A Phase 1, Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics and Safety of Obeldesivir in Participants With Normal Renal Function and Renal Impairment

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Conclusions

- Renal clearance of GS-441524, the circulating metabolite of the antiviral drug obeldesivir, decreased with increasing severity of baseline renal impairment
- Plasma exposures of GS-441524 increased as baseline renal function decreased
- Single doses of obeldesivir were generally safe and well tolerated in participants with renal impairment and matched control participants with normal renal function

Plain Language Summary

- Obeldesivir is a medication that has been shown to work against several viruses in laboratory experiments and animal studies
- In the body, obeldesivir is converted to another molecule called GS-441524, which is removed by the kidneys
- This study evaluated how a single dose of obeldesivir moved through the body and was cleared out by the kidneys in people with mild, moderate, and severe kidney impairment, as well as in people with normal kidney function, for comparison
- Results showed that the removal of GS-441524 from the body decreased as kidney function worsened and that people with moderate and severe kidney impairment had higher levels of GS-441524 in their blood
- Obeldesivir was generally safe and well tolerated, with no serious harmful events or major changes in laboratory tests in any of the groups

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Introduction

- Obeldesivir (ODV) is an orally administered ester prodrug of the parent nucleoside, GS-441524, that has shown in vitro antiviral activity against a variety of respiratory viruses[1-4]
- ODV is extensively hydrolyzed presystematically to GS-441524, which is then intracellularly metabolized to an active nucleoside triphosphate[5,6]
- GS-441524 is predominantly renally eliminated[5-7]
- While intravenous administration of remdesivir, an antiviral that also yields GS-441524, has been shown to be safe in individuals with renal impairment (RI),[8] the elimination profile of GS-441524 following ODV administration has yet to be characterized in this population

Objective

- To evaluate the pharmacokinetic (PK) properties, safety, and tolerability of a single dose of ODV in participants with RI compared with matched control participants with normal renal function

Methods

Study Design

- A Phase 1, multicenter, open-label, parallel-group, single-dose study was conducted in participants aged 18 to 79 years with a body mass index of ≥18.0 to ≤38.0 kg/m^2
  - Participants with RI must have had an unchanged RI classification during the 3 months prior to screening with no evidence of worsening of RI within the screening period
- Eligible participants with RI at baseline were enrolled into 3 groups based on their estimated glomerular filtration rate (eGFR), which was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatine equation[9]; groups included:
  - Mild RI (eGFR 60 to <90 mL/min/1.73 m^2)
  - Moderate RI (eGFR 30 to <60 mL/min/1.73 m^2)
  - Severe RI (eGFR 15 to <30 mL/min/1.73 m^2)
  - Matched control participants with normal renal function (eGFR ≥90 mL/min/1.73 m^2)
- Participants with mild or moderate RI and their matched control participants with normal renal function received a single 350 mg dose of ODV, and participants with severe RI and their matched control participants with normal renal function received a single 175 mg dose of ODV
  - Participants with normal renal function could serve as a matched control participant for both the mild and moderate RI groups if matching criteria were met

PK Analyses

- The PK analysis set included all participants who received the correct dose of the study drug and had ≥1 PK concentration value reported for the corresponding analyte
- Intensive plasma and urine PK samples were collected up to 120 and 72 hours post dose, respectively, and analyzed using validated liquid chromatography with tandem mass spectrometry methods
  - Plasma PK parameters for GS-441524 included the maximum observed concentration (C_{max}), area under the concentration-time curve extrapolated to infinite time (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), and time to maximum observed concentration (T_{max}); urine PK parameters for GS-441524 included the amount excreted (A_e), renal clearance (CL$_r$), and % fraction excreted (%F_e)
  - Phoenix WinNonlin® software and standard noncompartmental methods were used to estimate PK parameters for all participants across all renal function groups
  - Geometric least squares mean (GLSM) ratios with 90% CIs were calculated between participants with RI and their matched control participants with normal renal function

Safety Assessment

- Safety was evaluated in the safety analysis set (ie, all enrolled participants who received study drug) according to treatment-emergent adverse events (AEs), physical exams, and clinical laboratory tests

Results

Participants

- A total of 56 participants were enrolled across all renal function and matched control groups (**Table 1**)

Table 1. Participant Demographic and Baseline Characteristics (Safety Analysis Set)

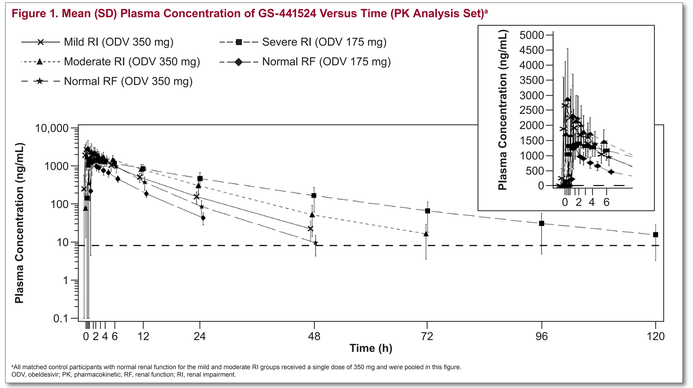
Characteristic	Mild RI (ODV 350 mg; n = 10)	Matched Control (ODV 350 mg; n = 6)	Moderate RI (ODV 350 mg; n = 10)	Matched Control (ODV 350 mg; n = 8)	Severe RI (ODV 175 mg; n = 10)	Matched Control (ODV 175 mg; n = 12)	Total (N = 56)
Sex, n (%)							
Male	6 (60)	4 (67)	4 (40)	2 (25)	7 (70)	9 (75)	32 (57)
Female	4 (40)	2 (33)	6 (60)	6 (75)	3 (30)	3 (25)	24 (43)
Mean (SD) age, y	66 (9.5)	62 (6.9)	66 (12.7)	62 (12.1)	67 (7.4)	61 (7.9)	64 (9.6)
Race, n (%)							
White	5 (50)	4 (67)	4 (40)	5 (63)	8 (80)	11 (92)	37 (66)
Black	5 (50)	1 (17)	6 (60)	3 (38)	2 (20)	1 (8)	18 (32)
Asian	0	1 (17)	0	0	0	0	1 (2)
Mean (SD) BMI, kg/m^2	27.2 (2.7)	26.0 (1.7)	29.1 (3.3)	27.4 (2.0)	28.1 (3.3)	27.8 (2.7)	27.7 (2.8)
Mean (SD) eGFR, mL/min/1.73 m^2	73 (9.1)	97 (10.6)	48 (6.7)	96 (13.4)	24 (6.6)	98 (6.7)	71 (29.8)
Mean (SD) serum creatinine, mg/dL	1.0 (0.2)	0.8 (0.2)	1.4 (0.3)	0.7 (0.1)	2.7 (0.6)	0.8 (0.1)	1.3 (0.8)

BMI, body mass index; eGFR, estimated glomerular filtration rate; ODV, obeldesivir; RI, renal impairment.

PK Analyses

- The mean (SD) plasma concentration-time profiles of GS-441524 after a single dose of ODV in participants with RI and matched control participants with normal renal function are shown in **Figure 1**

Figure 1. Mean (SD) Plasma Concentration of GS-441524 Versus Time (PK Analysis Set)[a]



[a]All matched control participants with normal renal function for the mild and moderate RI groups received a single dose of 350 mg and were pooled in this figure.
ODV, obeldesivir; PK, pharmacokinetic; RF, renal function; RI, renal impairment.

- Following a single dose of ODV in participants with RI or normal renal function, the C_{max} of GS-441524 in the plasma was achieved at ~0.5 to 1.5 hours post dose and remained detectable for 24 to 120 hours post dose (**Figure 1** and **Table 2**)
- GS-441524 plasma exposures (AUC_{inf}) were not significantly increased in participants with mild RI compared with those with normal renal function (**Table 2**)
- In participants with moderate and severe RI, GS-441524 plasma exposures were approximately 2-fold and 4-fold higher, respectively, compared with participants with normal renal function

Table 2. Summary Statistics and Statistical Comparisons of GS-441524 Plasma PK Parameters Between Participants With RI and Matched Control Participants With Normal Renal Function Following a Single, Oral Dose of ODV (PK Analysis Set)

PK Parameter	RI (n = 10)	Matched Control (n = 10)[a,b]	GLSM Ratio (%)	90% CI
Mild RI (ODV 350 mg)				
AUC_{inf}, h•ng/mL	19,391.6 (28.6)	16,158.7 (36.6)	123.2	95.3, 159.3
C_{max}, ng/mL	3001.0 (48.3)	2673.0 (48.1)	112.9	79.5, 160.1
T_{max}, h	0.8 (0.8, 1.5)	1.5 (0.8, 2.0)	–	–
$t_{1/2}$, h	7.6 (7.3, 9.1)	6.0 (4.6, 7.0)	–	–
Moderate RI (ODV 350 mg)				
AUC_{inf}, h•ng/mL	27,889.2 (27.9)	14,626.0 (32.4)	194.0	153.5, 245.1
C_{max}, ng/mL	3162.0 (42.1)	2329.0 (37.6)	135.6	100.0, 184.0
T_{max}, h	0.8 (0.8, 1.5)	1.5 (0.8, 1.5)	–	–
$t_{1/2}$, h	9.2 (8.5, 14.0)	6.0 (4.6, 7.2)	–	–
Severe RI (ODV 175 mg)				
AUC_{inf}, h•ng/mL	32,542.8 (39.2)	7714.5 (17.8)	403.4	323.0, 504.0
C_{max}, ng/mL	1547.0 (21.5)	1469.6 (27.1)	106.8	88.8, 128.5
T_{max}, h	1.1 (0.8, 2.0)	0.5 (0.5, 0.8)	–	–
$t_{1/2}$, h	20.1 (16.6, 22.6)	5.0 (4.5, 6.0)	–	–

AUC_{inf} and C_{max} were reported as mean (%CV), and T_{max} and $t_{1/2}$ were reported as median (Q1, Q3).
[a]Two matched control participants with normal renal function intended for comparison with the severe RI group received incorrect doses of ODV (350 mg instead of 175 mg). These 2 participants were replaced in the study and excluded from the PK analysis set.
[b]Participants with normal renal function could serve as a matched control participant for both the mild and moderate RI groups if matching criteria were met. Utilizing shared matched control participants between the mild and moderate RI groups enabled the inclusion of 10 participants per renal function group, thereby ensuring balanced participant characteristics across all groups for PK statistical analyses.
%CV, % coefficient of variation; AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; C_{max}, maximum observed concentration; GLSM, geometric least squares mean; ODV, obeldesivir; PK, pharmacokinetic; Q1, first quartile; Q3, third quartile; RI, renal impairment; $t_{1/2}$, terminal elimination half-life; T_{max}, time to maximum observed concentration.

- The mean CL$_r$ and %F_e of GS-441524 decreased as the baseline renal function decreased (**Table 3**)
  - The mean %F_e for GS-441524 in participants with mild RI, moderate RI, and normal renal function was consistent with that reported in previous studies[6,7]

Table 3. Urine PK Parameters of GS-441524 Following a Single, Oral Dose of ODV (PK Analysis Set)

PK Parameter	Mild RI (ODV 350 mg; n = 10)	Matched Control (ODV 350 mg[a]; n = 10)	Moderate RI (ODV 350 mg; n = 10)	Matched Control (ODV 350 mg[a]; n = 10)	Severe RI (ODV 175 mg; n = 10)	Matched Control[a,b] (ODV 175 mg; n = 10)
CL$_r$, mL/min	116.2 (52.3)	132.7 (36.3)	63.6 (29.3)	119.7 (39.1)	23.1 (38.0)	142.3 (27.3)
A_e, mg	127.1 (41.8)	122.2 (37.6)	100.0 (21.7)	99.7 (31.2)	38.1 (24.4)	63.6 (16.3)
%F_e	45.0 (41.8)	43.3 (37.6)	35.5 (21.7)	35.3 (31.2)	27.0 (24.4)	45.1 (16.3)

All PK parameters were reported as mean (%CV).
[a]Participants with normal renal function could serve as a matched control participant for both the mild and moderate RI groups if matching criteria were met. Utilizing shared matched control participants between the mild and moderate RI groups enabled the inclusion of 10 participants per renal function group, thereby ensuring balanced participant characteristics across all groups for PK statistical analyses.
[b]Two matched control participants with normal renal function intended for comparison with the severe RI group received incorrect doses of ODV (350 mg instead of 175 mg). These 2 participants were replaced in the study and excluded from the PK analysis set.
%CV, % coefficient of variation; %F_e, % fraction excreted; A_e, amount excreted; CL$_r$, renal clearance; ODV, obeldesivir; PK, pharmacokinetic; RI, renal impairment.

Safety

- AEs were reported for 0/10 participants with mild RI and 1/6 (17%) of their matched control participants with normal renal function, 2/10 (20%) participants with moderate RI and 2/8 (25%) of their matched control participants, and 0/10 participants with severe RI and 1/12 (8%) of their matched control participants
  - The most commonly reported AE was headache (3/56 [5%] participants); no other AEs were reported for >1 participant
  - All AEs and most laboratory abnormalities were Grade ≤2 in severity among all groups
  - No deaths or AEs leading to discontinuation from the study were reported; none of the laboratory abnormalities were considered clinically significant