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Pharmacokinetics of SARS-CoV-2 RNA Polymerase Inhibitor Remdesivir in Participants With Moderate and Severe Hepatic Impairment

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ABSTRACT

Remdesivir is an RNA polymerase inhibitor of severe acute respiratory syndrome coronavirus 2 administered intravenously (IV) that is approved for the treatment of coronavirus disease 2019 in hospitalized and nonhospitalized patients. The clinical dosing regimen is a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2, for a total duration of up to 10 days. The prodrug, remdesivir, undergoes metabolic activation inside the cell to form the intracellular active metabolite (GS-443902) along with two plasma metabolites (GS-704277 and GS-441524). The pharmacokinetics and safety of a single IV 100-mg dose of remdesivir were evaluated in a Phase 1, open-label, multicenter study in participants with moderate ($n = 10$) or severe ($n = 6$) hepatic impairment (Child–Pugh–Turcotte Class B or C, respectively) and participants with normal liver function ($n = 16$). Compared with the normal hepatic function group, plasma exposures (geometric least squares mean ratios of area under the concentration–time curve extrapolated to infinity and maximum concentration) of remdesivir, GS-704277, and GS-441524 were similar in the moderate hepatic impairment group and up to 1.56-fold, 2.41-fold, and 1.48-fold higher, respectively, in the severe hepatic impairment group. Remdesivir was generally safe and well tolerated in hepatically impaired individuals, and the modest exposure increases of remdesivir and its metabolites were not associated with adverse events. Based on these findings, no dose adjustment of remdesivir is recommended for patients with mild, moderate, or severe hepatic impairment.

1 | Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is responsible for > 770 million infections and > 6.9 million deaths worldwide since the first cases were reported in 2019 [1]. Remdesivir is an intravenous (IV) nucleotide prodrug that leads to the formation of an intracellular nucleoside triphosphate (GS-443902) known to have pharmacological activity against SARS-CoV-2 [2]. A rapid clinical development program informed the therapeutic regimen of remdesivir for use in typical and special populations, including patients with organ impairment [3]. Hepatic impairment is a decline in liver function that may lead to altered exposure of therapies that are primarily metabolized by the liver. Patients with chronic liver disease were more likely to have severe COVID-19 (pooled odds ratio, 1.48; $p = 0.001$) and a higher mortality rate (pooled odds ratio, 1.78; $p = 0.02$) based on a systemic review and meta-analysis of clinical studies [4].

The clinical dosing regimen of remdesivir is a single loading dose of 200 mg on Day 1 followed by maintenance doses of

Summary

- What is the current knowledge on the topic?
  - Remdesivir is an intravenous prodrug approved for the treatment of coronavirus disease 2019 (COVID-19). Remdesivir and its metabolite GS-704277 are eliminated primarily via the metabolizing enzymes carboxylesterase 1 and histidine triad nucleotide-binding protein 1, while the metabolite GS-441524 is eliminated renally. Pharmacokinetics of remdesivir and its metabolites have been previously characterized in healthy participants and in patients with COVID-19 but not in special populations, such as those with organ dysfunction.
- What question did this study address?
  - This Phase 1 study evaluated the pharmacokinetics and safety of remdesivir and its metabolites in participants with moderate or severe hepatic impairment.
- What does this study add to our knowledge?
  - Consistent with known elimination pathways, plasma exposures of remdesivir and GS-704277 were modestly increased with severe hepatic impairment compared with normal liver function. Exposure increases of remdesivir and its metabolites were not clinically relevant, and thus, no dose adjustment is needed in patients with any degree of hepatic impairment.
- How might this change clinical pharmacology or translational science?
  - This study described the impact of hepatic impairment on remdesivir and its metabolites, which, along with pharmacokinetic and safety data from the overall clinical development program, supports the extension of remdesivir treatment to the population with hepatic impairment.

100 mg once daily (QD) from Day 2 up to Day 10 through IV infusion [3]. Following IV administration, remdesivir is quickly and extensively metabolized intracellularly via carboxylesterase 1 (CES1) to the intermediate metabolite GS-704277, which is further metabolized by histidine triad nucleotide-binding protein 1 (HINT1) to form the nucleoside analog monophosphate [2]. The monophosphate is phosphorylated to form the active metabolite GS-443902 or dephosphorylated to form the renally eliminated metabolite GS-441524. While remdesivir, GS-704277, and GS-441524 are detectable in plasma, GS-443902 is only detectable intracellularly. Remdesivir is highly protein bound at 88% to 94%; metabolites GS-704277 and GS-441524 exhibit low plasma protein binding (1% and 2%, respectively) [3]. The bioactivating enzyme CES1 is abundantly and primarily expressed in the liver [4, 5], while tissue expression of HINT1 is less specific but also includes the liver [5]. Accordingly, an investigation was warranted to assess the impact of hepatic impairment on the disposition of remdesivir and its metabolites.

A Phase 1 study was conducted to assess the pharmacokinetics (PK) and safety of remdesivir and its metabolites in participants with moderate or severe hepatic impairment. Results from this study were utilized to inform dosing recommendations for remdesivir in patients with impaired liver function.

2 | Methods

2.1 | Study Design and Participants

This was a Phase 1, open-label, multicenter study in participants with impaired or normal hepatic function following a single 100-mg dose of IV remdesivir. The protocol and consent forms were approved by the sites' investigational review boards. This study was conducted at six sites in accordance with the clinical and ethical standards outlined by Good Clinical Practice, the International Council for Harmonization, and the Declaration of Helsinki.

Eligible participants were male or nonpregnant, nonlactating female individuals with impaired or normal hepatic function aged 18 through 75 years who had body mass index (BMI) ≥ 18 to $\leq 38\,kg/m^2$, 12-lead electrocardiogram (ECG) without clinically significant abnormalities, and creatinine clearance (CLcr) ≥ 60 mL/min (using the Cockcroft–Gault [C-G] formula). Participants with hepatic impairment must have had a diagnosis of chronic (> 6 months), stable hepatic impairment (moderate [Class B] or severe [Class C] by Child–Pugh–Turcotte classification) with no clinically significant change in hepatic status within 2 months prior to screening. Participants with normal hepatic function were paired with participants with hepatic impairment by age (± 10 years), sex, and BMI (± 20%). Participants were divided into two sequentially enrolled cohorts; individuals with moderate hepatic impairment and their matched controls were enrolled in Cohort 1, with enrollment of individuals with severe hepatic impairment and their matched controls in Cohort 2 following a midstudy safety review. Per the analysis plan, 10 participants with moderate hepatic impairment and six participants with severe hepatic impairment with matched participants with normal hepatic function were required to achieve statistical power.

Additional participant characteristics were determined in post hoc analyses, which included calculation of the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula (mL/min/1.73 m^2).

2.2 | PK Assessments and Bioanalysis

Blood samples for the assessment of remdesivir, GS-704277, and GS-441524 plasma concentrations were taken at predose and at 0.25 (middle of infusion), 0.5 (end of infusion), 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h postdose to fully capture the PK profile of each analyte. Remdesivir and metabolite concentrations were determined using validated liquid chromatography–tandem mass spectrometry methods [6, 7]. The predose sample was used to assess remdesivir plasma protein binding using equilibrium dialysis methods as previously described [8].

2.3 | PK and Statistical Analysis

PK parameters were estimated via noncompartmental analysis using Phoenix WinNonlin version 8.2 (Certara L.P., Princeton, NJ, USA). Parameters calculated included maximum observed

concentration (C_{max}), time of C_{max}, area under the concentration–time curve from time zero extrapolated to infinity (AUC_{inf}), plasma clearance, volume of distribution, and elimination half-life ($t_{1/2}$), as applicable. Unbound drug exposures of remdesivir were calculated using the percentage of unbound drug determined for each individual participant.

Statistical comparisons were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). For each analyte and exposure parameter, a parametric analysis of variance model including hepatic function as a fixed effect was used. Two-sided 90% confidence intervals were calculated for the geometric least squares mean (GLSM) ratios of AUC_{inf} and C_{max} from test (hepatic impairment) to reference (normal hepatic function). The predetermined no-effect interval was 0.50 to 2.00.

2.4 | Safety Assessments

Safety monitoring was performed for the duration of the study by clinical laboratory tests, 12-lead ECGs, periodic physical examinations including vital signs, and documentation of adverse events.

3 | Results

3.1 | Participants

A total of 32 participants were enrolled in the study: 10 individuals with moderate hepatic impairment, 6 individuals with severe hepatic impairment, and 16 individuals with normal hepatic function. All 32 participants received 100-mg IV remdesivir and completed the study. All participants were included in the safety and PK analyses.

Overall, median age was 58 years and median BMI was 28.8 kg/m^2 in study participants, with an equal distribution of male and female participants (Table 1). Participant demographic and baseline characteristics were well matched by age, sex, and BMI between the hepatic impairment groups and the matched normal hepatic function groups.

Baseline renal function was determined by two methods: CLcr (using C-G) for enrollment purposes and eGFR (using MDRD) as part of an additional post hoc analysis. Median (range) CLcr was 104 (58.7, 196) mL/min, with most participants (78.1%, 25/32) classified as having normal renal function (≥ 90 mL/min). Median (range) eGFR values were lower at 87.0 (53.7, 133) mL/min/1.73 m^2, with most participants (62.5%, 20/32) classified as having mild or moderate renal impairment (30 to < 90 mL/min/1.73 m^2).

3.2 | PK

Plasma concentration–time profiles for remdesivir and metabolites are shown in Figure 1, and the respective PK parameters are presented in Table 2 (individual exposures relative to Child–Pugh–Turcotte scores can be found in Figures S1 through S6). Compared with the matched normal hepatic function groups, the moderate hepatic impairment group had similar plasma concentrations of remdesivir, while the severe hepatic impairment group had slightly increased concentrations. Median $t_{1/2}$ for remdesivir remained unchanged at approximately 1 h across all hepatic function groups. Plasma concentrations of GS-704277 were also similar between the moderate hepatic impairment group and the normal hepatic function group, while a modest increase was observed in the severe hepatic impairment group. Elimination of GS-704277 was slower in the severe hepatic impairment group, as evidenced by the change in the concentration–time profile and increase in median $t_{1/2}$ from 1.14 to 1.86 h. For GS-441524, plasma concentrations were comparable across all hepatic function groups.

For remdesivir and its metabolites, plasma exposures were relatively unchanged in the moderate hepatic impairment group compared with the normal hepatic function group, as GLSM ratios of AUC_{inf} and C_{max} ranged from 0.90 to 1.38 (Table 3). In the severe hepatic impairment group, the AUC_{inf} of remdesivir, GS-704277, and GS-441524 were 1.56-fold, 2.41-fold, and 1.31-fold higher, respectively, than matched participants with normal hepatic function. A 1.48-fold increase in C_{max} of GS-441524 was also detected in the severe impairment group; no other significant differences in C_{max} were detected.

Median (range) free fractions of remdesivir in plasma were 4.62% (3.62%, 6.24%), 5.19% (4.51%, 7.03%), and 6.94% (4.92%, 7.27%) in the pooled normal hepatic function, moderate hepatic impairment, and severe hepatic impairment groups, respectively. There were no significant differences in unbound remdesivir exposures in the moderate hepatic impairment group. However, $AUC_{inf,\ unbound}$ and $C_{max,\ unbound}$ were 2.44-fold and 1.57-fold higher, respectively, in the severe hepatic impairment group (Table 3).

3.3 | Safety

Adverse events were observed in 8 (25.0%) of 32 participants (Table 4; listing in Table S1). There were no Grade 3 or 4 adverse events or deaths. All Grade 1 adverse events resolved by study completion. In Cohort 1, 2 (20.0%) of 10 participants in the moderate hepatic impairment group and 2 (20.0%) of 10 matched participants with normal hepatic function reported adverse events. All adverse events in Cohort 1 were Grade 1, and all were related to study drug. Laboratory abnormalities were reported in 8 (80.0%) of 10 participants in the moderate hepatic impairment group and in 3 (30.0%) of 10 matched participants with normal hepatic function; these were predominantly Grade 1 or 2. In Cohort 2, 2 (33.3%) of 6 participants in the severe hepatic impairment group and 2 (33.3%) of 6 matched participants with normal hepatic function reported adverse events. All adverse events in Cohort 2 were Grade 1 or 2, and none were related to study drug. Laboratory abnormalities were reported in 6 (100%) of 6 participants in the severe hepatic impairment group and in 6 (100%) of 6 matched participants with normal hepatic function; these ranged from Grade 1 to 3 in severity.

TABLE 1 | Demographic and baseline characteristics.

Characteristic	Cohort 1		Cohort 2		
	Moderate hepatic impairment ($N=10$)	Matched normal hepatic function ($N=10$)	Severe hepatic impairment ($N=6$)	Matched normal hepatic function ($N=6$)	Total ($N=32$)
Age, years	59 (40, 69)	60 (39, 73)	56 (41, 64)	56 (51, 64)	58 (39, 73)
Sex at birth					
Male	6 (60.0)	6 (60.0)	2 (33.3)	2 (33.3)	16 (50.0)
Female	4 (40.0)	4 (40.0)	4 (66.7)	4 (66.7)	16 (50.0)
Race					
Black	0	3 (30.0)	0	1 (16.7)	4 (12.5)
White	10 (100)	7 (70.0)	6 (100)	5 (83.3)	28 (87.5)
Ethnicity					
Hispanic or Latino	7 (70.0)	5 (50.0)	4 (66.7)	6 (100)	22 (68.8)
Not Hispanic or Latino	3 (30.0)	5 (50.0)	2 (33.3)	0	10 (31.3)
BMI, kg/m^2	29.8 (24.0, 37.0)	28.8 (22.9, 35.4)	29.1 (21.9, 34.7)	28.0 (22.9, 34.6)	28.8 (21.9, 37.0)
CLcr (C-G), mL/min	116 (58.7, 196)	105 (64.0, 143)	104 (81.6, 115)	95.7 (86.5, 139)	104 (58.7, 196)
eGFR (MDRD), mL/min/1.73 m^2	89.6 (55.6, 133)	88.7 (75.4, 110)	78.4 (53.7, 121)	88.3 (74.2, 108)	87.0 (53.7, 133)
Renal impairment (C-G)	3 (30.0)	2 (20.0)	1 (16.7)	1 (16.7)	7 (21.9)
CLcr, mL/min	84.0 (58.7, 85.4)	75.0 (64.0, 85.9)	81.6	86.5	84.0 (58.7, 86.5)
Renal impairment (MDRD)	5 (50.0)	5 (50.0)	5 (83.3)	5 (83.3)	20 (62.5)
eGFR, mL/min/1.73 m^2	62.9 (55.6, 87.1)	84.3 (75.4, 86.6)	74.4 (53.7, 87.6)	86.9 (74.2, 89.7)	82.5 (53.7, 89.7)

Note: Values reported as median (minimum, maximum) for continuous data or as *n* (%) for categorical data. Renal impairment was defined as CLcr < 90 mL/min or eGFR < 90 mL/min/1.73 m^2.
Abbreviations: BMI, body mass index; C-G, Cockcroft–Gault; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

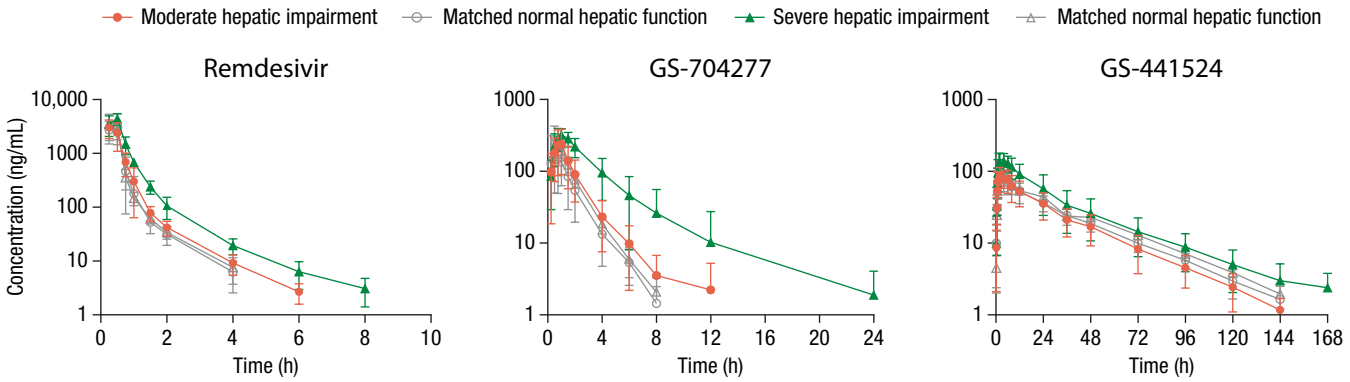

FIGURE 1 | Plasma concentration versus time for remdesivir, GS-704277, and GS-441524. Data are shown as mean ± SD. Plasma concentrations of remdesivir, GS-704277, and GS-441524 were similar in the moderate hepatic impairment group compared with the matched normal hepatic function group. Plasma concentrations of remdesivir and GS-704277 were higher in the severe hepatic impairment group compared with the matched normal hepatic function group. SD, standard deviation.

TABLE 2 | PK parameters of remdesivir, GS-704277, and GS-441524.

	Cohort 1		Cohort 2	
	Moderate hepatic impairment (*N*=10)	**Matched normal hepatic function (*N*=10)**	**Severe hepatic impairment (*N*=6)**	**Matched normal hepatic function (*N*=6)**
Remdesivir				
AUC_{inf}, h•ng/mL	1690 (34.5)	1460 (35.6)	2850 (26.7)	1820 (24.3)
C_{max}, ng/mL	3050 (37.2)	2910 (40.8)	4520 (29.1)	4570 (42.5)
$AUC_{inf,\ unbound}$, h•ng/mL	95.6 (53.2)	77.5 (23.3)	189 (17.6)	78.5 (24.5)
$C_{max,\ unbound}$, ng/mL	171 (53.4)	155 (32.2)	295 (24.8)	197 (42.8)
T_{max}, h	0.25 (0.25, 0.25)	0.38 (0.25, 0.50)	0.50 (0.50, 0.50)	0.50 (0.25, 0.50)
CL, mL/h	64,100 (26.7)	86,600 (76.2)	37,000 (22.7)	57,900 (25.2)
$t_{1/2}$, h	0.84 (0.80, 1.01)	0.90 (0.68, 0.91)	0.96 (0.85, 1.68)	0.82 (0.76, 0.90)
V_z, mL	82,800 (29.2)	104,000 (89.5)	55,800 (27.1)	66,200 (33.4)
GS-704277				
AUC_{inf}, h•ng/mL	482 (52.3)	330 (35.2)	108 (47.8)	422 (22.4)
C_{max}, ng/mL	251 (61.8)	216 (82.6)	333 (28.5)	331 (45.1)
T_{max}, h	0.88 (0.75, 1.00)	0.75 (0.50, 0.75)	1.00 (1.00, 1.00)	0.63 (0.50, 0.75)
$t_{1/2}$, h	1.28 (1.02, 1.87)	1.15 (0.98, 1.36)	1.86 (1.33, 2.16)	1.14 (0.93, 1.35)
GS-441524				
AUC_{inf}, h•ng/mL	2490 (36.0)	2680 (25.5)	4280 (46.7)	3040 (9.2)
C_{max}, ng/mL	93.0 (25.9)	88.0 (36.2)	145 (29.0)	96.7 (17.7)
T_{max}, h	2.00 (1.50, 4.00)	2.00 (2.00, 2.00)	2.97 (1.50, 4.00)	2.00 (2.00, 4.00)
$t_{1/2}$, h	23.6 (22.8, 26.4)	29.5 (26.1, 33.0)	34.7 (30.0, 35.7)	27.7 (25.3, 30.6)

Note: All parameters reported as arithmetic mean (%CV) except T_{max} and $t_{1/2}$, which are reported as median (minimum, maximum).
Abbreviations: %CV, percent coefficient of variation; AUC_{inf}, area under the concentration–time curve from time zero extrapolated to infinity; $AUC_{inf,\ unbound}$, area under the concentration–time curve from time zero extrapolated to infinity for unbound remdesivir; CL, plasma clearance; C_{max}, maximum observed concentration; $C_{max,\ unbound}$, maximum observed concentration for unbound remdesivir; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; T_{max}, time of maximum observed concentration; V_z, volume of distribution.

4 | Discussion

This Phase 1 study characterized the effect of moderate and severe hepatic impairment on the PK and safety of remdesivir and its metabolites in adults. In participants with moderate hepatic impairment, plasma exposures of remdesivir, GS-704277, and GS-441524 were not significantly different from those in participants with normal hepatic function. Modest increases in AUC_{inf} of remdesivir and GS-704277 (1.56-fold and 2.41-fold, respectively) were detected in participants with severe hepatic impairment, in line with metabolism being the primary elimination pathway of these analytes. Considering the short $t_{1/2}$ of both remdesivir and GS-704277 (approximately 1–2 h), these increases in plasma exposures are transient and no accumulation is expected after repeat QD dosing. In addition, exposure increases of remdesivir and GS-704277 in severe hepatic impairment were less than those observed in a Phase 1 drug interaction study of remdesivir and coadministered perpetrators [3]. In that study, coadministration with cyclosporine, an inhibitor of hepatic uptake transporters, led to exposure increases of 1.89-fold for remdesivir and 2.97-fold for GS-704277. These increases were deemed not clinically relevant, and concomitant use of remdesivir with such inhibitors has been allowed with no dose adjustment.

When corrected for plasma protein binding, the exposure increase of unbound remdesivir was up to 2.44-fold with severe hepatic impairment, larger than the exposure increase observed for total drug (up to 1.56-fold). This is an artifact of a numerical, but clinically irrelevant, difference in the percentage of unbound remdesivir between those with severe hepatic impairment and those with normal hepatic function. In this study, the free fraction of remdesivir trended slightly lower than the previously reported range of 7% to 12% [3]. Participants with normal hepatic function had unbound remdesivir values ranging from 3.64% to 6.24%, while nearly all participants with severe hepatic impairment had approximately 7% unbound, which is within the expected range for remdesivir. These values also do not deviate significantly from the 4.2% to 5.4% range observed across the spectrum of renal impairment in a Phase 1, single-dose study of remdesivir [9]. Thus, the increase in unbound remdesivir exposures with

TABLE 3 | Statistical comparisons of remdesivir, GS-704277, and GS-441524 exposures in participants with moderate or severe hepatic impairment versus matched participants with normal hepatic function.

	GLSM ratio (90% CI)	
	Moderate hepatic impairment (*N* = 10)	**Severe hepatic impairment (*N* = 6)**
Remdesivir		
AUC_{inf}, h•ng/mL	1.21 (0.87, 1.67)	1.56 (1.20, 2.03)
C_{max}, ng/mL	1.10 (0.75, 1.60)	1.03 (0.70, 1.51)
$AUC_{inf,\ unbound}$, h•ng/mL	1.15 (0.86, 1.54)	2.44 (1.93, 3.08)
$C_{max,\ unbound}$, ng/mL	1.04 (0.73, 1.48)	1.57 (1.08, 2.29)
GS-704277		
AUC_{inf}, h•ng/mL	1.38 (0.92, 2.07)	2.41 (1.70, 3.42)
C_{max}, ng/mL	1.29 (0.54, 3.08)	1.07 (0.70, 1.63)
GS-441524		
AUC_{inf}, h•ng/mL	0.90 (0.69, 1.17)	1.31 (0.93, 1.84)
C_{max}, ng/mL	1.09 (0.86, 1.38)	1.48 (1.17, 1.86)

Abbreviations: AUC_{inf}, area under the concentration–time curve from time zero extrapolated to infinity; $AUC_{inf,\ unbound}$, area under the concentration–time curve from time zero extrapolated to infinity for unbound remdesivir; CI, confidence interval; C_{max}, maximum observed concentration; $C_{max,\ unbound}$, maximum observed concentration for unbound remdesivir; GLSM, geometric least squares mean.

TABLE 4 | Adverse events and laboratory abnormalities.

	Cohort 1		Cohort 2	
Adverse event	**Moderate hepatic impairment (*N* = 10)**	**Matched normal hepatic function (*N* = 10)**	**Severe hepatic impairment (*N* = 6)**	**Matched normal hepatic function (*N* = 6)**
Participants with any adverse event	2 (20.0)	2 (20.0)	2 (33.3)	2 (33.3)
Participants with any laboratory abnormality	8 (80.0)	3 (30.0)	6 (100)	6 (100)
Gastrointestinal disorders				
Abdominal pain (upper)	0	0	1 (16.7)	0
Nausea	0	0	1 (16.7)	0
Infection				
Herpes zoster	0	0	1 (16.7)	0
Musculoskeletal disorders				
Neck pain	0	0	0	1 (16.7)
Pain in extremity	0	0	1 (16.7)	0
Nervous system disorders				
Headache	2 (20.0)	1 (10.0)	0	0
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	0	0	1 (16.7)	0
Skin and subcutaneous tissue disorders				
Dry skin	0	0	0	1 (16.7)
Rash	0	1 (10.0)	0	0

Note: Values reported as *n* (%).

severe hepatic impairment is not considered clinically relevant and is consistent with what has been demonstrated for most drugs, as there are limited cases of when protein binding changes are clinically relevant [10]. Benet et al have described that changes in plasma protein binding are not usually clinically relevant except in rare cases of a drug with all of the following criteria: (i) high extraction ratio, (ii) narrow therapeutic index, (iii) parenteral administration, and (iv) very rapid PK-pharmacodynamic equilibrium half-life (e.g., antiarrhythmic or anesthetic agents that have drug effects directly related to unbound drug concentrations) [10]. Remdesivir does not match all of the aforementioned criteria.

For the renally eliminated GS-441524, exposures trended higher in the liver-impaired groups; however, this may be attributed to the decreased renal function in these participants. Per the study's inclusion criteria, participants with normal renal function or mild renal impairment were allowed, defined as CLcr $\geq$60 mL/min using the C-G method. When an additional analysis of renal function was performed after study completion, differences were noted compared with eGFR calculations using the MDRD method. The majority of participants were classified as having normal renal function when assessed by C-G (78.1% with CLcr $\geq$90 mL/min) but mild or moderate renal impairment when assessed by MDRD (62.5% with eGFR 30 to $<$90 mL/min/1.73 m^2). Previous studies suggest that MDRD is a more accurate measure of renal function than C-G [11], and remdesivir was previously investigated in a Phase 1 renal impairment study according to eGFR classifications using MDRD [9]. In participants with concurrent renal dysfunction, eGFR as estimated by MDRD trended lower in the hepatic impairment groups (minimum 55.6 or 53.7 mL/min/1.73 m^2) compared with the normal hepatic function groups (minimum 75.4 or 74.2 mL/min/1.73 m^2), which may account for the changes in GS-441524 exposures (Table 2).

Following the emergency use authorization of remdesivir, a whole-body physiologically based PK (PBPK) model predicting plasma and tissue exposures in organ-impaired populations was described by US Food and Drug Administration scientists, while clinical development in special populations, such as this Phase 1 study, was ongoing [12]. Model simulations of a 5-day treatment course predicted increases in the plasma area under the concentration–time curve (AUC) of unbound remdesivir and GS-704277 with severe hepatic impairment, consistent with our observed study results. Unlike the Phase 1 study results, the PBPK model predicted an unchanged plasma AUC for total remdesivir and a slight decrease in plasma AUC for GS-441524 across mild, moderate, and severe hepatic impairment. In general, the magnitude of exposure change with varying degrees of hepatic impairment was underpredicted by the PBPK model. Differences between these model predictions and our clinical observations may be due to the lack of data at the time of model development, such as enzyme levels of CES1 and HINT1, and plasma protein binding of remdesivir under the conditions of hepatic impairment. These differences underscore the value of observed clinical data in furthering model development and validating model predictions, which, as it relates to GS-441524, could not account for renal impairment occurring concurrently in hepatically impaired individuals.

Overall, a single dose of remdesivir was safe and well tolerated in Phase 1 participants with hepatic impairment. Incidence rates of adverse events were not impacted by hepatic impairment status or concurrent renal impairment and were consistent with remdesivir safety results from prior studies. The safety of remdesivir was previously demonstrated to be comparable to that of placebo in Phase 3 participants with COVID-19 with acute kidney injury, chronic kidney disease, or kidney failure [13]. Treatment-emergent laboratory abnormalities in the hepatically impaired groups were consistent with known abnormalities present in patients with hepatic impairment. In addition, no safety concerns were identified in 166 Phase 3 participants with COVID-19 and a baseline medical history of chronic liver disease (e.g., hepatic cirrhosis, nonalcoholic steatohepatitis; data on file). Given this favorable safety profile, increased exposures of remdesivir and its metabolites due to hepatic impairment were determined as not clinically relevant.

Based on the results of this Phase 1 study, no dose adjustment of remdesivir is warranted, and the full dosing regimen (200-mg loading dose on Day 1 followed by 100 mg QD from Day 2 up to Day 10) is recommended for individuals with reduced liver function of any severity, as the increased exposures of remdesivir and its observed metabolites are not clinically relevant. Remdesivir is currently approved for treatment of COVID-19 in hepatically impaired patients in the United States and European Union.

Author Contributions

S.R., R.H., L.C., M.A., S.D., A.B., G.S., R.H.H., and A.K. wrote the manuscript. R.H. designed the research. S.R., M.A., S.D., and A.B. performed the research. S.R., R.H., L.C., M.A., S.D., A.B., G.S., R.H.H., and A.K. analyzed the data.

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Conflicts of Interest

Sean Regan, Luzelena Caro, Mazin Abdelghany, Santosh Davies, Gong Shen, Robert H. Hyland, and Aryun Kim are stockholders and employees of Gilead Sciences, Inc. Rita Humeniuk and Amarylliz Baysa are stockholders and former employees of Gilead Sciences, Inc.

References

1. World Health Organization, "Weekly Epidemiological Update on COVID-19 - 1 September 2023," accessed August 29, 2024, https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---1-september-2023.

2. R. Humeniuk, A. Mathias, B. J. Kirby, et al., "Pharmacokinetic, Pharmacodynamic, and Drug-Interaction Profile of Remdesivir, a SARS-CoV-2 Replication Inhibitor," *Clinical Pharmacokinetics* 60 (2021): 569–583.

3. Veklury, *Prescribing Information* (Gilead Sciences, Inc., 2023).

4. A. J. Kovalic, S. K. Satapathy, and P. J. Thuluvath, "Prevalence of Chronic Liver Disease in Patients With COVID-19 and Their Clinical

Outcomes: A Systematic Review and Meta-Analysis," *Hepatology International* 14 (2020): 612–620.

5. "Human Protein Atlas," accessed August 29, 2024, Version 23, https://www.proteinatlas.org/about/releases#23.0.

6. R. Humeniuk, A. Mathias, H. Cao, et al., "Safety, Tolerability, and Pharmacokinetics of Remdesivir, an Antiviral for Treatment of COVID-19, in Healthy Subjects," *Clinical and Translational Science* 13 (2020): 896–906.

7. D. Xiao, K. H. John Ling, T. Tarnowski, et al., "Validation of LC-MS/MS Methods for Determination of Remdesivir and Its Metabolites GS-441524 and GS-704277 in Acidified Human Plasma and Their Application in COVID-19 Related Clinical Studies," *Analytical Biochemistry* 617 (2021): 114118.

8. A. Wen, A. R. Qin, T. Tarnowski, et al., "Plasma Protein Binding Determination for Unstable Ester Prodrugs: Remdesivir and Tenofovir Alafenamide," *Journal of Pharmaceutical Sciences* 112 (2023): 3224–3232.

9. H. Zhang, R. Humeniuk, S. Regan, et al., "Clinical Pharmacokinetics and Safety of Remdesivir in Phase I Participants With Varying Degrees of Renal Impairment," *Clinical Pharmacokinetics* 64 (2025): 67–78.

10. L. Z. Benet and B. A. Hoener, "Changes in Plasma Protein Binding Have Little Clinical Relevance," *Clinical Pharmacology and Therapeutics* 71 (2002): 115–121.

11. W. M. Michels, D. C. Grootendorst, M. Verduijn, E. G. Elliott, F. W. Dekker, and R. T. Krediet, "Performance of the Cockcroft-Gault, MDRD, and New CKD-EPI Formulas in Relation to GFR, Age, and Body Size," *Clinical Journal of the American Society of Nephrology* 5 (2010): 1003–1009.

12. J. Fan, Y. Yang, M. Grimstein, et al., "Whole Body PBPK Modeling of Remdesivir and Its Metabolites to Aid in Estimating Active Metabolite Exposure in the Lung and Liver in Patients With Organ Dysfunction," *Clinical Pharmacology and Therapeutics* 111 (2022): 624–634.

13. M. E. Sise, J. R. Santos, J. D. Goldman, et al., "Efficacy and Safety of Remdesivir in People With Impaired Kidney Function Hospitalized for COVID-19 Pneumonia: A Randomized Clinical Trial," *Clinical Infectious Diseases* 79 (2024): 1172–1181.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.