# Introduction

- Patients requiring treatment for coronavirus disease 2019 (COVID-19) resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have preexisting renal impairment (RI) or experience acute kidney injury because of the infection<sup>1</sup>
- Chronic kidney disease has been reported as one of the most prevalent risk factors for severe COVID-19<sup>2</sup>
- Despite this, antiviral treatment options for patients with severely impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m<sup>2</sup>) or kidney failure (eGFR <15 mL/min/1.73 m<sup>2</sup>) are limited
- Remdesivir (RDV) is a broad-spectrum antiviral approved for the treatment of COVID-19 in patients who are hospitalized, or those who are not hospitalized and are at risk for progression to severe disease<sup>3</sup>
- Physiologic changes in RI, such as impaired excretion and altered protein binding, can affect concentrations of drugs dominated by renal clearance (CL), which may result in toxicity<sup>1</sup>
- When RDV was initially approved for the treatment of COVID-19, it was not recommended for use in patients with severely impaired renal function because the pharmacokinetics (PK) of RDV, its metabolites, and its sulfobutylether- $\beta$ -cyclodextrin sodium (SBECD) excipient had not been evaluated in patients with RI<sup>4</sup>
- RDV is primarily eliminated via carboxylesterase 1 enzymatic cleavage; renal elimination represents a primary and secondary elimination pathway for its metabolites GS-441524 and GS-704277, respectively. The excipient SBECD is also renally eliminated<sup>5</sup>
- Following intravenous (IV) administration, RDV is rapidly distributed into cells and tissues and simultaneously metabolized into GS-704277 in plasma<sup>6</sup>
- Intracellularly, RDV is converted to the pharmacologically active nucleotide triphosphate metabolite, GS-443902, or the inactive nucleoside, GS-441524. Only the GS-441524 is subsequently detectable in plasma<sup>6</sup>
- As RDV is the primary source of the active metabolite (GS-443902) at the site of action (lung epithelium), RDV levels are used as a surrogate for efficacious exposures<sup>6</sup>
- The safety of higher exposures to GS-441524 and SBECD was evaluated in REDPINE, a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in hospitalized participants with COVID-19 and severely impaired renal function, including those with end-stage kidney disease on dialysis

# Objectives

- To evaluate the PK disposition of RDV and its metabolites (GS-441524 and GS-704277) in participants with COVID-19 and severely impaired renal function using population PK (PopPK) modeling
- To assess the need for RDV dose adjustments in participants with impaired renal function

# Methods

- ◆ PK samples for RDV, GS-441524, and GS-704277 were collected in the following studies: – In REDPINE (GS-US-540-5912), eligible participants (hospitalized with confirmed SARS-CoV-2,  $\geq$ 12 years of age, O<sub>2</sub> saturation  $\leq$ 94% on room air or requiring O<sub>2</sub> supplementation, and eGFR <30 mL/min/1.73 m<sup>2</sup>) were randomized 2:1 to IV RDV (200 mg on Day 1 followed by 100 mg daily up to Day 5) or placebo (saline) to match – Phase 1 study in non–COVID-19–infected individuals with impaired renal function (GS-US-540-9015, ranging from mild RI [60-90 mL/min/1.73 m<sup>2</sup>] to kidney failure on dialysis)
- PopPK model(s) for RDV, GS-704277, and GS-441524 have been developed previously and refined using concentration-time data from the REDPINE and GS-US-540-9015 studies.<sup>7</sup> The full list of studies included in the PopPK analysis is shown in **Table 1**
- The development of the PopPK model(s) was performed sequentially, starting with the parent RDV data, then moving on to GS-704277 data, and ending with GS-441524 data - Each model was informed by the post hoc PopPK parameters from the previous model(s)
- Upon IV administration of RDV, plasma concentrations of RDV, GS-704277, and GS-441524 were best described in adults by sequential 2-compartment models for RDV and GS-704277 and by a 3-compartment model for GS-441524 with first-order elimination in healthy volunteers (**Figure 1**)
- The effect of body weight on the PK of RDV and its metabolites was explained with fixed allometry by setting CL-related body weight exponents to 0.75 and volume of distribution–related body weight exponents to 1.0
- Model-based inferences were carried out via forest plots to illustrate the effect of the different demographic factors and other variables of interest (intrinsic and extrinsic factors) in the exposure of RDV and its metabolites<sup>8</sup>
- SBECD PK were analyzed using a liquid chromatography-tandem mass spectrometry method in GS-US-540-9015 in non–COVID-19 participants who received a 100 mg dose of RDV (containing 3000 mg SBECD)

# Pharmacokinetics Inform Remdesivir Dosing for Patients With Severe Renal Impairment

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### Table 1. Studies Included in the PopPK Analysis

Study	Summary	Participants with evaluable PK (n)
Phase 3		
GS-US-540-5912 (REDPINE)	Efficacy and safety of RDV in participants hospitalized for COVID-19 with severely reduced kidney function	90
GS-US-540-9012 (PINETREE)	Efficacy and safety of RDV for COVID-19 in an outpatient setting	148
CO-US-540-5844 (REMDACTA)	Efficacy and safety of RDV plus tocilizumab compared with RDV plus placebo in hospitalized patients with severe COVID-19 pneumonia	289
Phase 1		
GS-US-399-1812	Safety, tolerability, and PK of RDV and its metabolites following a single dose in healthy adult participants	96
GS-US-399-1954	Safety, tolerability, and PK of RDV and its metabolites following multiple doses in healthy adult participants	24
GS-US-399-5505	Safety, tolerability, and PK of RDV in healthy adult participants	28
GS-US-540-9015	A single-dose study in non–COVID-19 participants with RI	84

PopPK, population pharmacokinetics; PK, pharmacokinetics; RDV, remdesivir; COVID-19, coronavirus disease 2019; RI, renal impairment

#### Figure 1. PopPK Model Schematic for RDV, GS-704277, and GS-441524



# Results

#### Impact of Statistically Significant Covariates on RDV, GS-704277, and **GS-441524 Exposure**

- In the population analysis including participants across the full spectrum of eGFR, baseline eGFR did not impact RDV disposition but did impact the plasma exposure (area under the concentration-time curve over the dosing interval [AUC<sub>tau</sub>]) of metabolites; median change (90% confidence interval) was 220% (206%-237%) for GS-441524 at eGFR = 10.11 mL/min/1.73 m<sup>2</sup> and 60% (41%-82%) for GS-704277 at eGFR =  $10.11 \text{ mL/min}/1.73 \text{ m}^2$  (Figure 2)
- The effect of hospitalization was identified as having a statistically significant impact on RDV and GS-704277 exposures
- The decrease in AUC<sub>tau</sub>, median change (90% confidence interval) in nonhospitalized participants compared with hospitalized participants was 50% (43%-59%) for RDV and 25% (21%-29%) for GS-704277 (**Figure 2**)
- ◆ Age was found to affect GS-441524 and GS-704277 exposures; however, this needs to be carefully considered as eGFR and age are correlated

### Evaluation of the Impact of Baseline eGFR on RDV Metabolites in **Hospitalized Populations With COVID-19**

- Baseline eGFR was highly correlated with increasing GS-441524 and, to a lesser degree, GS-704277 exposures; in those with kidney failure (5th percentile eGFR of 2.54 mL/min/1.73 m<sup>2</sup>), median GS-704277 and GS-441524 AUC<sub>tau</sub> increased up to 2-fold and 5-fold, respectively (Figure 3)
- The increased PK exposures for GS-704277 and GS-441524 were not associated with new safety signals in REDPINE (RDV, n = 163; placebo, n = 80)

max, maximum observed concentration; CI, confidence interval

The 5th and 95th percentiles were calculated from the pooled analysis dataset.

		RDV Steat	ly-stat	e AU	C <sub>tau</sub> (n	ng•h/mL)	Median (90% Cl		RDV s	steady-st	ate C <sub>n</sub>	ax (ng/	/mL)	Median (
							fold change	, J						fold ch
95th percentile: _ 79 years	Age			•			1 (1-1)	_ Age			•			-   1 (1
5th percentile: _ 28.95 years	-			• • •			1 (1-1)				•			1 (1
95th percentile: 7 mL/min/1.73 m <sup>2 -</sup>	Baccon			•			1 (1-1)	-						-   1 (1
5th percentile: _ 1 mL/min/1.73 m <sup>2</sup>				• -	+		1 (1-1)				• 			-   1 (1
No –	Hospitalization	<b>_</b>					0.50 (0.59-0.43)	- Hospitalizatio	on					0.60 (0.6
95th percentile:														
135.62 kg <sup>–</sup> 5th percentile:	Weight						- 0.70 (0.70-0.70)	Weight						- 0.68 (0.0
60.28 kg							1.29 (1.29-1.29)				     			1.32 (1.3
	(50	0. Fold cl	70 0.80 nange re	1.00 1.	1.25 1.43 to refere	ence			0. Folo	70 0.80 d change re	1.00 1 lative to	.25 1.43 reference	ce	
	(56)	ears, 84.8 kg, 81	.04 mL/r	min/1.7	/3 m², h	nospitalized p	patient)	(5	6 years, 84.8 kg	, 81.04 mL/ı	nin/1.73	m², hos	pitalized pa	atient)
	, in the second s	55-704277 St	eady-s	state /	AUC <sub>ta</sub>	<sub>au</sub> (ng∙n/m	Median (90% Cl fold change	)	GS-7042	// steady	y-state	C <sub>max</sub>	(ng/mL)	Median fold c
95th percentile: _ 79 years							1 (1-1)	] _						1.13 (1.
5th percentile: _ 28.95 vears	Age			•			1 (1-1)	Age						- 0.80 (0.
95th percentile:								] [						
7 mL/min/1.73 m <sup>2 –</sup> 5th percentile:	BeGFR			1 1 1				BeGFR						
1 mL/min/1.73 m <sup>2</sup>	·						1.60 (1.82-1.41)							
No –	Hospitalization	•					0.25 (0.29-0.21)	- Hospitalizatio	on					- 0.84 (0.
95th percentile: 135.62 kg							0.70 (0.70-0.70)			•				0.63 (0.
5th percentile:	Weight						1.29 (1.29-1.29)	Weight						_ 1.40 (1.
00.20 Kg			0.70 1.	00 1.4	43					0.70 0.80 1.	00 1.25 1.4	3		
	(56 )	Fold cl /ears, 84.8 kg, 8′	nange re .04 mL/r	lative to min/1.7	to refere 73 m², h	ence nospitalized p	patient)	(5	Folo 6 years, 84.8 kg	d change re , 81.04 mL/r	lative to nin/1.73	referenc m², hos	ce pitalized pa	atient)
	, , , , , , , , , , , , , , , , , , ,	<b>3S-441524</b> st	eady-s	state /	AUC <sub>ta</sub>	₃, (ng•h/m	IL)		GS-4415	24 stead	y-state	C <sub>max</sub>	(ng/mL)	
							fold change	) ] [			- -			Median fold c
95th percentile: _ 79 years								-						-   1.11 (1.
5th percentile: _ 28.95 years	Age			     			- 0.82 (0.86-0.77)	Age			     			- 0.80 (0
95th percentile:							0.68 (0.69-0.67)							0.77 (0.
/ IIIL/IIIII/ 1.7 3 III-	BeGFR						- 3.20 (3.37-3.06)	BeGFR						2.59 (2.
5th percentile: _				i i										
5th percentile: _ 1 mL/min/1.73 m <sup>2</sup>								] [			1			
5th percentile: _ 1 mL/min/1.73 m <sup>2</sup> No -	Hospitalization						1 (1-1)	- Hospitalizatio	on					1.11 (1.
5th percentile: _ 1 mL/min/1.73 m <sup>2</sup> No - 95th percentile: 135.62 kg <sup>-</sup>	Hospitalization						1 (1-1) 0.70 (0.70-0.70)	- Hospitalizatio	on					- 1.11 (1. - 0.68 (0.
5th percentile: _ 1 mL/min/1.73 m <sup>2</sup> No - 95th percentile: 135.62 kg 5th percentile: 60.28 kg	Weight (56 )	Fold cł rears, 84.8 kg, 81 ation pharmac	0.70 0.70 nange re .04 mL/r okinetic	1.00 lative to min/1.7	1.43 to refere 73 m <sup>2</sup> , h	ence hospitalized p ndesivir; AL	1 (1-1) 0.70 (0.70-0.70) 1.29 (1.30-1.29)	Hospitalizatio Hospitalizatio Weight (5 the concentration	Folo 66 years, 84.8 kg, n-time curve ov	0.70 d change re , 81.04 mL/r ver the dos	1.00 1 lative to min/1.73	.43 reference m <sup>2</sup> , hos erval; C	ce pitalized pa ; <sub>max</sub> , maxir	atient)
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5th percentile: _ 1 mL/min/1.73 m <sup>2</sup> No - 95th percentile: 135.62 kg 5th percentile: 60.28 kg pharmacokinetics centration; CI, con 5th and 95th percentile: 5th and 95th percentile: 60.28 kg 0 pPK Mod 0 pPK percentile: 0 pPK percentile: 0 pPK percentile: 0 pPK mod 0 pPK	Hospitalization Weight (56 ) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels dels dels dels dels dels dels dels	Fold cl rears, 84.8 kg, 81 ation pharmac I; BeGFR, base ilculated from t ts Gene ompare and C <sub>ma</sub> 3S-704277 st	0.70 0.70	d U Eff Ho:	1.43 to refere 73 m <sup>2</sup> , h DV, rem ed glon halysis	ence hospitalized p ndesivir; AL merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	<ul> <li>1 (1-1)</li> <li>0.70 (0.70-0.70)</li> <li>1.29 (1.30-1.29)</li> <li>0.30 (1.30-1.29)</li> <li>Datient)</li> <li>JC<sub>tau</sub>, area under tation rate.</li> <li>Paramete aseline et aseline</li></ul>	Hospitalization Weight (5 the concentration of Uncerta GFR on (4 ants Baseline eGFR Baseline inter 1000000000000000000000000000000000000	Fold 56 years, 84.8 kg n-time curve ov ainty (Bo A) GS-70 GS-704277 st	0.70 d change re 81.04 mL/r ver the dos <b>Dotstr</b> <b>04277</b>	aps and te C <sub>ma</sub>	.43 reference m <sup>2</sup> , hos erval; C b <b>Fr</b> d <b>(B</b> , <b>(ng/r</b>	Ce spitalized pa max, maxir om F ) GS- nL) Me 0.1 1.1 1.1	<ul> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>mum obse</li> <li>4415</li> <li>edian (90% fold change</li> <li>97 (0.98-0.9</li> <li>01 (1.01-1.0</li> <li>01 (1.01-1.0</li> <li>02 (1.03-1.0</li> </ul>
5th percentile: _ 1 mL/min/1.73 m <sup>2</sup> No - 95th percentile: 135.62 kg - 5th percentile: 60.28 kg - 5th and 95th percentile: 5th and 95th percentile: 5th and 95th percentile: 60.28 kg - 5th and 95th percentile: 5th and 95th percentile: 95th percentile: 60.28 kg - 5th and 95th percentile: 60.28 kg - 5th and 95th percentile: 95th percentile: 90.57 mL/min/1.73 95th percentile: 95th percentile: 95th percentile: 90.57 mL/min/1.73 95th percentile: 95th percentile: 95th percentile: 135.62 kg - 135.62	Hospitalization Weight (56 y) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels dels to C dels to C dels to C dels to C d	Fold cl rears, 84.8 kg, 81 lation pharmac l; BeGFR, base alculated from t ts Gene ompare and C <sub>ma</sub> 3S-704277 st	0.70 0.70	d U Effo Hos	1.43 to refere 73 m <sup>2</sup> , h DV, rem ed glon alysis	ence hospitalized p ndesivir; AU merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	<ul> <li>1 (1-1)</li> <li>0.70 (0.70-0.70)</li> <li>1.29 (1.30-1.29)</li> <li>Datient)</li> <li>JC<sub>tau</sub>, area under ation rate.</li> <li>Paramete aseline edition rate.</li> <li>Participa</li> <li>Median (90% CI) fold change</li> <li>0.83 (0.87-0.79)</li> <li>1.04 (1.06-1.03)</li> <li>1.14 (1.19-1.10)</li> <li>1.15 (1.19-1.10)</li> </ul>	Hospitalization Weight (5 the concentration GFR on (4 ants Baseline eGFR Baseline i Moderate	Fold Fold 56 years, 84.8 kg, n-time curve ov ainty (Bo A) GS-70 GS-704277 st	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta	aps and te C <sub>ma</sub>	A3 reference m <sup>2</sup> , hos erval; C <b>) Fr</b> <b>d (B</b> <b>x (ng/r</b>	Ce spitalized pa max, maxir om F ) GS- nL) Me 0.1 1.1 1.1 1.1	<ul> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>mum obse</li> <li>atial (90%)</li> <li>fold change</li> <li>97 (0.98-0.9</li> <li>01 (1.01-1.0</li> <li>02 (1.03-1.0</li> <li>02 (1.03-1.0</li> </ul>
Sth percentile: _1 No - 95th percentile: 135.62 kg 5th percentile: 60.28 kg 5th percentile: 60.28 kg 3th and 95th percentile: 5th and 95th percentile: 90.57 mL/min/1.73 5th percentile: 90.57 mL/min/1.73 5th percentile: 90.57 mL/min/1.73 5th percentile: 90.57 mL/min/1.73 5th percentile: 95th percentile: 95th percentile: 90.57 mL/min/1.73 5th percentile: 95th per	Hospitalization Weight (56 ) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels to	Fold cl rears, 84.8 kg, 81 ation pharmac l; BeGFR, base alculated from t <b>ts Gene</b> <b>ompare</b> <b>and C</b> ma <b>3S-704277 st</b>	0.70 0.70	d U Eff Hos	1.43 to refere 73 m <sup>2</sup> , h DV, rem ed glon halysis	ence nospitalized p ndesivir; AU merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC <sub>tau</sub> , area under ation rate.         Paramete aseline e         A Particip         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)	Hospitalization Weight (5 the concentration of Uncerta GFR on (4 ants Baseline eGFR Baseline i Moderate	Fold 56 years, 84.8 kg n-time curve ov ainty (Bo A) GS-70 GS-704277 st	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta	raps and ative to min/1.73 sing inte	.43 reference m <sup>2</sup> , hos erval; C <b>) Fr</b> <b>d</b> ( <b>B</b> <b>x</b> ( <b>ng</b> / <b>r</b>	Ce spitalized pa max, maxir om F ) GS- nL) Me 0.1 1.1 1.1 1.1	<ul> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>num obse</li> <li>adian (90% fold change</li> <li>97 (0.98-0.9</li> <li>01 (1.01-1.0</li> <li>02 (1.03-1.0</li> <li>05 (1.07-1.0</li> </ul>
5th percentile:         1 mL/min/1.73 m²         No -         95th percentile:         135.62 kg         5th percentile:         60.28 kg         5th and 95th percentile:         60.28 kg         5th and 95th percentile:         60.28 kg         95th percentile:         60.28 kg         95th percentile:         60.28 kg         95th percentile:         60.28 kg         95th percentile:         60.11 mL/min/1.73         95th percentile:         95th percentile:     <	Hospitalization Weight (56 ) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels te	Fold cl rears, 84.8 kg, 81 lation pharmac l; BeGFR, base alculated from t ts Gene ompare and C <sub>ma</sub> 3S-704277 st	0.70 0.70	d U Effo Ho:	1.43 to refere 73 m <sup>2</sup> , h DV, rem ed glon halysis	ence hospitalized p ndesivir; AL merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	<ul> <li>1 (1-1)</li> <li>0.70 (0.70-0.70)</li> <li>1.29 (1.30-1.29)</li> <li>0.129 (1.30-1.29)</li> <li>0.129 (1.30-1.29)</li> <li>0.129 (1.30-1.29)</li> <li>0.129 (1.30-1.29)</li> <li>0.129 (1.30-1.29)</li> <li>0.129 (1.00 (1)</li> <li>0.129 (1)</li> <li>0.129 (1.00 (1)</li> <li>0.129</li></ul>	Hospitalization Weight (5 the concentration of Uncerta GFR on (4 ants Baseline eGFR Baseline i Moderate i Moderate	on Fold 56 years, 84.8 kg n-time curve ov ainty (Bo A) GS-70 GS-704277 st	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta	aps and te C <sub>ma</sub>	43 reference m <sup>2</sup> , hos erval; C <b>) Fr</b> <b>d</b> ( <b>B</b> <b>x</b> ( <b>ng</b> / <b>r</b>	Ce spitalized pa max, maxin om F ) GS- nL) Me 0.9 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0	<ul> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>num obse</li> <li>adian (90%</li> <li>fold change</li> <li>97 (0.98-0.9</li> <li>01 (1.01-1.0</li> <li>02 (1.03-1.0</li> <li>02 (1.03-1.0</li> <li>05 (1.07-1.0</li> <li>09 (1.12-1.0</li> </ul>
Sth percentile: _ Mo - 95th percentile: 135.62 kg 5th percentile: 60.28 kg 5th and 95th percentile: 60.28 kg 000000000000000000000000000000000000	Hospitalization Weight (56 y) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels dels to C dels to C dels to C dels to C d	Fold cl rears, 84.8 kg, 81 lation pharmac l; BeGFR, base alculated from t ts Gene ompare and C <sub>ma</sub> 3S-704277 st	o.70 o.70 o.70 okinetic eline es he pool rate the ax in eady-s	d U Eff Hos	I.43 to refere 73 m <sup>2</sup> , h OV, rem ed glon alysis Jsin ects spit AUC <sub>ta</sub>	ence nospitalized p ndesivir; AU merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC <sub>tau</sub> , area under ation rate.         Paramete aseline e <b>A Particip</b> 0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.04 (1.06-1.03)         1.15 (1.19-1.10)         1.33 (1.45-1.24)         1.56 (1.77-1.39)	Hospitalization Weight (5 the concentration <b>FR on (</b> <b>Ants</b> Baseline eGFR <b>Baseline</b> <b>Baseline</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b> <b>Contact</b>	on Fold 56 years, 84.8 kg n-time curve ov ainty (Ba A) GS-7 GS-704277 st	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta	aps and te C <sub>ma</sub>	43 reference m <sup>2</sup> , hos erval; C <b>) Fr</b> <b>d (B</b> <b>x (ng/r</b>	Ce spitalized pa max, maxir om F ) GS- nL) Me 0.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1	<ul> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>num obse</li> <li>inal</li> <li>4415</li> </ul>
5th percentile: _ mL/min/1.73 m <sup>2</sup> No - 95th percentile: 135.62 kg 5th percentile: 60.28 kg 5th percentile: 60.28 kg 5th and 95th percentile: 60.28 kg 60.28 kg 5th and 95th percentile: 95th and 95th percentile: 90.57 mL/min/1.73 5th percentile: 90.57 mL/min/1.73 95th percentile: 95th percentile	Hospitalization Weight (56 y) s; PopPK, population ridence intervation centiles were cat orest Plo dels to C dels te	Fold cl rears, 84.8 kg, 81 ation pharmac l; BeGFR, base alculated from t <b>ts Gene</b> <b>ompare</b> <b>and C</b> ma <b>3S-704277 st</b>	o.70 o.70 o.70 okinetic eline es he pool rate the ax in eady-s	d U Eff Hos	1.43 to refere 73 m <sup>2</sup> , h OV, rem ed glon halysis	ence hospitalized p ndesivir; AU merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC <sub>tau</sub> , area under ation rate.         Paramete aseline e         A Particip         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.56 (1.78-1.39)         2.33 (2.96-1.86)	Hospitalization Weight (5 the concentration of Uncerta GFR on (4 ants Baseline eGFR Baseline i Moderate i Moderate i Severe i Severe	on Fold 56 years, 84.8 kg n-time curve ov ainty (Ba A) GS-7 GS-704277 st	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta	aps and te C <sub>ma</sub>	43 reference m <sup>2</sup> , hos erval; C ) <b>Fr</b> d ( <b>B</b> , (ng/r	Ce spitalized pa max, maxin om F ) GS- nL) Me 0.1 1.1 1.1 1.1 1.1 1.1 1.1	<ul> <li>1.11 (1</li> <li>0.68 (0</li> <li>1.33 (1</li> <li>1.33 (1</li> <li>1.33 (1</li> <li>1.33 (1</li> <li>1.33 (1</li> <li>1.33 (1</li> <li>4415</li> <li>4415</li> <li>601 (1.01-1.</li> <li>01 (1.01-1.</li> <li>02 (1.03-1.</li> <li>02 (1.03-1.</li> <li>05 (1.07-1.</li> <li>09 (1.12-1.</li> <li>09 (1.12-1.</li> <li>09 (1.12-1.</li> <li>1.31-1.</li> </ul>
5th percentile:	Hospitalization Weight (56 ) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels t	Fold cl Fold cl /ears, 84.8 kg, 87 ation pharmac its Gene ompare and C <sub>ma</sub> 3S-704277 st	o.70 o.70 okinetic eline es he pool rate the ax in eady-s eady-s	d U Eff Hos state	1.43 to refere 73 m <sup>2</sup> , h DV, rem ed glon alysis <b>Jsin</b> <b>ects</b> <b>spit</b> <b>AUC</b> ta	ence nospitalized p ndesivir; AU merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         UC <sub>tau</sub> , area under ation rate.         Paramete aseline e         A Particip         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.34 (1.46-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)	Hospitalizatio Weight (5 the concentration GFR on (4 ants Baseline eGFR Baseline eGFR Mild	on Fold 56 years, 84.8 kg n-time curve ov ainty (Ba A) GS-7 GS-704277 st GS-704277 st 0.7 Fold char	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta 04277	aps and ative to min/1.73 sing inte	A3 reference m <sup>2</sup> , hos erval; C ) Fr d (B , (ng/r	Ce spitalized pa max, maxin om F ) GS- nL) Me 0.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1	<ul> <li>1.11 (1</li> <li>0.68 (0</li> <li>1.33 (1</li> <li>atient)</li> <li>num obse</li> <li>fold change</li> <li>97 (0.98-0.9</li> <li>01 (1.01-1.9</li> <li>01 (1.01-1.9</li> <li>02 (1.03-1.9</li> <li>02 (1.03-1.9</li> <li>05 (1.07-1.9</li> <li>05 (1.07-1.9</li> <li>09 (1.12-1.9</li> <li>09 (1.12-1.9</li> <li>09 (1.12-1.9</li> <li>1.12-1.9</li> <li></li></ul>
5th percentile: _ ML/min/1.73 m <sup>2</sup> No - 95th percentile: 135.62 kg 5th percentile: 60.28 kg 5th percentile: 60.28 kg 0harmacokinetics entration; CI, cou 5th and 95th percen 5th and 95th percen 9 <b>DFK Mod</b> eady-stat A. 95th percen 90.57 mL/min/1.73 5th percen 89.86 mL/min/1.73 5th percen 89.86 mL/min/1.73 5th percen 30.18 mL/min/1.73 5th percen 30.18 mL/min/1.73 5th percen 15 mL/min/1.73 5th percen 2.54 mL/min/1.73	Hospitalization Weight (56 y) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels to C dels to C de AUC tau Baseline eGFR Mild mile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> mile: 3 m <sup>2</sup> tile: 3 tile: 3 tile: 5 tile: 5 tile: 5 tile: 5 tile: 5 tile:	Fold cl rears, 84.8 kg, 87 ation pharmac l; BeGFR, base alculated from t SS-704277 st SS-704277 st	o.70 o.70 o.70 okinetic eline es he pool rate the ax in eady-s eady-s o.70 o.	d U Eff Hos state /	1.43 to refere 73 m <sup>2</sup> , h OV, rem ed glon halysis <b>Jsin</b> <b>ects</b> <b>spit</b> <b>AUC</b> ta <b>AUC</b> ta <b>I.43</b> to refere 73 m <sup>2</sup> , h	ence nospitalized p ndesivir; AL merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC <sub>tau</sub> , area under ation rate.         Paramete aseline edition rate.         J Particip         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)	Hospitalizatio Weight (5 the concentration TUNCERTA GFR ON (A ants Baseline eGFR Baseline eGFR Mild Mild	on Fold 56 years, 84.8 kg n-time curve ov ainty (Ba A) GS-7 GS-704277 st GS-704277 st GS-704277 st 0.7 Fold char urs, 84.8 kg, 81.04	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta 10 100 100 100 100 100 100 100	aps and and and and and and and and and and	A3 reference m <sup>2</sup> , hos erval; C d (B , (ng/r	Ce spitalized pa max, maxin om F ) GS- nL) Me 0.9 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0	<ul> <li>1.11 (1</li> <li>0.68 (0</li> <li>1.33 (1</li> <li>atient)</li> <li>num obs</li> <li>adian (90%</li> <li>fold change</li> <li>97 (0.98-0.</li> <li>01 (1.01-1.)</li> <li>02 (1.03-1.)</li> <li>02 (1.03-1.)</li> <li>02 (1.03-1.)</li> <li>05 (1.07-1.)</li> <li>09 (1.12-1.)</li> <li>09 (1.12-1.)</li> <li>09 (1.12-1.)</li> <li>1.112-1.)</li> <li>1.11</li></ul>
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5th percentile: _ No - 95th percentile: 135.62 kg 5th percentile: 60.28 kg 5th percentile: 60.28 kg 5th percentile: 60.28 kg 5th percentile: 60.28 kg 5th and 95th percentile: 95th and 95th percentile: 95th percentile: 90.57 mL/min/1.73 95th percentile: 95th percentile: 15 mL/min/1.73 95th percentile: 95th percentile: 90.57 mL/min/1.73	Hospitalization Weight (56 y) s; PopPK, popul nfidence interva centiles were ca orest Plo dels to C dels to C te AUC <sub>tau</sub> Baseline eGFR Mild mile: 3 m <sup>2</sup> Mild mile: 3 m <sup>2</sup> Mild mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mild mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Moderate (56 y) Baseline eGFR	Fold cl /ears, 84.8 kg, 8' lation pharmac l; BeGFR, base alculated from t <b>ts Gene</b> <b>ompare</b> <b>and C</b> ma <b>3S-704277 st</b> <b>3S-704277 st</b> <b>SS-704277 st</b>	o.70 o.70	d U Eff HOS state /	LA3 to reference all sin ects spit AUCta LA3 to reference all sin all sin ects spit AUCta AUCta	ence nospitalized p ndesivir; AU merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	1 (1-1)         1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         UC <sub>tau</sub> , area under ation rate.         Paramete aseline e         Dattion rate.         Median (90% CI) fold change         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.15 (1.19-1.10)         1.33 (1.45-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         Median (90% CI) fold change         0.49 (0.50-0.47)         1.17 (1.18-1.16)	Hospitalization Weight (5 the concentration Baseline eGFR Baseline eGFR Mild Mild Mild Mild Severe (56 yea Baseline eGFR	on Fold 56 years, 84.8 kg n-time curve ov ainty (Ba A) GS-7 GS-704277 st GS-704277 st 0.7 Fold char 0.7 Fold char 0.7 GS-441524 st	0.70 d change re 81.04 mL/r ver the dos <b>Dotstr</b> <b>04277</b> <b>teady-sta</b> 70 1.00 nge relative 4 mL/min/1. <b>ceady-sta</b>	aps and and and and and and and and and and	A3 reference m <sup>2</sup> , hos erval; C ) <b>Fr</b> d (B , (ng/r	Ce spitalized pa max, maxin om F ) GS- nL) Me 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.	<ul> <li>1.11 (1.</li> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>num obse</li> <li>inal</li> <li>4415,</li> <li>edian (90%</li> <li>fold change</li> <li>97 (0.98-0.9</li> <li>01 (1.01-1.0</li> <li>02 (1.03-1.0</li> <li>02 (1.03-1.0</li> <li>05 (1.07-1.0</li> <li>09 (1.12-1.0</li> <li>09 (1.12-1.0</li> <li>09 (1.12-1.0</li> <li>09 (1.12-1.0</li> <li>09 (1.12-1.0</li> <li>05 (1.07-1.0</li> <li>09 (1.12-1.0</li> <li>05 (1.07-1.0</li> <li>06 (1.03-1.0</li> <li>07 (1.03-1.0</li> <li>07 (1.03-1.0</li> <li>08 (0.69-0.6</li> </ul>
5th percentile: _ No - 95th percentile: 135.62 kg - 5th percentile: 60.28 kg - 5th percentile: 60.28 kg - 5th and 95th percentile: 60.28 kg - 5th percentile: 95th percentile: 90.57 mL/min/1.73 95th percentile: 95th percentile: 90.57 mL/min/1.73	Hospitalization Weight (56) S; PopPK, popul nfidence interva centiles were ca  Orest Plo dels to C dels to C dels to C dels to C de AUC <sub>tau</sub> Baseline eGFR  tile: 3 m <sup>2</sup> Mild Moderate 3 m <sup>2</sup> Mild file: 3 m <sup>2</sup> Mi	Fold cl /ears, 84.8 kg, 87 lation pharmac l; BeGFR, bask alculated from t <b>ts Gene</b> <b>ompare</b> <b>and C</b> ma <b>3S-704277 st</b> <b>3S-704277 st</b> <b>SS-704277 st</b>	o.70 o.70 o.70 o.70 o.70 o.70 o.70 o.70 eady-s 0.70 o.70	d U Eff Ho: tate /	Jsin ects Spit AUC <sub>ta</sub>	ence nospitalized p ndesivir; AL merular filtra dataset. au (ng•h/m ence nospitalized p au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC <sub>tau</sub> , area under ation rate.         Paramete aseline e         A Participa         J Participa         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.15 (1.19-1.10)         1.33 (1.45-1.24)         1.34 (1.46-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         1.17 (1.18-1.16)         1.18 (1.19-1.17)	Hospitalizatio Weight (5 the concentration Fr Uncerta GFR on (4 ants Baseline eGFR Mild Mild Moderate Severe Severe (56 yea Baseline eGFR	on       Fold         56 years, 84.8 kg,         56 years, 84.8 kg,         n-time curve ov         ainty (Ba         A) GS-70         GS-704277 st         0.7         Fold char         0.7         SS-441524 st	0.70 d change re 81.04 mL/r ver the dos <b>Dotstr</b> <b>O4277</b> <b>teady-sta</b> 70 1.00 nge relative 4 mL/min/1. <b>teady-sta</b>	aps and ative to min/1.73 aing inte and ate C <sub>ma</sub> a 1.43 to refere 73 m <sup>2</sup> , h te C <sub>ma</sub>	A3 reference m <sup>2</sup> , hos erval; C b c c c c c c c c c c c c c c c c c c	Ce spitalized pa max, maxin om F ) GS- nL) Me 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.	<ul> <li>1.11 (1.</li> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>num obse</li> <li>atian (90%</li> <li>fold change</li> <li>97 (0.98-0.9</li> <li>01 (1.01-1.0</li> <li>02 (1.03-1.0</li> <li>02 (1.03-1.0</li> <li>05 (1.07-1.0</li> <li>05 (1.07-1.0</li> <li>09 (1.12-1.0</li> <li>09 (1.12-1.0</li> <li>09 (1.12-1.0</li> <li>09 (1.12-1.0</li> <li>05 (1.07-1.0</li> <li>1.12 (1.13-1.1</li> </ul>
5th percentile: _ No - 95th percentile: 135.62 kg 5th percentile: 60.28 kg 5th percentile: 60.11 mL/min/1.73 5th percentile: 95th percentile: 95th percentile: 95th percentile: 95th percentile: 15 mL/min/1.73 5th percentile: 95th percentile: 95th percentile: 95th percentile: 15 mL/min/1.73 5th percentile: 95th percentile: 95th percentile: 15 mL/min/1.73 5th percentile: 95th percentile: 95th percentile: 95th percentile: 95th percentile: 95th percentile: 95th percentile: 95th percentile: 90.57 mL/min/1.73 95th percentile: 90.57 mL/min/1.73 95th percentile: 90.57 mL/min/1.73	Hospitalization Hospitalization Weight (56 ) S; PopPK, popul nfidence interva centiles were ca  Orest Plo dels to C de AUC <sub>tau</sub> Baseline eGFR file: 3 m <sup>2</sup> Mild Moderate 3 m <sup>2</sup> Mild (56 ) Baseline (56 ) Kiney failure (56 ) Comparison (56 ) Compa	Fold cl /ears, 84.8 kg, 87 lation pharmac l; BeGFR, base alculated from t <b>ts Gene</b> <b>ompare</b> <b>and C</b> ma <b>3S-704277 st</b> <b>3S-704277 st</b> <b>SS-704277 st</b> <b>SS</b> <b>S</b> -704257 <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b> <b>S</b>	o.70 o.70	d U Effo Ho: state /	1.43 to reference allysis Jsin ects spit AUC <sub>ta</sub>	ence nospitalized p ndesivir; AL merular filtra dataset. ng PK s of Ba talizec au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC <sub>tau</sub> , area under aseline e <b>Paramete A Particip</b> 1.04 (1.06-1.03)         1.15 (1.19-1.10)         1.34 (1.46-1.24)         1.56 (1.77-1.39)         1.56 (1.77-1.39)         1.56 (1.78-1.39)         2.33 (2.96-1.86)         Datient)         1.18 (1.19-1.17)         1.64 (1.69-1.60)	Hospitalization Weight (5 the concentration Baseline eGFR on (A ants Baseline eGFR     Moderate   Moderate     Moderate 	on Fold 56 years, 84.8 kg 56 years, 84.8 kg 56 years, 84.8 kg 56 years, 84.8 kg 66 years, 84.8 kg 7 6 6 7 7 7 7 7 7 7 7 7 8 7 7 7 7 7 7 7	0.70 d change re 81.04 mL/r ver the dos <b>Dotstr</b> <b>O4277</b> <b>teady-sta</b> 70 1.00 nge relative 4 mL/min/1. <b>ceady-sta</b>	aps and ative to min/1.73 sing inte and and and and and and and and and and	A3 reference m <sup>2</sup> , hos erval; C <b>) Fr</b> <b>d (B</b> <b>, (ng/r</b> ence ospitaliz	Ce spitalized pa smax, maxin om F ) GS- nL) Me 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.	<ul> <li>1.11 (1.</li> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>num obse</li> <li>atiani</li> <li>atiani</li></ul>
5th percentile:         1 mL/min/1.73 m²         No -         95th percentile:         135.62 kg -         5th percentile:         60.28 kg -         5th and 95th percentile:         60.78 kg -         60.71 mL/min/1.73         5th percentile:         60.71 mL/min/1.73         95th percentile:         60.71 mL/min/1.73         95th percentile:         95th percentile:         60.11 mL/min/1.73         95th percentile:         90.57 mL/min/1.73         95th percentile:         95th percentile:         95th percentile:         90.57 mL/min/1.73         95th percentile:         95th percentile:         95th percentile:         90.57 mL/min/1.73         95th perce	Hospitalization Weight (56 y) S; PopPK, popul nfidence interval centiles were ca Orest Plo dels to C baseline eGFR Mild mile: 3 m <sup>2</sup> Mild mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Mile: 3 m <sup>2</sup> Moderate Mile: 3 m <sup>2</sup> Moderate (56 y) Baseline eGFR (56 y) Baseline (56 y) Baseline (56 y) (56 y) (56 y) (56 y) (56 y) (56 y) Baseline (56 y) (56 y) (56 y) Baseline (56 y) (56 y) (56 y) Baseline (56 y) Baseline (57 y) (56 y) Baseline (57 y) (56 y) (56 y) (56 y) (56 y) (57	Fold cl /ears, 84.8 kg, 8' lation pharmac l; BeGFR, base alculated from t ts Gene ompare and C <sub>ma</sub> 3S-704277 st SS-704277 st	o.70 okinetic eline es he pool rate the ax in eady-s o.70 nange re 0.70 au eady-s control eady-s	d U Eff HO state	1.43 to refere 73 m <sup>2</sup> , h DV, rem ed glon halysis Jsin ects Spit AUC <sub>ta</sub> 1.43 to refere 73 m <sup>2</sup> , h	ence nospitalized p ndesivir; AL merular filtra dataset. ng PK s of B talizec au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         Uctau, area under ation rate.         Paramete aseline e         Darticipa         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         1.18 (1.19-1.17)         1.64 (1.69-1.60)         1.65 (1.70-1.61)         2.62 (0.75-0.61)	Hospitalization Weight (5 the concentration GFR on (4 ants Baseline eGFR Mild Moderate GFR (5 failure (5 gegere (5 gegere (1 g	on Fold 56 years, 84.8 kg, n-time curve ov ainty (Ba A) GS-70 GS-704277 st GS-704277 st GS-704277 st 0.7 Fold char 0.7 Fold char 0.7 Sold char 0	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta 0 1.00 nge relative 4 mL/min/1. ceady-sta	aps and and and and and and and and and and	A3 reference m <sup>2</sup> , hos erval; C d (B d (B d (B d (B d (B d (B d (B d (B	Ce spitalized pa smax, maxin om F ) GS- nL) Me on 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0	$ \begin{array}{c c}     1.11 (1. \\     0.68 (0. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.33 (1. \\     1.31 (1. \\     1.01 (1.01 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     02 (1.03 - 1.0 \\     03 (1.12 - 1.0 \\     03 (1.12 - 1.0 \\     1.12 (1.13 - 1.1 \\     1.3 (1.46 - 1.4 \\     1.4 \\     1.3 (1.46 - 1.4 \\     $
5th percentile:         1 mL/min/1.73 m²         No -         95th percentile:         135.62 kg ~         5th percentile:         60.28 kg ~         5th percentile:         60.28 kg ~         oharmacokinetica:         entration; Cl, constant of the percentile:         otharmacokinetica:         entration; Cl, constant of the percentile:         60.28 kg ~         oharmacokinetica:         entration; Cl, constant of the percentile:         for percentile:         60.11 mL/min/1.73         95th percentile:         95th percentile:         90.57 mL/min/1.73         95th percentile:         90.57 mL/min/1.73         95th percentile:         90.57 mL/min/1.73         95th percentile:         15 mL/min/1.73         95th percentile:         95th percentile:         95th percentile:         95th percentile:         95th percentile:         90.57 mL/min/1.73         95th percentile:         95th percentile:         95th percentile:         90.57 mL/min/1.73         95th percentile:         90.57 mL/min/1.73 <td>Hospitalization Weight (56 ) s; PopPK, popU fidence interva centiles were ca Orest Plo dels to C baseline eGFR file: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> Moderate a<sup>1</sup> Mild tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> Moderate tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> Moderate tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> tile: 3 m<sup>2</sup> Moderate</td> <td>Fold cl /ears, 84.8 kg, 87 lation pharmac l; BeGFR, bask alculated from t ompare and C<sub>ma</sub> 3S-704277 st SS-704277 st SS-704275 st SS</td> <td>o.70 okinetic eline es he pool rate the the ax in eady-s 0.70 a. ange re o.70 a. ange</td> <td>d U Eff HO state tate tate tate tate tate tate tate tate tate tate</td> <td>Jsin ect spit</td> <td>ence nospitalized p ndesivir; AL merular filtra dataset. au (ng•h/m ence nospitalized p au (ng•h/m</td> <td>1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC<sub>tau</sub>, area under ation rate.         Paramete aseline e         A Particip         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         1.18 (1.19-1.10)         1.17 (1.18-1.16)         1.18 (1.19-1.17)         1.64 (1.69-1.60)         1.18 (1.19-1.17)         1.64 (1.69-1.60)</td> <td>Hospitalization Hospitalization Weight (5 the concentration Baseline eGFR ON (A ants Baseline eGFR Mild Moderate Kidney failure (56 yea Mild Mild</td> <td>on Fold 56 years, 84.8 kg n-time curve ov ainty (Ba A) GS-7 GS-704277 st GS-704277 st 0.7 Fold char 0.7 Fold char 0.7 SS-441524 st 0.7 CS-441524 st</td> <td>0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta 0 0 1.00 nge relative 4 mL/min/1. ceady-sta</td> <td>aps and and and and and and and and and and</td> <td>A3 reference m<sup>2</sup>, hos erval; C d (B , (ng/r</td> <td>Ce spitalized pa max, maxin om F ) GS- nL) Me 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.</td> <td><math display="block">   \begin{bmatrix}     1.11 \\     </math></td>	Hospitalization Weight (56 ) s; PopPK, popU fidence interva centiles were ca Orest Plo dels to C baseline eGFR file: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> Moderate a <sup>1</sup> Mild tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> Moderate tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> Moderate tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> tile: 3 m <sup>2</sup> Moderate	Fold cl /ears, 84.8 kg, 87 lation pharmac l; BeGFR, bask alculated from t ompare and C <sub>ma</sub> 3S-704277 st SS-704277 st SS-704275 st SS	o.70 okinetic eline es he pool rate the the ax in eady-s 0.70 a. ange re o.70 a. ange	d U Eff HO state tate tate tate tate tate tate tate tate tate tate	Jsin ect spit	ence nospitalized p ndesivir; AL merular filtra dataset. au (ng•h/m ence nospitalized p au (ng•h/m	1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC <sub>tau</sub> , area under ation rate.         Paramete aseline e         A Particip         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         1.18 (1.19-1.10)         1.17 (1.18-1.16)         1.18 (1.19-1.17)         1.64 (1.69-1.60)         1.18 (1.19-1.17)         1.64 (1.69-1.60)	Hospitalization Hospitalization Weight (5 the concentration Baseline eGFR ON (A ants Baseline eGFR Mild Moderate Kidney failure (56 yea Mild Mild	on Fold 56 years, 84.8 kg n-time curve ov ainty (Ba A) GS-7 GS-704277 st GS-704277 st 0.7 Fold char 0.7 Fold char 0.7 SS-441524 st 0.7 CS-441524 st	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta 0 0 1.00 nge relative 4 mL/min/1. ceady-sta	aps and and and and and and and and and and	A3 reference m <sup>2</sup> , hos erval; C d (B , (ng/r	Ce spitalized pa max, maxin om F ) GS- nL) Me 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.	$   \begin{bmatrix}     1.11 \\     $
5th percentile:       No         No       95th percentile:         135.62 kg       5th percentile:         60.28 kg       60.28 kg         5th percentile:       60.28 kg         5th and 95th percentile:       60.28 kg         5th and 95th percentile:       60.28 kg         5th and 95th percentile:       60.28 kg         60.11 ml 95th percentile:       60.28 kg         95th percentile:       60.17 ml/n1.73         95th percentile:       60.11 ml/min/1.73         95th pe	Hospitalization Weight (56) (56) (56) (56) (56) (56) (56) (56)	Fold cl /ears, 84.8 kg, 8' lation pharmac l; BeGFR, base alculated from t ts Gene ompare and C <sub>ma</sub> 3S-704277 st 3S-704277 st SS-704277 st		d U Effo Ho: tate /	1.43 to refere 73 m <sup>2</sup> , h DV, rem ed glon halysis Jsin ects spit AUC <sub>ta</sub>	ence nospitalized p ndesivir; AL merular filtra dataset. ng PK s of B talizec au (ng•h/m au (ng•h/m	1 (1-1)         1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         JC tau, area under ation rate.         Paramete aseline e         A Participa         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.34 (1.46-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         L)         Median (90% CI) fold change         1.14 (1.19-1.10)         1.15 (1.19-1.10)         1.33 (1.45-1.24)         1.14 (1.19-1.17)         1.64 (1.69-1.60)         1.18 (1.19-1.17)         1.64 (1.69-1.60)         2.65 (2.78-2.51)         2.65 (2.78-2.53)         3.65 (3.84-3.45)	Hospitalization Weight (5 the concentration GFR on (4 ants Baseline eGFR Mild Moderate Severe Concentration Baseline eGFR Moderate Concentration	on Fold 56 years, 84.8 kg on-time curve ov ainty (Bo A) GS-70 GS-704277 st GS-704277 st GS-704275 st GS-70427	o.70 d change re 81.04 mL/n ver the dos <b>Dotstr</b> <b>04277</b> <b>teady-sta</b> 70 1.00 nge relative 4 mL/min/1. <b>ceady-sta</b>	aps and and and and and and and and and and	A3 reference m <sup>2</sup> , hos erval; C d (B , (ng/r	Ce spitalized pa smax, maxin om F ) GS- nL) Me 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.1 1.	<ul> <li>1.11 (1.</li> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>atient)</li> <li>num obse</li> <li>atial (1.33 (1.</li> <li>atial (1.01-1.0)</li> <li>02 (1.03-1.0)</li> <li>03 (1.07-1.0)</li> <li>04 (1.01-1.0)</li> <li>05 (1.07-1.0)</li> <li>05 (1.07-1.0)</li> <li>09 (1.12-1.0)</li> <li>01 (1.12-1.1)</li> <li>11 (1.12-1.1)</li> <li>12 (1.13-1.1)</li> <li>14 (1.46-1.4)</li> <li>14 (1.46-1.4)</li></ul>
5th percentile:         1 mL/min/1.73 m²         No -         95th percentile:         135.62 kg ~         5th percentile:         60.28 kg ~         5th and 95th percentile:         60.74 mL/min/1.73         5th percentile:         60.75 mL/min/1.73         95th percentile:         95th percentile:         90.57 mL/min/1.73         95th percentile:         90.57 mL/min/1.73         95th percentile:         90.57 mL/min/1.73         95th percentile:         95th percentile:         90.57 mL/min/1.73         95th percentile:         95th percentile	Hospitalization Weight (56 ) (56 ) (56 ) (57 ) (56 ) (58 ) (	Fold cl /ears, 84.8 kg, 81 lation pharmac l; BeGFR, base alculated from t <b>ts Gene</b> <b>ompare</b> <b>and C</b> <sub>ma</sub> <b>3S-704277 st</b> <b>3S-704277 st</b> <b>SS-704277 st</b>	o.70 okinetic eline es he pool rate the ax in eady-s a 0.70 cady-s a 0.70 cady-s a a a a a a a a a a a a a	d U Eff HO state i i i i i i i i i i i i i i i i i i i	Jsin alysis Jsin alysis AUC <sub>ta</sub>	ence nospitalized p ndesivir; AL merular filtra dataset. au (ng•h/m ence nospitalized p au (ng•h/m	1 (1-1)         1 (1-1)         0.70 (0.70-0.70)         1.29 (1.30-1.29)         Datient)         Uctau, area under aseline e <b>Paramete A Particip</b> Disting         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.33 (1.45-1.24)         1.34 (1.46-1.24)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         L)         Median (90% CI)         fold change         0.83 (0.87-0.79)         1.04 (1.06-1.03)         1.14 (1.19-1.10)         1.15 (1.19-1.10)         1.33 (1.45-1.24)         1.14 (1.9-1.10)         1.56 (1.77-1.39)         2.33 (2.96-1.86)         Datient)         L)         Median (90% CI)         fold change         0.49 (0.50-0.47)         1.17 (1.18-1.16)         1.164 (1.69-1.60)         1.65 (1.70-1.61)         2.63 (2.75-2.51)         2.65 (2.78-2.53)         3.65 (3.84-3.45)         3.66 (3.86-3.46)	Hospitalization Weight (5 the concentration GFR on (4 ants Baseline eGFR Moderate Mild Moderate Severe Kidney failure	on Fold Fold Fold Fold Fold Fold Fold Fold Fold Cas-441524 st Cas-441524 st Cas-441524 st Fold Fold Fold Cas-441524 st Cas-441524 st Cas-4	0.70 d change re 81.04 mL/r ver the dos 04277 teady-sta 1 0 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	aps and and and and and and and and and and	A3 reference m <sup>2</sup> , hos erval; C d (B d (B d (B d (B d (B d (B d (B d (B	Ce spitalized pa max, maxim om F ) GS- nL) Me on 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0	<ul> <li>1.11 (1.</li> <li>1.11 (1.</li> <li>0.68 (0.</li> <li>1.33 (1.</li> <li>1.33 (1.</li> <li>1.33 (1.</li> <li>1.33 (1.</li> <li>1.33 (1.</li> <li>4.4.1 5.</li> <li>4.4.1 5.</li> <li>4.4.1 5.</li> <li>6.1 (1.01-1.0)</li> <li>7 (0.98-0.9)</li> <li>7 (0.98-0.9)</li> <li>1 (1.01-1.0)</li> <li>0 (1.03-1.0)</li> <li>0 (1.03-1.0)</li> <li>0 (1.03-1.0)</li> <li>0 (1.03-1.0)</li> <li>0 (1.03-1.0)</li> <li>0 (1.12-1.0)</li> <li>0 (1.12-1.0</li></ul>

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# **PK of SBECD in Participants With RI**

- SBECD PK were characterized by a short terminal elimination half-life (t<sub>1/2</sub>; 1.6 hours) in normal renal function to 5.7 hours in severe RI) and plasma CL (7.9 to 9.5 L/h in normal renal function; **Table 2**)
- An analysis of SBECD in severe RI (REDPINE) is ongoing, but accumulation is not expected based on its observed short plasma  $t_{1/2}$

## Table 2. GM (%CV)<sup>a</sup> SBECD Plasma PK Parameters in Adult Participants Following IV Administration of a Single 100 mg RDV Dose

Geometric mean (%CV)	Mild RI (n = 10)	Mild RI healthy- matched control (n = 7)	Moderate RI (n = 10)	Moderate RI healthy- matched control (n = 9)	Simulated severe RI <sup>b</sup> (n = 20)
C <sub>max</sub> , µg/mL	247 (87.1)	156 (32.1)	217 (28.4)	204 (22.2)	231 (16.2)
AUC <sub>0-4h</sub> , h∙µg/mL	345 (18.4)	235 (25.6)	447 (27.6)	315 (25.8)	503 (17.4)
AUC <sub>inf</sub> , h•µg/mL	396 (22.3)	316 (16.9)	808 (42.0)	380 (33.1)	1273 (21.2)
t <sub>1/2</sub> , h <sup>a</sup>	0.95 (0.83, 1.74)	1.65 (1.61, 1.87)	3.80 (2.48, 4.54)	1.60 (1.36, 1.79)	5.67 (3.97, 7.37)
V <sub>z</sub> , L	12.8 (38.0)	24.1 (24.4)	17.8 (19.2)	17.9 (16.9)	19.3 (23.9)
CL, L/h	7.6 (19.6)	9.5 (18.4)	3.7 (41.7)	7.9 (28.8)	2.4 (19.1)

GM, geometric mean; %CV, percentage coefficient of variation; SBECD, sulfobutylether-β-cyclodextrin sodium; PK, pharmacokinetics IV, intravenous; RDV, remdesivir; RI, renal impairment; C<sub>max</sub>, maximum observed concentration; AUC<sub>0-4b</sub>, partial area under the concentration-time curve from time 0 hours to time 4 hours; AUC<sub>inf</sub>, area under the concentration-time curve extrapolated to infinite time; t<sub>1/2</sub>, terminal elimination half-life; NA. not appropriate to calculate; V<sub>2</sub>, volume of distribution of terminal phase; CL, clearance; Q1, quartile 1; Q3, quartile 3 <sup>a</sup>Data are presented as GM (%CV), with the exception of  $t_{1/2}$ , which are presented as median (Q1, Q3). Simulated 100 mg dose-normalized values based on a population PK model built on GS-US-540-9015 mild, moderate, and severe RI cohorts and healthy matched controls.

## **Steady-state Exposures in REDPINE Study Participants**

PopPK-estimated exposures and basic demographic information for participants with PK samples collected in the REDPINE study are summarized in **Table 3** 

Characteristic	<b>GM (%CV)</b>
Number of participants	90ª (severe RI; kidney failu
eGFR, mL/min/1.73 m <sup>2</sup> , median (min, max)	14.7 (2.5, 41.7) <sup>b</sup>
Body weight, kg	79.0 (43.0, 148.0)
RDV AUC <sub>tau</sub> , ng•h/mL	2950 (63.1) (3250 [68.5]; 2670 [56.
RDV C <sub>max</sub> , ng/mL	3850 (56.3) (4170 [58.9]; 3570 [53.
GS-704277 AUC <sub>tau</sub> , ng•h/mL	1550 (57.5) (1480 [55.1]; 1660 [55.
GS-704277 C <sub>max</sub> , ng/mL	378 (67.0) (397 [73.3]; 370 [59.2
GS-441524 AUC <sub>tau</sub> , ng•h/mL	15,400 (44.6) (11,600 [38.3]; 20,200 [2
GS-441524 C <sub>max</sub> , ng/mL	703 (41.5) (548 [36.7]; 893 [28.1
GS-441524 C <sub>tau</sub> , ng/mL	377 (40.3) (321 [38.7]; 440 [35.3

 $\Theta$ GFR, estimated glomerular filtration rate; AUC<sub>tau</sub>, area under the concentration-time curve over the dosing interval;  $C_{max}$ , maximum observed concentration: PK. pharmacokinetics: Among REDPINE participants with available PK data, 47.8% (43/90) had severe RI (eGFR, 15-29 mL/min/1.73 m<sup>2</sup>) and 51.1% (46/90) had kidney failure (eGFR, <15 mL/min/1.73 m<sup>2</sup>); 45.6% (41/90) needed renal replacement therapy; 5.6% (5/90) received intermittent hemodialysis Protocol enrollment criterion was baseline eGFR <30 mL/min/1.73 m<sup>2</sup> for REDPINE

# Conclusion

Given the observed PK measures and the absence of any new safety signals associated with increased GS-441524 metabolite and SBECD levels in the REDPINE study, no dose adjustment is recommended for RDV in COVID-19 patients with eGFR <30 mL/min/1.73 m<sup>2</sup>, regardless of the need for dialysis

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1.18-1.08) (0.86-0.73) (0.99-0.98) .13 - 1.07).87-0.82)

(1.40 - 1.39)

an (90% Cl) I change (1.14-1.09) (0.83-0.76 (0.78-0.76 (2.70 - 2.49)1.11-1.10



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