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Veklury® (remdesivir) Pharmacokinetic Profile

This document is in response to your request for information regarding Veklury® (remdesivir [RDV]) and its pharmacokinetic (PK) profile.

This response was developed according to evidence-based medicine and contains data from phase 1 studies and phase 3 clinical studies.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Summary

Product Labeling[1]

The PK properties of RDV and metabolites and multiple dose PK parameters in adults with COVID-19 are summarized below in Table 1 and Table 2, respectively.

PK Data for RDV[2]

- The PK properties of RDV have been investigated in phase 1 studies with healthy volunteers.
- RDV is primarily (80%) metabolized via carboxylesterase 1 in the liver.
- The $T_{1/2}$ of RDV is approximately 1 hour.
- Renal clearance is the major elimination pathway for metabolite GS-441524; however, a majority of RDV elimination is nonrenal.

PK of RDV in Specific Populations

- The PK of RDV and its metabolites were evaluated in non-COVID-infected participants with impaired renal function ranging from mild renal impairment to kidney failure on dialysis (GS-US-540-9015) and hospitalized participants in the REDPINE study with COVID-19 who had severely reduced kidney function, including those with end-stage kidney disease on dialysis. RDV plasma exposure was not affected by renal function.[3,4]
- The PK of RDV and its metabolites were evaluated in healthy participants and those with moderate or severe hepatic impairment. In general, mean exposures of RDV and its metabolites were similar in participants with moderate hepatic impairment and higher in participants with severe hepatic impairment compared to participants with normal hepatic function. The exposure differences in participants with severe hepatic impairment were not associated with safety events and were consistent with the exposure ranges observed in phase 3 trials.[5]

Product Labeling[1]

Pharmacokinetics

The PK properties of RDV and metabolites are provided in Table 1. The multiple dose PK parameters of RDV and metabolites in adults with COVID-19 are provided in Table 2.

Table 1. PK Properties of RDV and Metabolites (GS-441524 and GS704277)[1]

		RDV	GS-441524	GS-704277
Absorption	T_{max},[a] h	0.67–0.68	1.51–2	0.75–0.75
Distribution	% bound to human plasma proteins	88–93.6[b]	2	1
	Blood-to-plasma ratio	0.68–1	1.19	0.56
Elimination	$T_{1/2}$,[c] h	1	27	1.3
Metabolism	Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	Not significantly metabolized	Histidine triad nucleotide-binding protein 1
Excretion	Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism
	% of dose excreted in urine[d]	10	49	2.9
	% of dose excreted in feces[d]	Not detected	0.5	Not detected

[a]RDV administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.
[b]Range of protein binding for RDV from 2 independent experiments show no evidence of concentration-dependent protein binding for RDV.
[c]Median (Study GS-US-399-4231).
[d]Mean (Study GS-US-399-4231).

Table 2. Multiple Dose PK Parameters[a] of RDV and Metabolites (GS-441524 and GS-704277) Following IV Administration of RDV 100 mg to Adults With COVID-19[1]

Parameter Mean[b] (95% CI)	RDV	GS-441524	GS-704277
C_{max}, ng/mL	2700 (2440–2990)	143 (135–152)	198 (180–218)
AUC_{τ}, ng·h/mL	1710 (1480–1980)	2410 (2250–2580)	392 (348–442)
C_{trough}, ng/mL	Not detectable[c]	61.5 (56.5–66.8)	Not detectable[c]

Abbreviation: C_{trough}=observed drug trough concentration.
[a]Population PK estimates for 30-minute IV infusion of RDV for 3 days (Study GS-US-540-9012; n=147).
[b]Geometric mean estimates.
[c]Not detectable at 24 hours post-dose

Please refer to the US FDA-approved prescribing information for additional information regarding PK of RDV in and its circulating metabolites (GS-441524 and GS-704277) in specific populations including pregnant individuals, patients with renal impairment, patients with hepatic impairment, and pediatric patients.

PK Data for RDV

Phase 1 Studies: PK of RDV in Healthy Volunteers

The PK of RDV have been evaluated in healthy adult volunteers in single-dose and multiple-dose phase 1 trials.[2] The lyophilized and solution formulations of RDV provided similar PK parameters and supported infusion durations of 30 to 120 minutes. The regimen of an RDV 200 mg loading dose followed by once-daily RDV 100 mg maintenance doses was based on results from both in vivo and PK analyses in rhesus monkeys and healthy adult participants.[2,6,7]

Multiple-dose study[2]

A phase 1, randomized, blinded, placebo-controlled clinical trial was conducted in healthy volunteers who received RDV 200 mg on Day 1 followed by 100 mg via IV infusion daily for either 4 days (Cohort 1; n=10 [RDV, n=8; placebo, n=2]) or 9 days (Cohort 2; n=25 [RDV, n=20; placebo, n=5]). Baseline characteristics were generally balanced between the cohorts. Healthy volunteers had a median (range) age of 31 (20–44) years, 80.6% were male, and 61.1% were White.

The PK of RDV, GS-704277, and GS-441524 metabolites in plasma and the PK of GS-443902 in PBMCs were similar at Days 5 (Cohort 1) and 10 (Cohort 2). The median time to peak RDV concentration was approximately 0.7 hours after the start of the 30-minute IV infusion (Table 3). The steady state of GS-441524 was reached on Day 4, and neither RDV nor GS-704277 showed evidence of accumulation. High intracellular trough concentrations of the active triphosphate metabolite, GS-443902, were observed in PBMCs after administration of both single and multiple doses of RDV, which suggested efficient conversion from RDV into the triphosphate form.

Table 3. PK Parameters of RDV and Metabolites After Single and Multiple Doses[2]

PK Parameter	Day 1 (n=28)	Days 5 and 10 (n=26)
RDV in plasma		
C_{max}, mean (CV), ng/mL	4380 (23.5)	2230 (19.2)
T_{max}, median (IQR), h	0.67 (0.25–0.68)	0.68 (0.25–0.75)
$T_{1/2}$, median (IQR), h	0.9 (0.8–1.03)	0.96[a] (0.86–1.08)
CL_{ss}, mean (CV), L/h	–	65.1[a] (19.8)
V_d, mean (CV), L	–	92.6[a] (29.5)
AUC,[b] mean (CV), h·ng/mL	2860 (18.6)	1590[a] (16.6)
GS-441524 in plasma		
C_{max}, mean (CV), ng/mL	143 (21.5)	145 (19.3)
C_T, mean (CV), ng/mL	–	69.2 (18.2)
T_{max}, median (IQR), h	2 (1.5–4)	1.51 (1.5–2)
$T_{1/2}$, median (IQR), h	–	27.4 (25.3–30.3)
AUC,[b] mean (CV), h·ng/mL	2190 (19.1)	2230 (18.4)
GS-704277 in plasma		
C_{max}, mean (CV), ng/mL	370 (29.3)	246 (33.9)
T_{max}, median (IQR), h	0.75 (0.67–0.75)	0.75 (0.75–0.78)
$T_{1/2}$, median (IQR), h	1.27 (1.14–1.45)	1.23 (1.15–1.38)
AUC,[b] mean (CV), h·ng/mL	698 (25.9)	462 (31.4)

PK Parameter	Day 1 (n=28)	Days 5 and 10 (n=26)
GS-443902 in PBMCs		
AUC,[b] mean (CV), h·μM	157 (32.9)	240 (25.4)
C_{max}, mean (CV), μM	9.8 (46.6)	14.6 (40.6)
C_{τ},[a] mean (CV), μM	–	10.2 (49.5)
$T_{1/2}$,[c] median (IQR), h	–	43.4 (38.7–48.9)

Abbreviations: CL_{ss}=steady-state clearance; V_d=volume of distribution.
[a]n=25.
[b]AUC_{0-24h} is presented for Day 1, after a single RDV 200 mg dose. AUC_{τ} is presented for Days 5 and 10, after multiple RDV 100 mg doses.
[c]n=20.

Overall, RDV was generally well tolerated, and no serious AEs, Grade ≥3 AEs, or deaths were reported. The most frequently reported Grade ≤2 AE was infusion-site phlebitis (40%).

PK of RDV in Specific Populations

Renal Impairment

The PK of RDV and its metabolites were evaluated in non-COVID-infected participants with impaired renal function ranging from mild renal impairment to kidney failure on dialysis (GS-US-540-9015) and hospitalized participants in the REDPINE study with COVID-19 who had severely reduced kidney function, including those with end-stage kidney disease on dialysis.[3,4]

- Baseline eGFR was highly correlated with increasing exposure of the renally eliminated metabolite, GS-441524; in those with kidney failure (5th percentile eGFR of 2.54 mL/min/1.73 m^2), median GS-441524 AUC_{τ} increased up to 5 fold compared with that observed in participants with normal renal function.[3,4] In GS-US-540-9015, PK exposures of RDV were not affected by renal function or timing of RDV administration around dialysis. Exposures of GS-441524 and GS-704277 were up to 7.9-fold and 2.8-fold, respectively, in those with renal impairment compared to those with normal renal function. These changes are not considered to be clinically significant.[1]
- SBECD PK exposures (AUC_{τ}) increased up to 26 fold in participants with kidney failure compared with that observed in participants with normal renal function.[4] In GS-US-540-9015, exposures of SBECD were up to 21-fold higher in those with renal impairment compared to those with normal renal function. These changes are not considered to be clinically significant.[1]
- RDV plasma exposure was not affected by renal function.[4]
- No new safety signals were identified with increasing plasma exposures of the predominant metabolite, GS-441524, or the excipient SBECD in REDPINE (RDV, n=163; placebo, n=80).[3,4]

Hepatic Impairment[5]

The PK of RDV and its metabolites (GS-704277, GS-441524, and GS-443902) were evaluated in a phase 1, open-label study (GS-US-540-9014) in participants with chronic, stable hepatic impairment and healthy volunteers. The study enrolled participants with moderate (CPT score, 7–9) or severe (CPT score, 10–15) hepatic impairment and healthy volunteers who were matched to participants with hepatic impairment according to age, sex,

and BMI. All participants received a single IV dose of 100 mg of RDV, and plasma and PBMC samples were collected for 8 days for PK analyses.

- Mean plasma exposure parameters (AUC_{inf} and C_{max}) of RDV and its metabolites in participants with moderate hepatic impairment (n=10) were comparable with those in matched participants with normal hepatic function (n=10).
- Some mean plasma exposure parameters in participants with severe hepatic impairment (n=6) were increased compared with those in matched participants with normal hepatic function (n=6): the unbound AUC_{inf} and C_{max} of RDV in plasma were approximately 2.4-fold and 1.6-fold higher, respectively; the AUC_{inf} of GS-704277 in plasma was approximately 2.4-fold higher; and the C_{max} of GS-441524 in plasma was approximately 1.5-fold higher.
- GS-443902 AUC and C_{max} were comparable in participants with moderate and severe hepatic impairment.
- The incidences of AEs were similar between participants with hepatic impairment and matched participants with normal hepatic function. All AEs were Grade ≤2.
- The authors noted that in participants with hepatic impairment, the increased exposure parameters were not associated with the occurrence of safety events and that exposure values were consistent with the exposure ranges observed in phase 3 studies.

References

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Abbreviations

AE=adverse event
AUC=area under the plasma concentration-time curve
$AUC_{0–24h}$=AUC over 24 hours
AUC_{inf}=AUC from time 0 to infinity
AUC_{T}=AUC over the dosing interval
C_{max}=maximum plasma concentration
CPT=Child-Pugh-Turcotte
C_{T}=observed drug concentration at the end of the dosing interval
CV=coefficient of variation
GS-441524=predominant circulating metabolite of RDV
GS-443902=active triphosphate metabolite
GS-704277=intermediate metabolite of RDV
PBMC=peripheral blood mononuclear cell
PK=pharmacokinetic(s)
RDV=remdesivir
SBECD=sulfobutylether-β-cyclodextrin sodium salt
$T_{1/2}$=half-life
T_{max}=time of occurrence of C_{max}
V_{d}=volume of distribution

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Veklury US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Follow Up

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