0 to 5; BID, twice daily; ODV, obeldesivir; QD, once daily; RSV, respiratory syncytial virus.

Limitation

- The PK/safety analysis for Grade ≥3 CrCL TELAs was conducted using ODV study data in participants with COVID-19. Since COVID-19 alone has been reported to impact CrCL,[11] the ODV PK/safety analysis may be confounded by COVID-19 and preexisting renal impairment