CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Date: July 16, 2020

From: Neil Hartman, PhD, Marlene Kim, PhD, Naomi Kruhlak, PhD, Rebecca Racz, PharmD, Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: James Weaver Ph.D., Consult Lead and David Strauss M.D., Ph.D., Director; DARS/OCP

To: Neha Gada, Division of Pharmacovigilance II, Office of Surveillance and Epidemiology

Subject: In silico Analyses on the Potential Association of Remdesivir with Renal and Hepatic Events (NDA 21487)

Executive Summary

Remdesivir is currently approved under an Emergency Use Authorization (EUA) for COVID-19. It is closely related to adenosine and the adenosine nucleotides in structure. Multiple adverse events have been reported to the Agency, including acute kidney injury. Additionally, the Emergency Use Authorization describes a known risk of increased transaminase elevations during remdesivir treatment. However, as COVID-19 can also lead to serious outcomes, including acute kidney injury, the contribution of remdesivir to these adverse events is unclear. DARS performed multiple computational analyses, primarily based on structural similarity to other drugs, to evaluate remdesivir's potential association with these adverse events.

In silico pharmacologic target predictions performed using the software platform Clarity identified DNA polymerase as well as several adenosine and purine receptors as possible secondary targets of remdesivir and its metabolites. The sponsor-provided *in vitro* data found that most of these predictions were negative. Remdesivir did interact with DNA polymerase *in vitro* at clinically-relevant concentrations; however, development of toxicity through this mechanism generally requires chronic exposure and remdesivir is rapidly converted to its metabolites, which were not associated with DNA polymerase at clinically-relevant concentrations.

Remdesivir was also evaluated using (quantitative) structure-activity [(Q)SAR] models for hepatotoxicity and nephrotoxicity. Remdesivir was predicted to be positive for hepatotoxicity; however, considering the rapid metabolism of remdesivir this may not be clinically significant. Additionally, remdesivir's two metabolites, remdesivir triphosphate and GS-441524, were predicted to be positive for gall bladder disorders. All evaluated compounds were predicted to be negative or undeterminable for renal toxicity in the (Q)SAR models. Finally, a structural similarity search revealed several nucleoside analogs as potential comparators for remdesivir and GS-441524. Several of these closely related compounds are associated with some degree of kidney and/or liver issues and contain statements in their drug labels about the need for clinical monitoring of renal and liver function.

In conclusion, *in silico* analyses identified that remdesivir or its metabolites are structurally similar to other drugs that have been associated with some degree of renal and/or liver issues and their labels recommend monitoring renal and/or liver toxicity. Remdesivir's EUA does recommend daily monitoring of hepatic laboratory testing. These *in silico* analyses can be taken into account with other nonclinical and clinical data when evaluating the potential for remdesivir to be associated with renal or liver adverse events and the potential need for clinical monitoring.

Background

Remdesivir is currently approved under the Emergency Use Authorization (EUA) for COVID-19. It is a nucleotide analog of adenosine that inhibits viral RNA-dependent RNA polymerase, leading to early chain termination and inhibiting viral replication (Eastman et al 2020). It was previously under investigation as a treatment for several other viruses, including Ebola.

Multiple adverse events have been reported to the Agency, including acute kidney injury. However, as COVID-19 can be associated with adverse outcomes, it is not clear if remdesivir is causing these adverse events and conclusive data on the safety of remdesivir in patients with kidney injury or disease are lacking (Adamsick et al 2020). Additionally, the Emergency Use Authorization describes a known risk of increased transaminase elevations in healthy volunteers and patients with COVID-19 who received remdesivir during clinical trials. The Division of Pharmacoepidemiology II requested an analysis of the structure and adverse event potential of remdesivir.

Evaluation

Target Prediction

A target prediction evaluation was performed for remdesivir, two metabolites (remdesivir triphosphate and GS-441524), and the excipient sulfobutylether-beta-cyclodextrin to identify potential secondary targets that may result in renal adverse events (Table 1). Target prediction was performed with Clarity, a predictive analytics platform consisting of six integrated models that make predictions for secondary pharmacology activity based on drug structure and publicly-known primary target activity. As this tool has not been fully evaluated by the FDA, results should only be used for hypothesis generation.

The excipient sulfobutylether-beta-cyclodextrin was too large to analyze with Clarity and was therefore excluded from this analysis.

Table 1. Clarity predictions for remdesivir and metabolites. K: Known, Clarity has the interaction stored in the database from literature, patents, or other references. P: Predicted, Clarity made a prediction based on structural similarity or other properties of the molecule.

	Remdesivir	**Remdesivir Trisphophate**	**GS-441524**
DNA Polymerase	P	P	P
Adenosine receptor A1	P		P
Adenosine receptor A2	P		P
Adenosine receptor A3	P		P
Adenosine kinase			P
P2Y purinoceptor		P	

P2X purinoceptor		P	

One prediction of note is DNA polymerase. Many nucleoside analogs, such as remdesivir, can also act human DNA polymerase. This can lead to mitochondrial toxicity, which includes myopathy, neuropathy, hepatic steatosis, lactic acidosis, and nephropathy (Khungar and Han 2010). Of note, a study entitled "In Vitro Evaluation of GS-5734 [remdesivir] Effects on Mitochondrial DNA Content" submitted with the remdesivir IND application (IND 125566) found that at Ebola therapeutic concentrations (1 µM in rhesus macaques), no significant reduction in mitochondrial DNA was observed. At twice the therapeutic concentration (2 µM in rhesus macaques), 26% reduction in mitochondrial DNA occurred. For COVID-19, the Cmax after the Day 1 200 mg dose is approximately 9 µM (EMA), which is significantly higher than the concentration evaluated in the macaque study. For COVID-19, remdesivir is given for an additional 5 to 10 days at 100 mg. While remdesivir reaches relevant concentrations related to this *in vitro* assay, remdesivir is rapidly metabolized to remdesivir triphosphate (Warren et al 2016) and kidney adverse events due to mitochondrial toxicity are generally seen after months rather than days of treatment (Herlitz et al 2010). Thus, while this is unlikely to be the mechanism of potential kidney adverse events, it may deserve further investigation. An additional study in the IND application, "Interaction of GS-443902, the Active Nucleoside Triphosphate Metabolite of GS-5734, with Host RNA and DNA Polymerase Enzymes", found that at concentrations up to 200 µM, none of the DNA or RNA host (human) polymerases tested were inhibited. Remdesivir triphosphate only reaches a Cmax of 0.5 µM after the Day 1 dose (EMA). As kidney adverse effects due to mitochondrial toxicity are seen after months rather than days of treatment (Herlitz et al 2010) and the active metabolite does not reach concentrations significant to mitochondrial toxicity, it is unlikely that interaction with host polymerases contributes significantly to the toxicities observed.

Also of note, while both remdesivir and GS-441524 were predicted to bind at multiple adenosine receptors (which could subsequently lead to additional effects on heart rate, respiration, and blood pressure), secondary pharmacology screening for GS-441524 and a diastereomic mixture of remdesivir (GS-466547) submitted with the IND application indicated that neither compound demonstrated significant binding at adenosine A1, adenosine A2A, or the adenosine transporter.

Finally, while the P2R purinoceptors were predicted and are often associated with renal effects (Menzies et al 2017), confidence for these predictions was weak. Therefore, these predictions do not warrant further investigation at this time.

All other predicted targets had little to no effect on the renal or hepatobiliary system.

(Quantitative) Structural Activity Relationship Analysis

The DARS Computational Toxicology Consultation Service (CTCS) evaluated the four structures, remdesivir (API), remdesivir triphosphate, GS-441524, and cyclodextrin excipient for potential renal and liver toxicity effects using (quantitative) structure-activity relationship [(Q)SAR] models. Additionally, a structure-based search was performed to identify other drugs with high similarity to the three drugs that could serve as comparators.

The (Q)SAR models predicted remdesivir to be positive for hepatotoxicity; however, considering the rapid metabolism of remdesivir this may not be clinically significant (Warren et al 2016). Remdesivir

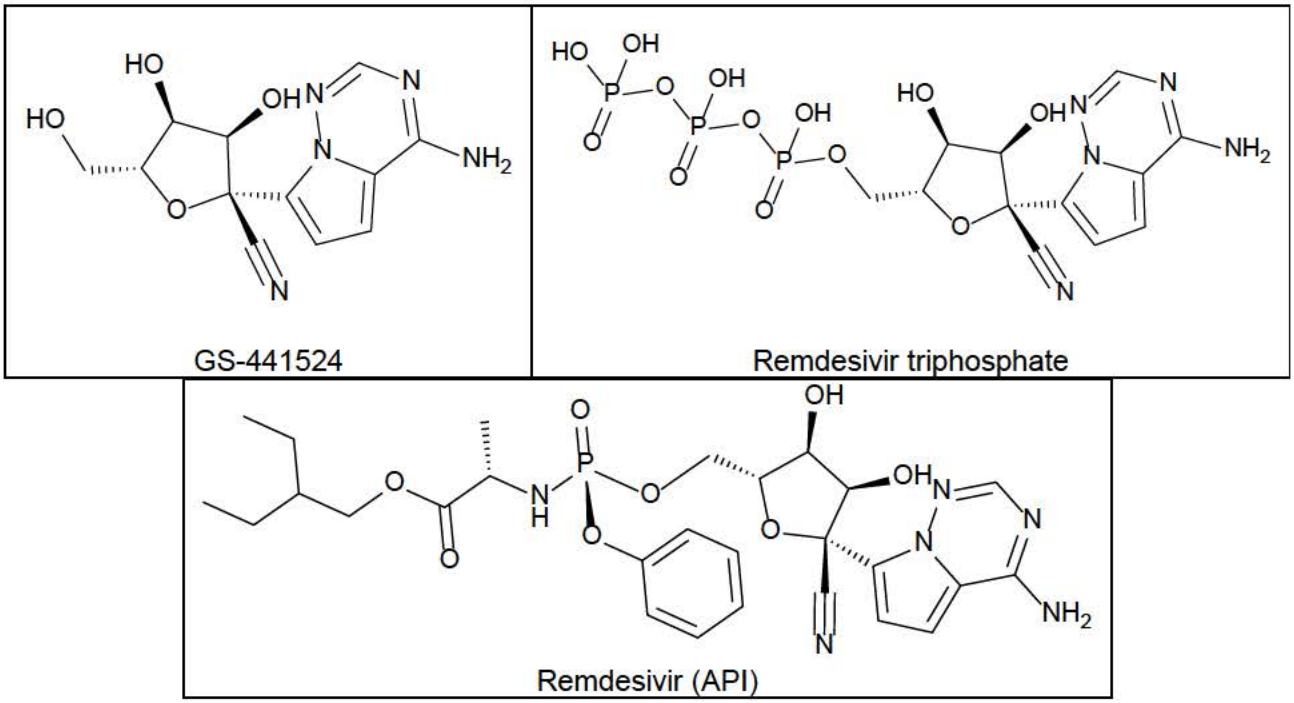
triphosphate was predicted to be positive for gall bladder disorders and equivocal for cholestasis and bile duct disorders. GS-441524 was predicted to be positive for gall bladder disorders and equivocal for bile duct disorders. Remdesivir, remdesivir triphosphate, GS-441524, and cyclodextrin excipient were predicted to be negative or undeterminable for renal toxicity disorders. The cyclodextrin excipient present in the formulation was predicted to be negative or undeterminable for all endpoints.

Structural Similarity Search

As remdesivir is a nucleoside analog, adenosine and guanosine analogs that are structurally similar were identified and evaluated for their potential to induce hepatic and renal adverse events based on pre- and post-market clinical experience. The drugs evaluated are analogs for both remdesivir and GS-441524. Several of these closely related compounds, particularly clofarabine, didanosine, and ganciclovir, contained statements in their drug labels on the need for clinical monitoring for renal and/or liver function.

These results support monitoring for these potential adverse effects, but they do not conclusively predict hepatotoxicity or renal toxicity for remdesivir, remdesivir triphosphate, or GS-441524.

Additional details may be found in the full report, located in Appendix 1.



Summary and Conclusions

Remdesivir is closely related to adenosine and the adenosine nucleotides in structure. It thus may be expected to interact with any enzyme using adenosine or adenosine triphosphate as a substrate. Target

predictions that were performed using the *in silico* Clarity platform identified DNA polymerase as well as several adenosine and purine receptors as possible secondary targets. The sponsor-provided *in vitro* data found that most of these predictions were negative. Remdesivir did interact with DNA polymerase *in vitro* at clinically-relevant concentrations; however, development of toxicity through this mechanism generally requires chronic exposure and remdesivir is rapidly converted to its metabolites, which were not associated with DNA polymerase at clinically-relevant concentrations. Remdesivir was also evaluated using (quantitative) structure-activity relationship ((Q)SAR) models for hepatotoxicity and nephrotoxicity. The (Q)SAR results suggested that remdesivir may be associated with hepatotoxicity; however, considering the rapid metabolism of remdesivir this may not be clinically significant. Remdesivir triphosphate was predicted to be positive for gall bladder disorders and equivocal for cholestasis and bile duct disorders. GS-441524 was predicted to be positive for gall bladder disorders and equivocal for bile duct disorders. In contrast, the cyclodextrin excipient present in the formulation was predicted to be negative or undeterminable for all endpoints. Additionally, remdesivir, remdesivir triphosphate, GS-441524, and cyclodextrin excipient were predicted to be negative or undeterminable for renal toxicity disorders. A structural similarity search revealed several nucleoside analogs as potential comparators to remdesivir and GS-441524. Several of these closely related compounds, particularly clofarabine, didanosine, and ganciclovir, contained statements in their drug labels on the need for clinical monitoring for renal and/or liver function.

In conclusion, *in silico* analyses identified that remdesivir and its metabolites are structurally similar to other drugs that have been associated with some degree of renal and/or liver issues and their labels recommend monitoring renal and/or liver toxicity. Remdesivir's EUA does recommend daily monitoring of hepatic laboratory testing. These *in silico* analyses can be taken into account with other nonclinical and clinical data when evaluating the potential for remdesivir to be associated with renal or liver adverse events and the potential need for clinical monitoring.

References and Supporting Documents

Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, et al. Remdesivir in Patients with Acute or Chronic Kidney Disease and COVID-19. *JASN*. 2020; 31: Epub.

Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, and Hall MD. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Cent Sci.* 2020; 6(5):672-83.

European Medicines Agency. Summary on compassionate use: remdesivir. Published April 3, 2020. Accessed July 16, 2020.

Herlitz LC, Mohan S, Stokes MB, Radhakrishnan J, D'Agati VD, and Markowitz GS. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney Int*. 2010; 78(11):1171-7.

Khungar V and Han SH. A Systematic Review of Side Effects of Nucleoside and Nucleotide Drugs Used for Treatment of Chronic Hepatitis B. *Curr Hepat Rep*. 2010; 9(2):75-90.

Menzies RI, Tam FW, Unwin RJ, and Bailey MA. Purinergic Signaling in Kidney Disease. *Kidney Int*. 2017;

91(2):315-23.

Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*. 2016; 531:381-85.

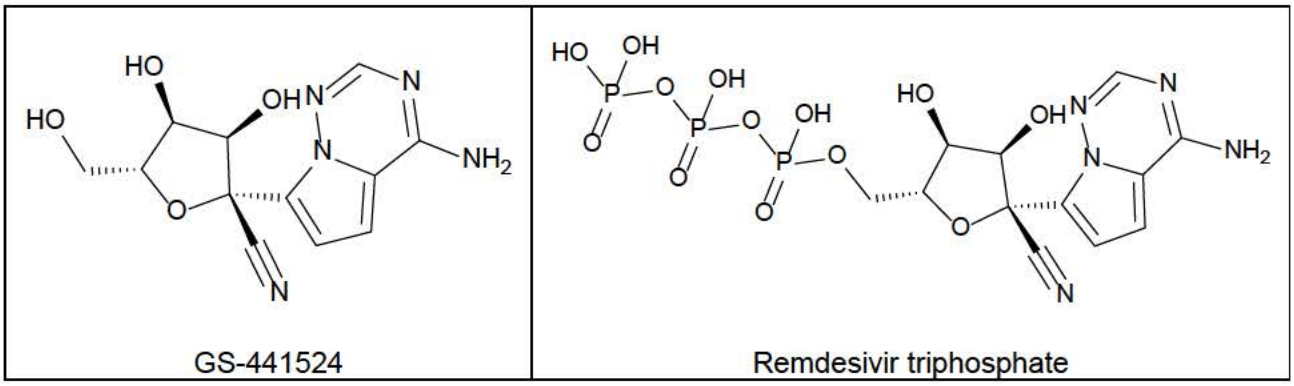
Appendix 1

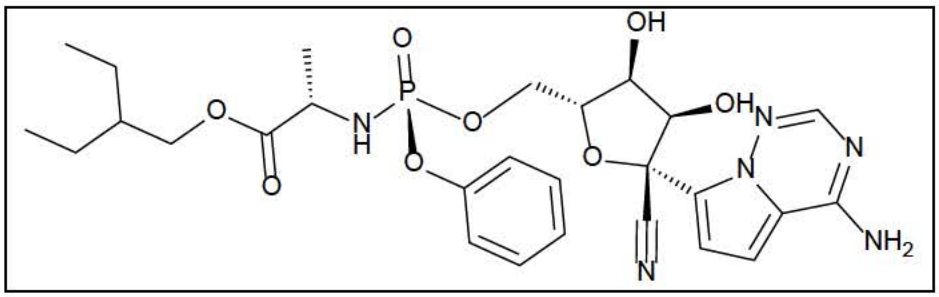
To: Neha Gada (CDER/OSE/OPE/DPVII)
cc: James Weaver (CDER/OTS/OCP/DARS)
From: CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service
Re: IND 147753, NDA 214787
Date: July 10, 2020

Summary

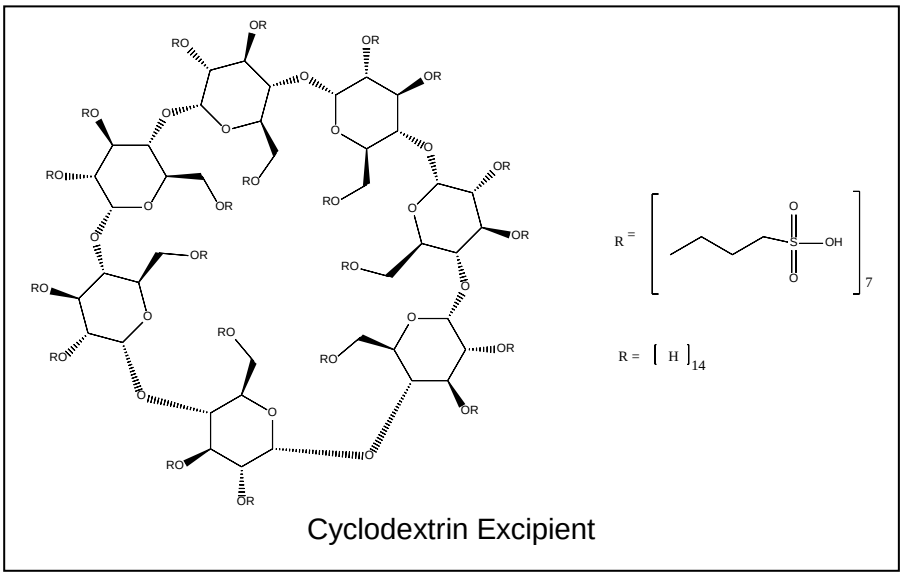
The DARS Computational Toxicology Consultation Service (CTCS) evaluated the four drug structures, **remdesivir (API), remdesivir triphosphate, GS-441524**, and **cyclodextrin excipient** for potential renal and liver toxicity effects using (quantitative) structure-activity relationship [(Q)SAR] models. Additionally, a structure-based search was performed to identify other drugs with high similarity to the three drugs that could serve as comparators.

The results showed that **remdesivir** is predicted to be positive for hepatotoxicity; however, considering the rapid metabolism of **remdesivir** this may not be clinically significant. **Remdesivir triphosphate** was predicted to be positive for gall bladder disorders and equivocal for cholestasis and bile duct disorders. **GS441524** was found to be positive for gall bladder disorders and equivocal for bile duct disorders. None of the three drugs was predicted to be positive for renal toxicity. The **cyclodextrin excipient** present in the formulation was found to negative or undeterminable for all endpoints. A structural similarity assessment identified several nucleoside compounds similar to **remdesivir** which were classified as positive in model training sets for hepatotoxicity and/or nephrotoxicity based on labeling and/or post-market experience. While these results suggest that additional monitoring for these effects may be warranted, the results did not conclusively predict the likelihood of hepatotoxicity or renal toxicity for **remdesivir, remdesivir triphosphate**, or **GS-441524**.





Remdesivir (API)



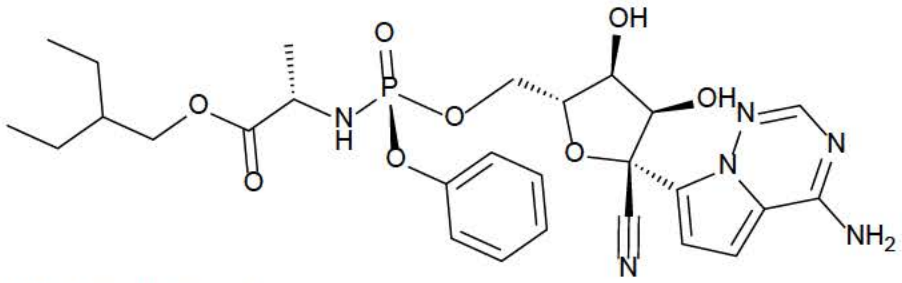
Cyclodextrin Excipient

Methods

Three software programs were used to predict liver and renal toxicity: *Derek Nexus* 6.1.0 (*DX*), *Leadscope Model Applier* 2.4.5-7 (*LMA*), *CASE Ultra* 1.8.0.2 (*CU*). *DX* is an expert rule-based platform, which uses a knowledgebase of structural alerts to support a prediction. In contrast, *LMA* and *CU* are statistical-based platforms containing models constructed through machine-learning. The *LMA* and *CU* models were constructed from training sets generated from post-market adverse event reports in FDA's Adverse Event Reporting System (FAERS). The hepatotoxicity training sets were further supplemented with data from drug labels and the published literature.

All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.

Chemical 1: Remdesivir (API)



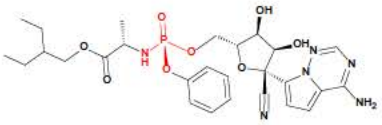
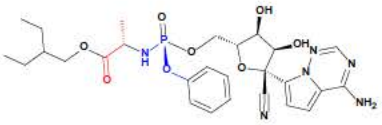
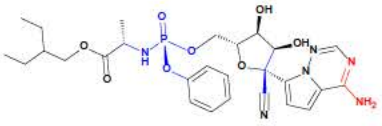
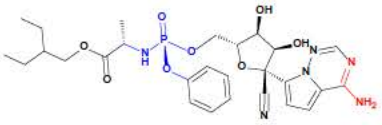
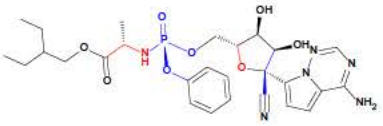
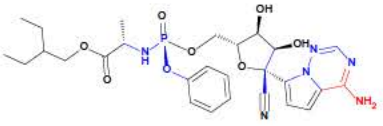
Hepatotoxicity (Q)SAR Predictions[1]

Software	Liver Damage	Liver Enzyme Abnormality	Cholestasis	Bile Duct Disorders	Gall Bladder Disorders
Derek Nexus	+				
Leadscope Model Applier	-	-	-	-	N/A
CASE Ultra	Eqv	Eqv	Eqv	+	+
Overall Expert Prediction	+	+	+	+	+

Remdesivir is predicted to be positive for liver damage, liver enzyme abnormality, cholestasis, bile duct, and gall bladder disorders. **Remdesivir** is predicted to be positive for hepatotoxicity by *DX*, due to the presence of the organophosphorus di- or tri ester moiety. *DX* cautions that while organophosphorus compounds can be shown to be hepatotoxic in experimental animals there is limited clinical evidence of hepatotoxicity of these compounds in the literature. The positive alert by *CU* for gall bladder disorders and the equivocal alerts for liver enzyme abnormality and cholestasis are due to a fragment of the adenine moiety. These alerts identifying the adenine group are also present in the endogenous substance adenosine monophosphate; however, many compounds closely related to **remdesivir** contain the adenine group and can be shown to be hepatotoxic (see structural similarity assessment below). The positive alerts by *CU* for bile duct disorders are present in endogenous peptides and can be discounted. All structural alerts are highlighted in red and unknown fragments highlighted in blue in the table below.

[1] + = positive; – = negative; Eqv = equivocal; NSA = no structural alerts are identified by *DX* (Derek Nexus cannot differentiate between a negative call and the inability to make a call because of no coverage); N/A = no model available; NC = test chemical features are not adequately represented in the model training data set, leading to a no call.

Structural Alerts

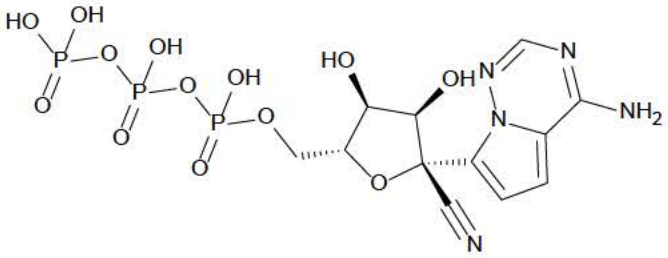
Endpoint	*DX* Alerts	*CU* Alerts
Liver Damage		
Liver Enzyme Abnormality	N/A	
Cholestasis	N/A	
Bile Duct Disorders	N/A	
Gall bladder disorders	N/A	

Renal toxicity (Q)SAR Predictions

Software	Bladder Disorder	Blood in Urine	Kidney Function Tests	Nephro-pathies	Renal Disorder	Urolithiasis
Derek Nexus	NSA					
Leadscope Model Applier	-	-	-	-	-	-
CASE Ultra	NC	NC	NC	NC	NC	NC
Overall Expert Predictions	-	-	-	-	-	-

Remdesivir (API) is predicted to be negative for renal toxicity disorders (bladder disorder, blood in urine, kidney function tests, nephropathies, renal disorder and urolithiasis).

Chemical 2: Remdesivir triphosphate

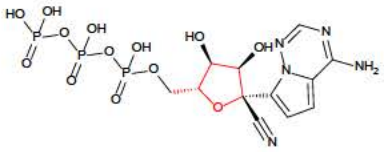
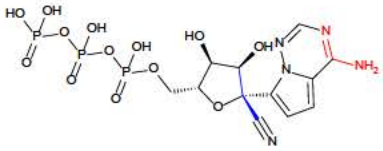
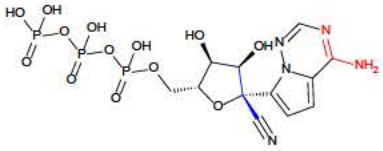
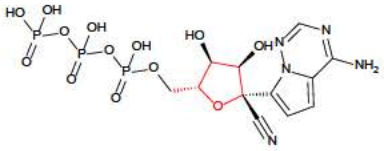
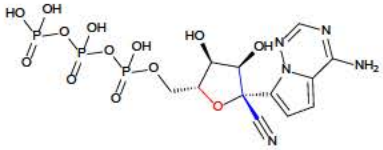
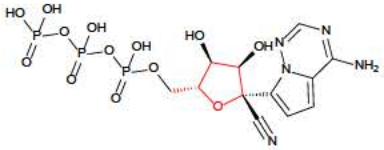
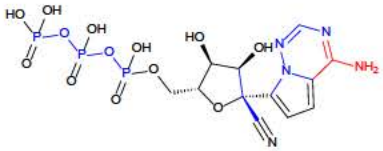


Hepatotoxicity (Q)SAR Predictions

Software	Liver Damage	Liver Enzyme Abnormality	Cholestasis	Bile Duct Disorders	Gall Bladder Disorders
Derek Nexus	NSA				
Leadscope Model Applier	Eqv	-	Eqv	Eqv	N/A
CASE Ultra	-	Eqv	Eqv	Eqv	+
Overall Expert Prediction	**-**	**-**	**Eqv**	**Eqv**	**+**

Remdesivir triphosphate is predicted to be positive for gall bladder disorders and equivocal for cholestasis and bile duct disorders. **Remdesivir triphosphate** is predicted to be negative for liver damage and liver enzyme abnormality. The positive alert by *CU* for gall bladder disorders and the equivocal alerts for liver enzyme abnormality, cholestasis, and bile duct disorders are due to a fragment of the adenine moiety. These alerts identifying the adenine group are also present in the endogenous substance adenosine triphosphate; however, many compounds closely related to **remdesivir triphosphate** contain the adenine group and can be shown to be hepatotoxic (see structural similarity assessment below). Likewise, the equivocal alerts by *LMA* for liver damage, cholestasis and bile duct disorders identify a fragment of the ribose moiety, which is also present in adenosine triphosphate. All structural alerts are highlighted in red and unknown fragments highlighted in blue in the table below.

Structural Alerts

Endpoint	*CU* Alerts	*LMA* Alerts
Liver Damage	N/A	
Liver Enzyme Abnormality		N/A
Cholestasis		
Bile Duct Disorders		
Gall Bladder Disorders		N/A

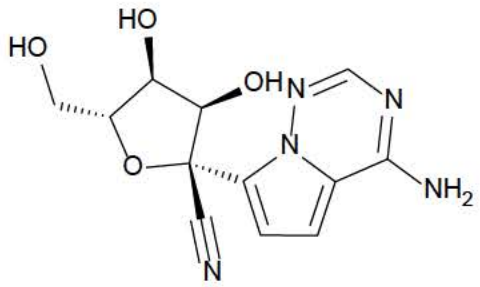
Renal toxicity (Q)SAR Predictions

Software	Bladder Disorder	Blood in Urine	Kidney Function Tests	Nephro-pathies	Renal Disorder	Urolithiasis
Derek Nexus	NSA					
Leadscope Model Applier	-	-	NC	NC	NC	-
CASE Ultra	NC	NC	NC	NC	NC	NC

Overall Expert Predictions	-	-	NC	NC	NC	-

Remdesivir triphosphate is predicted to be negative for bladder toxicity, blood in urine, and urolithiasis. No prediction could be made for kidney function tests, nephropathies, or renal disorders.

Chemical 3: GS441524

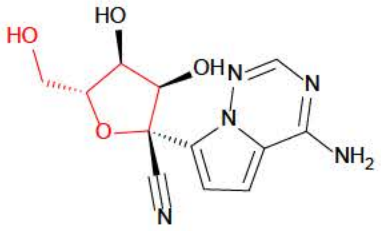
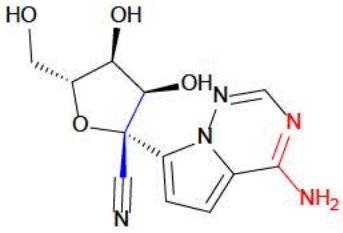
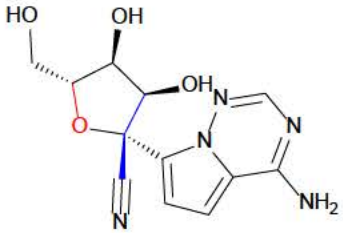
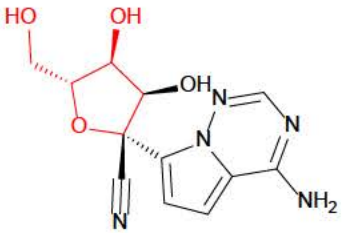
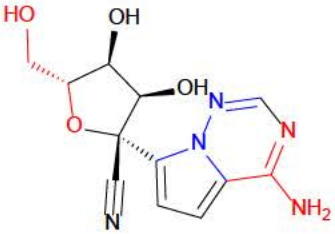


Hepatotoxicity (Q)SAR Predictions

Software	Liver Damage	Liver Enzyme Abnormality	Cholestasis	Bile Duct Disorders	Gall Bladder Disorders
Derek Nexus	NSA				
Leadscope Model Applier	Eqv	-	-	Eqv	N/A
CASE Ultra	-	Eqv	Eqv	Eqv	+
Overall Expert Prediction	**-**	**-**	**-**	**Eqv**	**+**

GS441524 is predicted to be positive for gall bladder disorders and equivocal for bile duct disorders. **GS441524** is predicted to be negative for liver damage, liver enzyme abnormality, and cholestasis. The positive alert by *CU* for gall bladder disorders and the equivocal alerts for liver enzyme abnormality, cholestasis and bile duct disorders are due to a fragment of the adenine moiety. These alerts identifying the adenine group are also present in the endogenous substance adenosine; however, many compounds closely related to **GS441524** contain the adenine group and can be shown to be hepatotoxic (see structural similarity assessment below). Likewise, the equivocal alerts by *LMA* for liver damage and bile duct disorders identify a fragment of the ribose moiety, which is also present in adenosine triphosphate. All structural alerts are highlighted in red and unknown fragments highlighted in blue in the table below.

Structural Alerts

Endpoint	*CU* Alerts	*LMA* Alerts
Liver Damage	N/A	
Liver Enzyme Abnormality; **Cholestasis**		N/A
Bile Duct Disorders		
Gall bladder disorders		N/A

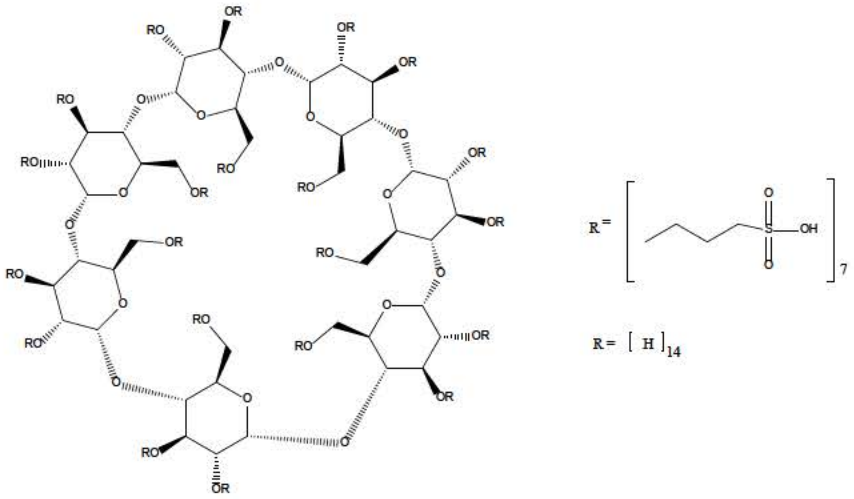
Renal toxicity (Q)SAR Predictions

Software	Bladder Disorder	Blood in Urine	Kidney Function Tests	Nephro-pathies	Renal Disorder	Urolithiasis
Derek Nexus	NSA					
Leadscope Model Applier	-	-	-	NC	-	-
CASE Ultra	NC	NC	NC	NC	NC	NC

Overall Expert Prediction	-	-	-	NC	-	-

GS441524 is predicted to be negative for bladder disorder, blood in urine, kidney function tests, renal disorder and urolithiasis. No prediction could be made for nephropathy.

Chemical 4: Cyclodextrin Excipient

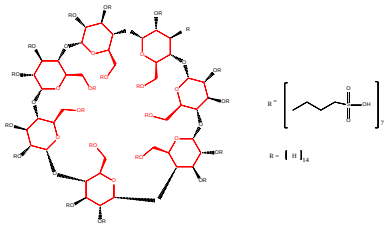
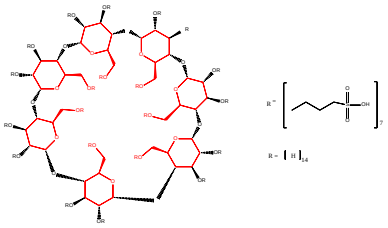
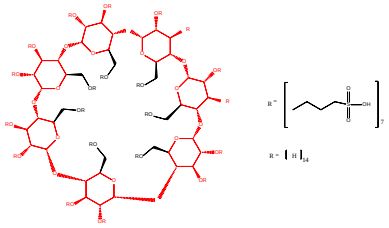
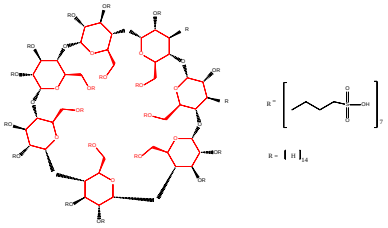
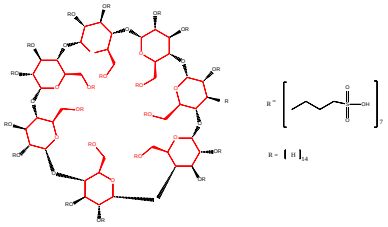
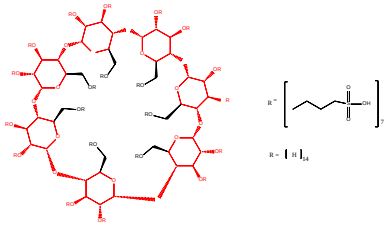
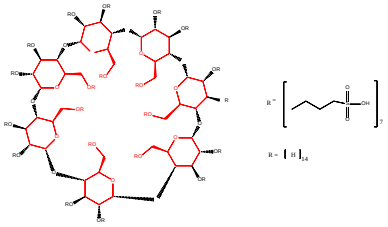
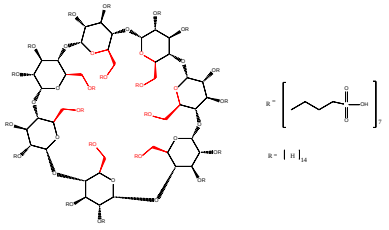


Hepatotoxicity (Q)SAR Predictions

Software	Liver Damage	Liver Enzyme Abnormality	Cholestasis	Bile Duct Disorders	Gall Bladder Disorders
Derek Nexus	NSA				
Leadscope Model Applier	+	+	+	+	N/A
CASE Ultra	+	Eqv	-	Eqv	Eqv
Overall Expert Prediction	-	-	-	-	NC

Cyclodextrin excipient is predicted to be negative for liver damage, liver enzyme abnormality, cholestasis, and bile duct disorders. No prediction can be made for gall bladder disorders. The positive predictions for *LMA* and *CU* are due to the presence of the glucopyran moiety. This is a relatively non-specific alert which identifies most glycosides. Hepatotoxic compounds containing this structure include the aminoglycoside and macrolide antibiotics, which **cyclodextrin excipient** does not resemble due to size and charge. These predictions are downgraded to negative. The equivocal predictions for *CU* are for fragments too small to be useful. These predictions are downgraded to negative as well.

Structural Alerts

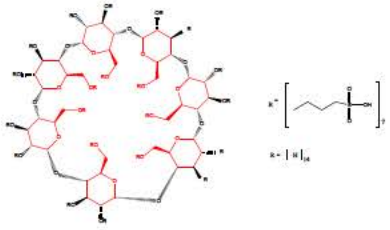
Endpoint	*CU* Alerts	*LMA* Alerts
Liver Damage		
Liver Enzyme Abnormality		
Cholestasis	N/A	
Bile Duct Disorders		
Gall bladder disorders		N/A

Renal toxicity (Q)SAR Predictions

Software	Bladder Disorders	Blood in Urine	Kidney Function Tests	Nephro-pathies	Renal Disorder	Urolithiasis
Derek Nexus	NSA					
Leadscope Model Applier	-	Eqv	+	+	+	Eqv
CASE Ultra	-	-	-	-	-	-
Overall Expert Predictions	-	-	-	-	-	-

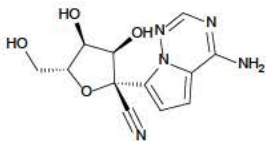
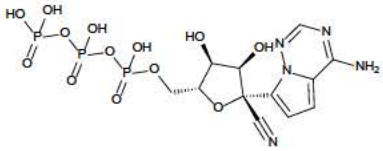
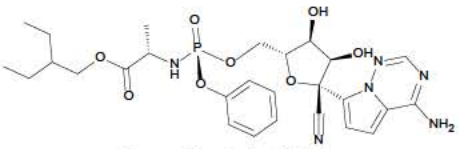
Cyclodextrin excipient is predicted to be negative for bladder disorders, blood in urine, kidney function tests, nephropathies, renal disorder and urolithiasis. The positive and equivocal predictions for *LMA* are due to the presence of the glucopyran moiety. This is a relatively non-specific alert which identifies most glycosides. Nephrotoxic compounds containing this structure include the aminoglycoside antibiotics, which **cyclodextrin excipient** does not resemble due to size and charge. These predictions are downgraded to negative.

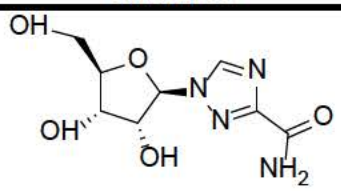
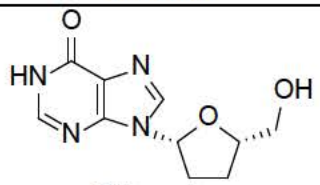
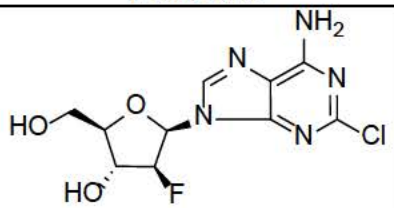
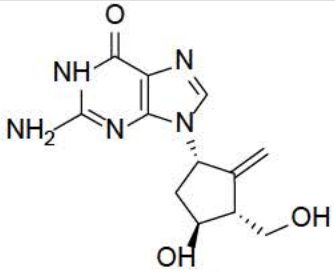
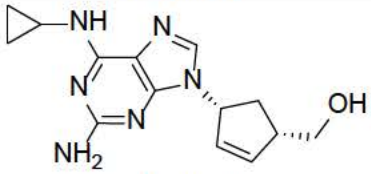
Structural Alerts

Endpoint	*LMA* Alerts
Blood in Urine; Kidney Function Tests; Nephropathies; Renal Disorder; Urolithiasis	

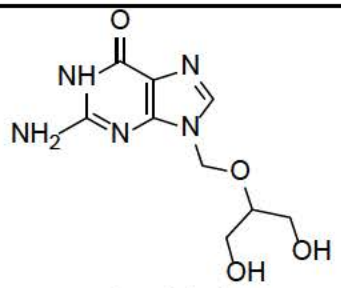
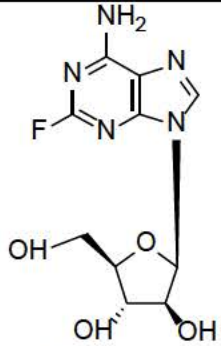
Structural Similarity Assessment of Remdesivir (API), Remdesivir triphosphate, and GS-441524 to Other Drugs

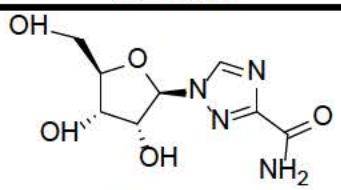
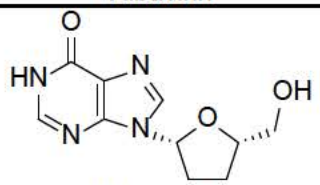
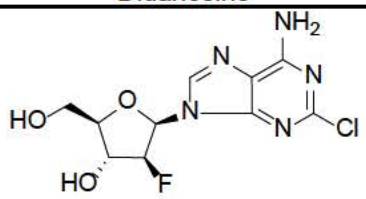
Remdesivir is a nucleotide analog. The following table lists adenosine and guanosine analogs that are structurally similar to remdesivir and GS-441524 from a class standpoint. The activity scores are given for the models in which the compounds are included in the training set.

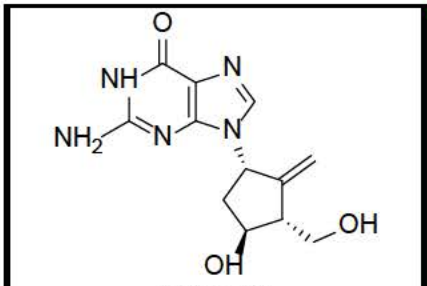
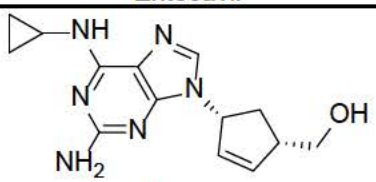
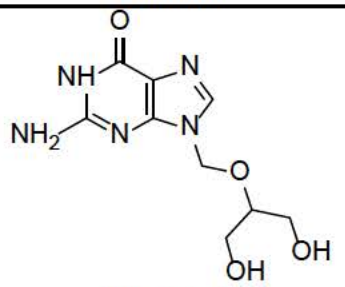
 GS-441524	 Remdesivir triphosphate	 Remdesivir (API)

Chemical	Hepatotoxicity Model Training Set Activities[2]				
	Liver Damage	Liver Enzyme Abnorm	Cholestasis	Bile Duct Disorder	Gall Bladder Disorder
 Ribavirin	P	N/A	N/A	N/A	N/A
 Didanosine	P	P	P	P	N/A
 Clofarabine	P	P	P	N/A	N/A
 Entecavir	P	P	N/A	N/A	N/A
 Abacavir	P	P	P	N/A	N/A

[2] N = Negative in clinical experience; P = Positive in clinical experience; N/A = No clinical information available.

 Ganciclovir	P	P	P	P	N/A
 Fludarabine	P	N	P	N	N/A

Chemical	Renal Toxicity Model Training Set Activities[2]					
	Bladder Disorder	Blood in Urine	Kidney Function Tests	Nephro-pathies	Renal Disorder	Urolithiasis
 Ribavirin	N	N	N	N	N	P
 Didanosine	N	N	N	P	N	P
 Clofarabine	N	N	P	N	P	N

 Entecavir	N	N	N	N	N	N
 Abacavir	N	N	N	P	N	N
 Ganciclovir	N	P	P	P	N	P

Conclusions

While it appears possible that **remdesivir**, **remdesivir triphosphate**, or **GS441524** may have significant hepatic toxicity, other factors should be considered. While **remdesivir** is predicted to be hepatotoxic due to the organophosphate moiety, this is mostly based on animal studies. There is limited evidence that this toxicity is significant clinically [Arao T, 2002]. Furthermore, **remdesivir** is rapidly metabolized to its active monophosphate form [Warren et al. 2016] and therefore the organophosphate moiety is unlikely to be an issue. **Remdesivir triphosphate** was predicted to be positive for gall bladder disorders and equivocal for cholestasis and bile duct disorders. **GS441524** was predicted to be positive for gall bladder disorders and equivocal for bile duct disorders. The alerting fragments for hepatotoxicity found in **remdesivir**, **remdesivir triphosphate**, and **GS441524**, are identical to groups found in the endogenous compounds adenosine monophosphate, adenosine triphosphate, and adenosine, respectively. The nitrile group—which is the main difference between **remdesivir**, **remdesivir triphosphate**, and **GS441524**—was either flagged as unknown to the model or was not detected as an alerting fragment. While these observations may seem to be deficiencies in the models, there are other compounds identified by these alerts, particularly fludarabine and clofarabine, which are structurally similar to **GS441524** and which have evidence of hepatotoxicity in their drug labels; therefore, the alerts should be taken seriously. In all models of nephrotoxicity, **remdesivir**, **remdesivir triphosphate**, and **GS441524** were either predicted as negative or no prediction was possible. It should be noted however that several closely related compounds, particularly clofarabine and ganciclovir, have clinically significant nephrotoxicity as documented in their drug labels.

Considering the unusual nature and high concentration of the **cyclodextrin excipient** present in the formulation, this compound was also evaluated for hepatotoxicity and nephrotoxicity. However, no evidence for toxicity at these endpoints was found.

Overall, the results identified some possible associations between structural attributes of **remdesivir, remdesivir triphosphate**, or **GS-441524** and liver/kidney toxicities, but they did not conclusively predict these effects.

References

Arao T, Fuke C, Takaesu H, Morinaga Y, Miazakai T. A case of fatal trichlorfon and methidathion poisoning. Legal Medicine 4:182-186 (2002).

Warren TK, Jordan R et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 531:381-285 (2016).

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09/22/2020 05:15:56 PM

Office of Clinical Pharmacology Review

NDA or BLA Number	214787
Link to EDR	DocuBridge
Submission Date	8/7/2020 (Final tier of rolling submission, SDN 20)
Submission Type	NME NDA
Brand Name	Veklury
Generic Name	Remdesivir (RDV)
Dosage Form and Strength	Lyophilized powder (100 mg) Solution (5 mg/mL)
Route of Administration	IV
Proposed Indication	(b) (4)
Applicant	Gilead
Associated IND	147753 (Sponsor: Gilead) 147771 (Sponsor: NIH)
OCP Review Team	Mario Sampson, PharmD, Justin Earp PhD, Hao Zhu, PhD, Yuching Yang, PhD, Manuela Grimstein, PhD, Vikram Arya, PhD, FCP
OCP Final Signatory	Kellie S. Reynolds, PharmD

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1. EXECUTIVE SUMMARY

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the virus that causes COVID-19 disease. SARS-CoV-2 uses an RNA-dependent RNA polymerase (RdRp) for replication. Remdesivir (RDV) is an inhibitor of the SARS-CoV-2 RdRp.

Phase 3 clinical studies were conducted to evaluate RDV for the treatment of COVID-19 in hospitalized adult patients. Pharmacokinetics of RDV and metabolites (GS-704277 and GS-441524) was not assessed in these trials.

The clinical pharmacology package included the following:

- Studies of safety, PK, and mass balance in healthy adults.
- In vitro assessment of ADME, enzyme and transporter substrate properties of RDV and metabolites, inhibitory effect of RDV and metabolites on enzymes and transporters and whether RDV and metabolites are inducers of drug metabolizing enzymes.
- Physiologically Based Pharmacokinetic (PBPK) Modeling and Population Pharmacokinetics (PopPK) analysis with the objective of predicting plasma exposures of RDV and metabolites in pediatric patients (this review only focused on the predicted exposure in pediatric patients 12 years of age and older and weighing at least 40 kg).

The clinical pharmacology review primarily focused on addressing the following two questions:

1) Based on the review of the in vitro enzyme and transporter studies, is there a need to conduct in vivo drug-drug interaction (DDI) trials?
2) Is the dosing regimen for pediatric patients 12 years of age and older and weighing at least 40 kg acceptable?

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal evidence of effectiveness comes from randomized, double-blind, placebo-controlled trial ACTT-1, which enrolled hospitalized subjects with mild, moderate, or severe COVID-19. Subjects in the RDV arm received 200 mg IV on day 1 and 100 mg IV on subsequent days for a total treatment duration of 10 days. The median time to recovery within 28 days of randomization (primary endpoint) was 10 days in the RDV group vs 14 days in the placebo group (recovery rate ratio 1.31, 95% CI 1.12 to 1.53). Supportive evidence comes from two open-label trials. GS-US-540-5773 evaluated hospitalized subjects with severe COVID-19 and GS-US-540-5774 evaluated hospitalized subjects with moderate COVID-19. Subjects in the RDV arm of these trials received 200 mg IV on day 1 and 100 mg IV on subsequent days for a total treatment duration of five or 10 days.

General dosing instructions	200 mg IV on day 1 and 100 mg IV daily for up to a total of 10 days. The recommended infusion duration is 30-120 minutes.
Dosing in patient subgroups (intrinsic and extrinsic factors)	<u>Drug interactions – effect of other drugs on RDV and metabolites</u> In vitro studies were conducted to evaluate RDV and metabolites as a substrate of various drug metabolizing enzymes and transporters as outlined in the 2020 In Vitro Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (referred to as the "drug interaction guidance" in the remainder of the review). RDV is approximately 80 % metabolized by carboxylesterases (CES) 1 and 2 with additional metabolism mediated by Cathepsin A (10 %) and CYP3A (10 %). RDV is a substrate of OATP1B1 and P-gp transporters. Metabolite GS-704277 is a substrate of OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established. Drug-drug interaction trials of RDV and other concomitant medications have not been conducted, however, the applicant will conduct a DDI trial of RDV with rifampin (broad spectrum inducer of enzymes/transporters) as a Post Marketing Requirement (PMR). <u>Drug Interactions – effect of RDV and metabolites on other drugs</u> In vitro studies were conducted to evaluate RDV and metabolites as an inhibitor or inducer of drug metabolizing enzymes and as an inhibitor of transporters. Using drug interaction guidance recommended equations for predicting the potential for clinically significant DDIs, RDV at day 1 C_{max} (after administration of 200 mg) is a potential inhibitor of CYP3A, UGT1A1, OATP1B1, OATP1B3, and MATE1. However, RDV at two hours after day 1 C_{max} is a potential inhibitor of only MATE1 and at four hours after day 1 C_{max} is not a potential inhibitor of any enzymes/transporters. GS-704277 and GS-441524 are not expected to affect enzymes or transporters recommended for evaluation in the drug interaction guidance. Overall, due to the short term (up to 10 days) duration of RDV therapy, short duration of predicted effect on substrate drugs (up to four hours of a 24-hour dosing interval on Day 1), and considering that the inhibitory effect on UGT1A1 or MATE-1 substrates is not generally clinically significant, we do not recommend additional human DDI trials to evaluate the effect of RDV on other drugs. <u>Renal Impairment</u> The most abundant metabolite of RDV, GS-441524, is primarily renally eliminated. Structurally related drugs to RDV such as sofosbuvir and tenofovir alafenamide also form metabolites that are renally eliminated and whose plasma exposures are significantly elevated in subjects with renal impairment. The PK of RDV and metabolites have not been evaluated in subjects with chronic renal impairment. Subjects with creatinine clearance (calculated by Cockcroft-Gault) ≥30 mL/min were enrolled in Phase 3 studies; however, screening was not conducted to determine if subjects with creatinine clearance <90 mL/min had acute or chronic renal impairment. Further, population PK analyses cannot support determination of the effect of renal impairment on RDV clearance as subjects included in the analysis (healthy subjects) had a minimum creatinine clearance value of 87 mL/min. There is an agreed upon PMR to conduct a renal impairment PK study in subjects with all categories of chronic renal impairment.

	Hepatic impairment RDV is primarily metabolized and conversion to its metabolite(s) could potentially be reduced in subjects with hepatic impairment. The PK of RDV and metabolites have not been evaluated in subjects with hepatic impairment. Clinical scoring for hepatic impairment (such as Child-Pugh or MELD score) was not conducted in Phase 3 studies. There is an agreed upon PMR to conduct a hepatic impairment study in subjects with moderate and severe hepatic impairment. This PMR also includes a requirement to evaluate the PK of RDV and its metabolites in subjects with mild hepatic impairment depending on results in those with moderate and severe hepatic impairment. Pediatrics (≥12 years of age and weighing ≥40 kg) Subjects <18 years of age were not enrolled in Phase 3 studies. Approval of the adult dose for pediatric patients ≥12 years of age and weighing ≥40 kg is based upon model-predicted comparable plasma exposures of RDV, GS-704277 and GS-441524 -relative to observed plasma exposures in healthy adults (4.3 Physiologically-based Pharmacokinetics Review, 4.4 Pharmacometrics Review) and safety data in lower body weight adults (40-50 kg) enrolled in Phase 3 studies. There is an agreed upon PMR to conduct a pediatric study in patients aged birth to <18 years of age. The primary endpoint is the assessment of pharmacokinetics of RDV and metabolites in the various age groups. Other intrinsic demographic factors In a popPK analysis of 123 healthy adults with intensive PK, demographic and clinical characteristics other than body weight were not found to significantly affect exposure of RDV or metabolites. Pregnancy Pregnant women were not enrolled in Phase 3 studies. However, extensive use in pregnant women is anticipated. There are various physiological changes during pregnancy that can potentially affect the PK of RDV, GS-704277 and GS-441524. There is an agreed upon Post Marketing Commitment (PMC) to conduct a PK study in pregnant women to evaluate the pharmacokinetics of RDV, GS-704277 and GS-441524.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable for an IV product. While only the lyophilized powder was evaluated in Phase 3 studies, there is no expectation that the other IV formulation (solution) would differ in bioavailability.

1.2 Post-Marketing Requirements and Commitments

The PMR/PMCs listed below are those agreed upon at the time of finalizing this review. See the action letter for the final list of PMR/PMCs.

PMC or PMR	Key issue(s) to be addressed	Rationale	Key considerations for design features
PMR	Effect of rifampin on the PK of RDV and metabolites	See Executive Summary	-study period to evaluate the PK of RDV and metabolites after a single rifampin dose PK (effect of OATP inhibition) -study period to evaluate the PK of RDV and metabolites after multiple rifampin dosing (effect of CES, OATP, and/or P-gp induction)
PMR	Renal impairment		-evaluation of mild, moderate, and severe renal impairment -measure unbound fraction
PMR	Hepatic impairment		-evaluation of moderate and severe hepatic impairment -measure unbound fraction
PMR	Pediatrics		-enrollment of ages birth - <18 years of age -primary endpoint of PK
PMC	Pregnancy		Comparison of PK in pregnant women vs an external control. Due to RDV being short-term therapy, PK during the post-partum period cannot serve as the control.
PMR	QT study	See QT/IRT review dated 8/21/2020 (NDA 214787)	

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

The PK properties of RDV and metabolites in healthy adult subjects are provided in Table 1.

Table 1. Pharmacokinetic properties of RDV and metabolites (GS-441524 and GS-704277) in healthy adult subjects.

	RDV	GS-441524	GS-704277
Absorption			
T_{max} (h)[a]	0.67-0.68	1.51-2.00	0.75-0.75
Distribution			
% bound to human plasma proteins	88-93.6[b]	2	1
Blood-to-plasma ratio	0.68-1.0	1.19	0.56
Elimination			
$t_{1/2}$ (h)[c]	1	27	1.3
Metabolism			
Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	Not significantly metabolized	HINT1
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]	ND	0.5	ND

HINT1 = Histidine triad nucleotide-binding protein 1, also known as adenosine 5'-monophosphoramidase. ND=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 remdesivir 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).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended RDV dosing regimen was determined to be effective vs placebo in hospitalized subjects with mild, moderate, and severe COVID-19 in Phase 3 trial ACTT-1 (see 3.3.2).

2.2.2 Therapeutic individualization

For patients with renal or hepatic impairment and pregnant women, PK data are unavailable to inform the need for dose adjustment and PK will be evaluated in these populations as part of PMR (in subjects with renal and hepatic impairment) and PMC (in pregnant women).

In a popPK analysis of 123 healthy adults with intensive PK, demographic and clinical characteristics other than body weight were not found to significantly affect exposure of RDV or metabolites. While there is an effect of body weight on RDV and metabolites exposure, the recommended dosing regimen applies to all patients ≥40 kg.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Changes to clinical pharmacology-related labeling statements are summarized below (Table 2). "Final labeling language" in Table 2 refers to labeling changes agreed upon with the Applicant as of the date this review is finalized. See approved labeling for the most current labeling.

Table 2. Summary of changes to clinical pharmacology-related labeling.

Section(s)	Topic	Applicant's initial labeling	Final labeling language	Notes / Rationale for differences between initial labeling and final labeling language
7 12.3	Effect of other drugs on RDV and metabolites and the effect of RDV on other drugs	Drug-drug interaction studies have not been performed with VEKLURY. (b) (4)	Clinical drug-drug interaction studies have not been performed with VEKLURY. In vitro, remdesivir is a substrate for drug metabolizing enzyme CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1. GS-704277 is a substrate for OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established. Remdesivir is not a substrate for CYP1A1, 1A2, 2B6, 2C9, 2C19, (b) (4) or OATP1B3. GS-704277 and GS-441524 are not substrates for CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, or 3A5. GS-441524 is also not a substrate for CYP2C19 or 3A4. GS-704277 and GS 441524 are not substrates for OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K. GS 441524 is also not a substrate for OATP1B1 or OATP1B3.	Text was initially present in section 7. Due to clinical significance not been established, the text was moved to section 12.3. We requested addition of pathways metabolites are a substrate of as well as pathways where RDV or metabolites are not a substrate. Note there are other enzymes/transporters that were evaluated in in vitro studies (such as non-CYP enzymes and certain transporters not mentioned in the drug interaction guidance (such as MRP, BSEP, etc). The enzymes/transporters listed in labeling are those recommended for routine evaluation according to FDA guidance.
12.3	Intrinsic factors	Pharmacokinetic differences based on sex, race, age, renal function and hepatic function on the exposures of remdesivir have not been evaluated.	No change.	

	Pediatrics (≥12 years of age and weighing ≥40 kg)	(b) (4)	Using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of remdesivir and metabolites in patients 12 years of age and older and weighing at least 40 kg as observed in healthy adults. [see Use in Specific Populations (8.4)].	Removed (b) (4) Described analyses as "modeling and simulation" because two approaches (PBPK and popPK) were used.
12.2	Effect on QT interval	(b) (4) .	Paragraph deleted.	The Applicant's RDV concentration-QT analysis of PK data from Phase 1 PK studies could not exclude the possibility of small increases in the QTc interval. There is an agreed upon PMR to conduct a thorough QT study using a (b) (4) dose. The QT study will be conducted (b) (4) (NDA 214787, QT/IRT review dated 8/21/2020).
12.2	Exposure-response	Not discussed.	Remdesivir and metabolites exposure-response relationships and the time course of pharmacodynamics response is unknown.	Per regulations, lack of exposure-response information should be described in labeling.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

RDV was initially developed for treatment of Ebola and was subsequently evaluated for treatment of COVID-19. The pivotal trial supporting approval for treatment of COVID-19 in hospitalized patients is randomized, double-blind, placebo-controlled trial ACTT-1, with supportive evidence from open-label trials GS-US-540-5773 and GS-US-540-5774.

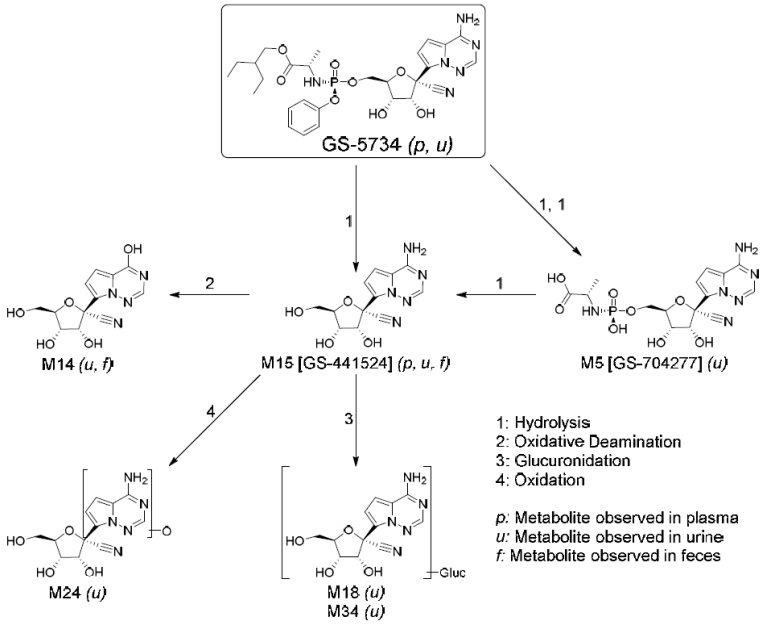
- The clinical pharmacology package included the following: Studies of safety, PK, and mass balance in healthy adults.
- In vitro assessment of ADME, enzyme and transporter substrate properties of RDV and metabolites, inhibitory effect of RDV and metabolites on enzymes and transporters and whether RDV and metabolites are inducers of drug metabolizing enzymes.
- Physiologically Based Pharmacokinetic (PBPK) Modeling and Population Pharmacokinetics (popPK analysis with the objective of predicting plasma exposures of RDV and metabolites in pediatric patients (this review only focused on the predicted data from pediatric patients 12 years of age and older and weighing at least 40 kg).

3.2 General Pharmacology and Pharmacokinetic Characteristics

RDV is a prodrug which requires hydrolytic cleavage prior to phosphorylation to the active triphosphate derivative (GS-443902). After administration of RDV to humans, moieties circulating in plasma include RDV and major inactive metabolites GS-441524 and GS-704277 (Figure 1).

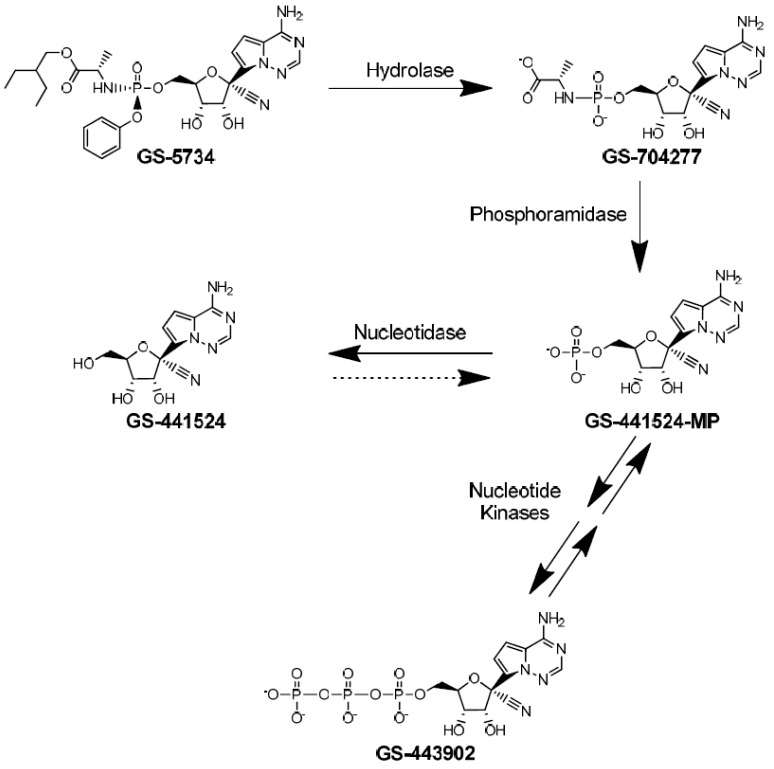
Based on calculated logD values, RDV is thought to passively enter cells with greater efficiency than GS-441524 and the double-anion GS-704277. Once inside the cell, RDV is primarily metabolized to GS-704277 by carboxylesterases (CES). CES1 is expressed in numerous human tissues, with greatest expression in liver, gallbladder and lung. CES expression in blood is relatively low. Intracellular GS-704277 is converted to GS-441524-monophosphate, which is phosphorylated to the active triphosphate GS-443902 or dephosphorylated to GS-441524 (Figure 2).

Figure 1. Applicant's proposed metabolic scheme for RDV (GS-5734).



Source: GS-US-399-4231. Note GS-704277 is also detected in plasma.

Figure 2. Applicant's proposed intracellular metabolic scheme for RDV (GS-5734).



Source: PK Written Summary.

PK of RDV and metabolites was not evaluated in Phase 3 studies of subjects hospitalized with COVID-19. The single and multiple dose PK parameters of RDV and metabolites in healthy adults administered RDV for five or 10 days are provided in Table 3.

Table 3. Mean (CV%) multiple dose PK parameters[a] of RDV and metabolites (GS-441524 and GS-704277) in plasma following IV administration of RDV 200 mg on day 1 and RDV 100 mg on subsequent days to healthy adults (n=28) in study GS-US-399-5505.

	RDV		GS-441524		GS-704277	
Day	1	5 or 10	1	5 or 10	1	5 or 10
C_{max} (ng/mL)	4378 (23.5)	2229 (19.2)	143 (21.5)	145 (19.3)	370 (29.3)	245 (33.9)
AUC[b] (ng•h/mL)	2863 (18.6)	1585 (16.6)	2191 (19.1)	2229 (18.4)	698 (25.9)	462 (31.4)
C_{trough} (ng/mL)	ND[c]		64.8 (20.8)	69.2 (18.2)	ND[c]	

Source: Prepared by reviewer from GS-US-399-5505. Treatment duration was five days in cohort 1 and 10 days in cohort 2. CV=Coefficient of Variation.
a. RDV administered as a 30 minute IV infusion
b. AUC_{0-24h} on day 1; AUC_{tau} on days 5 or 10.
c. ND=Not detectable (at 24 hours post-dose). In human plasma, RDV and GS-704277 are detected for up to six hours and eight hours post-dose.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The recommended RDV dosing regimen was determined to be effective vs placebo in hospitalized subjects with mild, moderate, and severe COVID-19 in Phase 3 trial ACTT-1. The median time to recovery within 28 days of randomization (primary endpoint) was 10 days in the RDV group vs 14 days in the placebo group (recovery rate ratio 1.31, 95% CI 1.12 to 1.53). PK of RDV and metabolites was not evaluated in this trial, thus exposure-response relationships are unknown.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

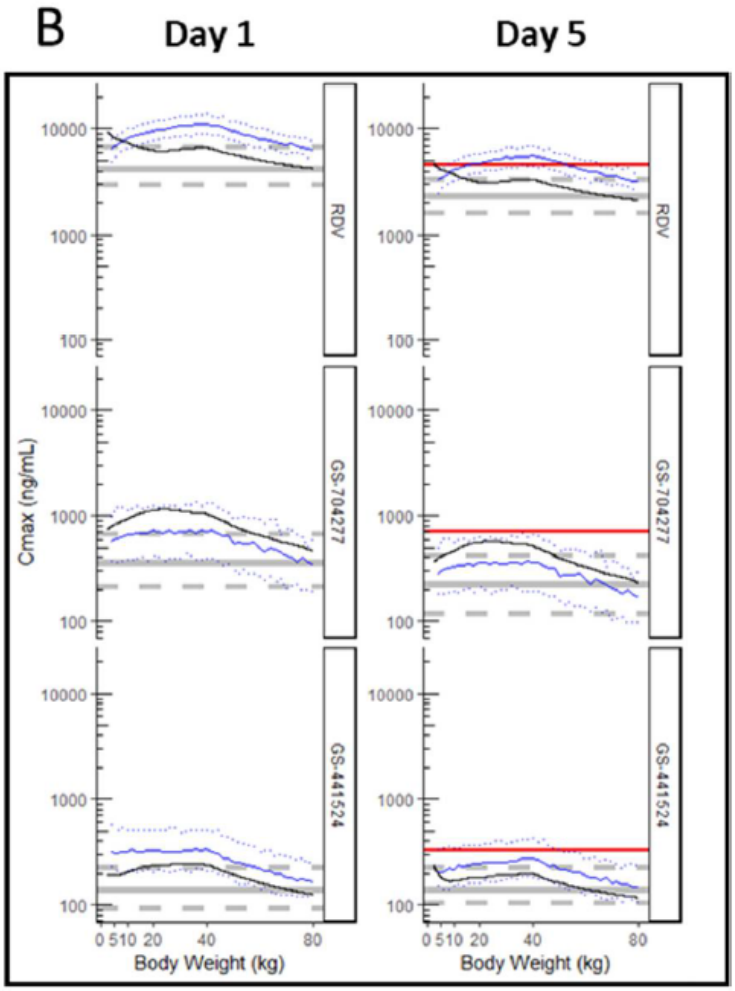
Yes. The indication includes adults (included in Phase 3 studies) as well as adolescents 12 - <18 years of age and weighing ≥40 kg (not included in Phase 3 studies). Efficacy and safety of RDV in hospitalized adults weighing ≥40 kg with COVID-19 was demonstrated vs placebo in Phase 3 trial ACTT-1.

The dosing regimen evaluated in ACTT-1 study was the same as that evaluated in a prior clinical trial for treatment of Ebola (200 mg on day 1 and 100 mg on subsequent days). Due to LFT elevations observed in healthy adult study GS-US-399-5505 (RDV administered 200 mg on day 1 and 100 mg daily for four or nine days), it may not be possible to further increase the RDV IV dose beyond 200 mg on day 1 and 100 mg on subsequent days.

Adolescents

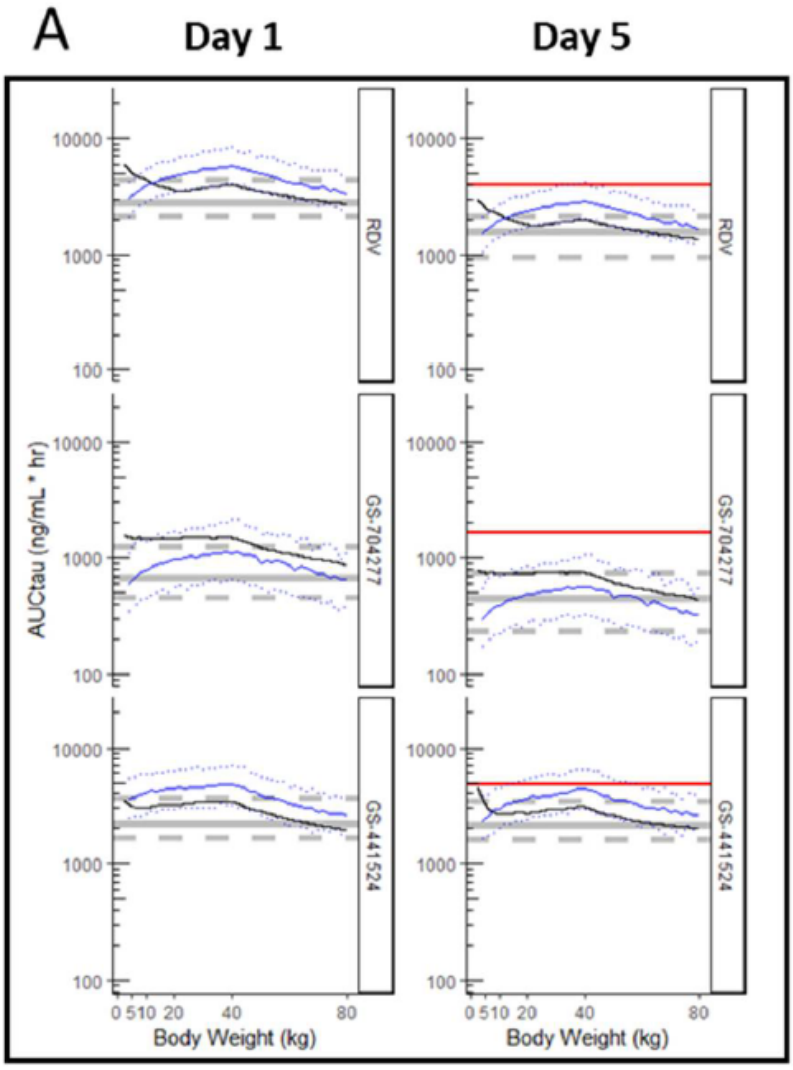
Extrapolation of efficacy is the approach used to support approval in adolescents 12 - <18 years of age and weighing ≥40 kg. Physiologically-based PK modeling (PBPK) and population PK modeling were used to predict exposures in patients 12 - <18 years of age and weighing ≥40 kg. PBPK accounts for age-dependent physiological changes, drug-specific physicochemical properties, and utilized observed PK data in healthy adults to predict plasma exposures in patients 12 - <18 years of age and weighing ≥40 kg. Population PK modeling used observed PK data in healthy adults (median [range] body weight of 77 kg [53, 101]) and allometric scaling to predict exposures in patients ≥40 kg. The recommended RDV dosing regimen is predicted to result in comparable plasma exposures of RDV, GS-704277 and GS-441524 across the weight range of 40-80 kg (Figure 3, Figure 4, Figure 5) (4.3 Physiologically-based Pharmacokinetics Review, 4.4 Pharmacometrics Review). The body weight range of 40-80 kg includes body weights typical for patients 12 - <18 years of age as well as adults. According to the Clinical review team, acceptable safety was observed in the general adult population enrolled in ACTT-1 as well as adults with a relatively low body weight (40-50 kg, n=30).

Figure 3. RDV, GS-441524, and GS-704277 C_{max} in patients 12 - <18 years of age and weighing ≥40 kg (model-predicted) and in healthy adults (observed).



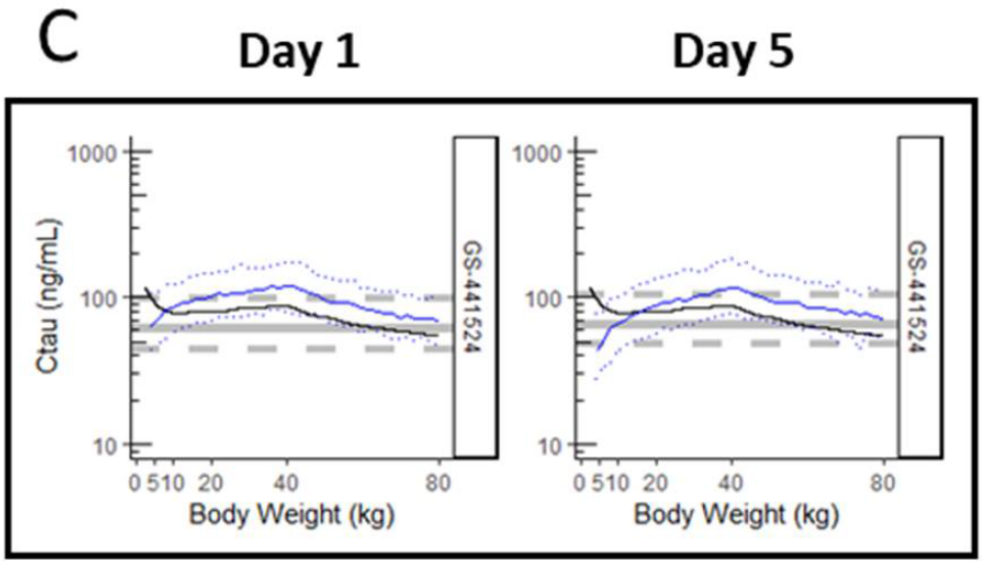
Source: (b) (4) 2020-1045. Blue = popPK: median simulated exposure using allometric scaling. Black = PBPK: Lowess smoother line of predicted exposure. Gray = adult reference: minimum, median, maximum observed exposure in healthy adults given 200 mg IV (day 1) or 100 mg daily (day 5). Red = adult maximum: value observed in adults administered 150 mg IV daily in study GS-US-399-1954 .

Figure 4. RDV, GS-441524, and GS-704277 AUC in patients 12 - <18 years of age and weighing ≥40 kg (model-predicted) and in healthy adults (observed).



Source: (b) (4) 2020-1045. Blue = popPK: median simulated exposure using allometric scaling. Black = PBPK: Lowess smoother line of predicted exposure. Gray = adult reference: minimum, median, maximum observed exposure in healthy adults given 200 mg IV (day 1) or 100 mg daily (day 5). Red = adult maximum: value observed in adults administered 150 mg IV daily in study GS-US-399-1954.

Figure 5. GS-441524 C_{tau} in patients 12 - <18 years of age and weighing ≥40 kg (model-predicted) and in healthy adults (observed).



Source: (b) (4) 2020-1045. Blue = popPK: median simulated exposure using allometric scaling. Black = PBPK: Lowess smoother line of predicted exposure. Gray = adult reference: minimum, median, maximum observed exposure in healthy adults given 200 mg IV (day 1) or 100 mg daily (day 5). Red = adult maximum: value observed in adults administered 150 mg IV daily.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Based on available data, there are no subpopulations requiring an alternative dosing regimen or management strategy. However, there are pending studies which will evaluate the impact of renal impairment, hepatic impairment, and pregnancy on the PK of RDV and metabolites (see

1.2 Post-Marketing Requirements and Commitments and 2.2.2 Therapeutic individualization).

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

As RDV is administered IV, food-drug interactions are not applicable.

Currently, there are no established or expected clinically significant PK-based DDIs associated with RDV.

Coadministration of RDV with chloroquine phosphate or hydroxychloroquine sulfate is not recommended. As described in the Warning and Precautions and Microbiology sections of labeling, the in vitro antiviral activity of RDV was antagonized by chloroquine phosphate. In cell culture, higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells See labeling or the Clinical Virology review for more details.

Effect of other drugs on RDV and metabolites

RDV and metabolites were evaluated in vitro as substrates of drug interaction guidance-recommended CYP enzymes and transporters. RDV is primarily metabolized by non-CYP enzymes and GS-441524 is not CYP metabolized. GS-704277 is a substrate of CYP3A4 and possibly CYP2C19. RDV is a substrate of OATP1B1 and P-gp transporters and GS-704277 is a substrate of OATP1B1 and OATP1B3 transporters. The clinical relevance of these in vitro assessments has not been established.

Due to its moderate to high extraction ratio of 0.6-0.8, it is unlikely that exposures of RDV or metabolites will be significantly affected by inhibitors of CES, CYP3A4, OATP, or P-gp. However, there is an agreed upon PMR for the Applicant to conduct a drug interaction trial of RDV coadministered with rifampin (broad spectrum inducer of enzymes/transporters).

Effect of RDV and metabolites on other drugs

In vitro studies recommended in the drug interaction guidance were conducted to evaluate RDV and metabolites as inhibitor of CYP enzymes and transporters, and for RDV as an inducer of CYP enzymes. P-gp inhibition by metabolites was not evaluated due to metabolites being more polar than parent drug (a rationale stated in FDA guidance). Nevertheless, the Applicant plans to conduct a study of P-gp inhibition by metabolites.

Where in vitro data suggested the need for follow up evaluations, drug interaction guidance-recommended equations were used to evaluate the potential for a clinically significant DDI. Using RDV day 1 (200 mg) or maintenance dose (100 mg) C_{max}, RDV is predicted to be an inhibitor of CYP3A, UGT1A1, OATP1B1, OATP1B3, and MATE1 (Table 4). However, by two hours after day 1 C_{max}, inhibition of only MATE1 is predicted and by four hours after day 1 C_{max}, no inhibition of any enzymes/transporters is predicted.

Table 4. Predicted inhibition of enzymes/transporters by RDV using basic and/or mechanistic static models.

Pathway	Model	RDV concentration	Cutoff value	Calculated value
CYP3A	$1 + (I_{max,u} / K_{i,u})$	C_{max} (200 mg)	≥1.02	1.75
CYP3A	Mechanistic static (AUCR)	C_{max} (200 mg) / C_{max} (100 mg) / C_{avg}	≥1.25	1.62 / 1.33 / 1.02
UGT1A1	$1 + (I_{max,u} / K_{i,u})$	C_{max} (200 mg)	≥1.02	1.98
UGT1A1	Mechanistic static (AUCR)	C_{max} (200 mg) / C_{max} (100 mg) / C_{avg}	≥1.25	1.65 / 1.36 / 1.02
OATP1B1	$I_{max,u} / IC_{50,u}$		≥1.1	1.19 / 1.098 / 1.01
OATP1B3			≥1.1	1.26 / 1.13 / 1.01
MATE1			≥0.1	0.31 / 0.16 / 0.01

Source: Prepared by reviewer from AD-540-2024. 200 mg = Day 1 RDV loading dose; 100 mg = maintenance dose; AUCR = substrate AUC ratio. Calculations for negative interactions with other pathways not shown.

Using drug interaction guidance criteria, human DDI studies or PBPK modeling should be considered to determine the effect of RDV on substrates of CYP3A, UGT1A1, OATP1B1, OATP1B3, and MATE1. Based on the following considerations, the review team does not recommend additional human DDI trials:

- Short term (up to 10 days) duration of RDV therapy.
- Short duration of predicted effect on substrate drugs (up to four hours of a 24-hour dosing interval on day 1), and
- Typically clinically insignificant DDIs for UGT or MATE-1 substrates.

4. APPENDICES

4.1 Individual Study Reviews

Human PK studies in healthy volunteers

Single and Multiple Ascending Dose

Study GS-US-399-1812 is a single ascending dose study to evaluate the safety and PK of IV remdesivir in healthy adults. Ninety-six subjects were enrolled (78 received remdesivir and 18 received placebo). Subjects were predominantly of white race (89%) and male (58%).

Cohorts 1-6 included dosing groups of 3, 10, 30, 75, 150 and 225 mg (N=8 active, N=2 placebo per group) where the solution formulation was infused over two hours. Cohorts 7-9 (N=10 active, N=2 placebo per

group) evaluated the lyophilized formulation at different doses and infusion durations (Cohort 7: 75 mg over two hours; Cohort 8: 150 mg over two hours; Cohort 9: 75 mg over 30 minutes).

Samples were collected from various matrices for measurement of remdesivir and metabolites:

- Plasma: intensive collection through 144 hours post-dose
- PBMCs: 12-24 hour intervals through 144 hours post-dose
- Urine: 6-12 hour intervals through 48 hours post-dose
- Semen: collected in male subjects pre-dose or three hours post-dose

Plasma PK in cohorts 1-6:

- Remdesivir C_{max} and AUC increased in proportion to dose with a T_{max} of 2 h and a half-life 0.66-1.1 hours
- GS-441524 C_{max} and AUC appeared to increase proportionally (cohorts 4 to 5) or more than proportionally (cohorts 1 to 3, 5 to 6) with dose, with a T_{max} of 3.5-5.0 h and a half-life of 13-31 hours
- GS-704277 C_{max} and AUC appeared to increase proportionally with dose, with a T_{max} of 2.0-2.3 h and a half-life of 1-2 hours

PK in PBMCs:

- GS-441524 C_{max} and AUC appeared to increase less than proportionally (cohorts 4 to 5), proportionally (cohorts 1 to 3), or more than proportionally (cohorts 3 to 4) with dose, with a half-life of 32-48 hours
- GS-441524 C_{max} and AUC increased approximately proportionally with dose in cohorts 7 to 8 with a half-life of 36-43 hours

PK in urine:

- Remdesivir: Across the 3-225 mg dose groups, the percentage of dose recovered was 7-10%
- GS-441524: Across cohorts 2-9, the percentage of dose recovered was 34-41%
- GS-704277: Not measured

PK in semen:

- Remdesivir was detected in all males in cohorts 7-9 at three hours post-dose and was not detectable in any pre-dose samples
- GS-441524 was detected at all timepoints in males except for one subject in each of cohort 7 and 9
- GS-704277 was detected at all timepoints in males through day three

Comparison of solution and lyophilized formulations (cohorts 4 vs 7 and 5 vs 8):

- RDV and GS-441524: similar exposures were observed in plasma after doses of 75 mg or 150 mg
- GS-704277: A statistical comparison was not conducted. Exposures of both formulations appear similar at a dose of 75 mg; exposures appear higher for the lyophilized formulation at a dose of 150 mg

Study GS-US-399-5505 is a multiple-dose safety and PK study of IV remdesivir (lyophilized formulation) in healthy adults. Plasma PK parameters from this study are included in labeling. Thirty-six subjects were enrolled; 29 received remdesivir and six received placebo. Subjects were predominantly of white race (61%) and male (81%).

Subjects received 200 mg IV on day 1 and 100 mg daily on days 2-5 (cohort 1) or days 2-10 (cohort 2). Infusion durations were 30 minutes. Intensive plasma PK samples were collected through 24 hours (day 1) or 96 hours (day 5) postdose. PBMCs were collected every 6-12 hours through 24 hours (day 1) or 96 hours (day 5) postdose.

Remdesivir was detectable in plasma for up to six hours postdose. The AUC accumulation ratio was 0.9. Half-lives of remdesivir and metabolites were consistent with study GS-US-399-1812 (Table 5, Table 6, Table 7, Table 8).

Table 5. Remdesivir plasma PK parameters.

PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Doses (100 mg) Day 5 and 10 (N = 26)[b]
C_{max} (ng/mL)	4377.9 (23.5)	2228.8 (19.2)
C_{last} (ng/mL)	8.8 (57.7)	8.1 (46.9)
T_{max} (h)	0.67 (0.25, 0.68)	0.68 (0.25, 0.75)
T_{last} (h)	6.00 (4.00, 6.00)	4.00 (4.00, 4.02)
$t_{1/2}$ (h)	0.90 (0.80, 1.03)	0.96 (0.86, 1.08)
AUC_{last} (h•ng/mL)	2850.3 (18.8)	1562.8 (17.0)
AUC[c] (h•ng/mL)	2862.5 (18.6)	1585.3 (16.6)
CL_{ss} (mL/h)	--	65058.7 (19.8)
V_z (mL)	--	92557.2 (29.5)

% CV = percentage coefficient of variation; IV = intravenous; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
Certain parameters are missing since Lambda_z is not reliably estimable.
a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).
b N = 25 for AUC_{tau}, $t_{1/2}$, CL_{ss}, and V_z.
c AUC_{0-24} is presented for single RDV dose (200 mg) on Day 1; AUC_{tau} is presented for multiple RDV doses (100 mg) on Days 5 and 10.

Source: Study report.

Table 6. GS-441524 plasma PK parameters.

PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Doses (100 mg) Day 5 and 10 (N = 26)
C_{max} (ng/mL)	142.9 (21.5)	145.0 (19.3)
C_{tau} (ng/mL)	--	69.2 (18.2)
C_{last} (ng/mL)	64.8 (20.8)	12.2 (50.0)
T_{max} (h)	2.00 (1.50, 4.00)	1.51 (1.50, 2.00)
T_{last} (h)	23.92 (23.92, 23.93)	96.00 (96.00, 96.00)
$t_{1/2}$ (h)	--	27.36 (25.29, 30.32)
AUC_{last} (h•ng/mL)	2186.4 (19.1)	4189.3 (17.7)
AUC[b] (h•ng/mL)	2191.4 (19.1)	2229.2 (18.4)

%CV = percentage coefficient of variation; IV = intravenous; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
Certain parameters are missing since Lambda_z is not reliably estimable.
a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).
b AUC_{0-24} is presented for single RDV dose (200 mg) on Day 1; AUC_{tau} is presented for multiple RDV doses (100 mg) on Days 5 and 10.

Source: Study report.

Table 7. GS-704277 plasma PK parameters.

PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Doses (100 mg) Day 5 and 10 (N = 26)
C_{max} (ng/mL)	370.4 (29.3)	245.5 (33.9)
C_{last} (ng/mL)	4.8 (35.8)	3.9 (27.5)
T_{max} (h)	0.75 (0.67, 0.75)	0.75 (0.75, 0.78)
T_{last} (h)	8.00 (8.00, 8.00)	8.00 (8.00, 8.00)
$t_{1/2}$ (h)	1.27 (1.14, 1.45)	1.23 (1.15, 1.38)
AUC_{last} (h•ng/mL)	688.5 (26.3)	454.4 (31.8)
AUC[b] (h•ng/mL)	697.5 (25.9)	461.5 (31.4)

%CV = percentage coefficient of variation; IV = intravenous; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
Certain parameters are missing since Lambda_z is not reliably estimable.
a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).
b AUC_{0-24} is presented for single RDV dose (200 mg) on Day 1; AUC_{tau} is presented for multiple RDV doses (100 mg) on Days 5 and 10.

Source: Study report.

Table 8. GS-443902 plasma PK parameters.

PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Dose (100 mg) Day 5 and 10 (N = 26)[b]
C_{max} (µmol)	9.8 (46.6)	14.6 (40.6)
C_{tau} (µmol)	--	10.2 (49.5)
C_{last} (µmol)	6.9 (45.8)	3.1 (41.7)
T_{max} (h)	6.00 (1.00, 12.02)	6.00 (1.00, 12.0)
T_{last} (h)	23.92 (23.92, 23.93)	96.00 (96.00, 96.00)
$t_{1/2}$ (h)	--	43.39 (38.70, 48.90)
AUC_{last} (h•µmol)	163.4 (32.1)	596.7 (25.5)
AUC[c] (h•µmol)	157.4 (32.9)	240.0 (25.4)

%CV = percentage coefficient of variation; IV = intravenous; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
Certain parameters are missing since Lambda_z is not reliably estimable.
a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).
b N = 25 for C_{tau} and N= 20 for $t_{1/2}$
c AUC_{0-24} is presented for single RDV dose (200 mg) on Day 1; AUC_{tau} is presented for multiple RDV doses (100mg) on Days 5 and 10.

Source: Study report.

Mass balance

Study GS-US-399-4231 evaluated the mass balance of remdesivir. Subjects received a 150 mg single IV dose of remdesivir (solution formulation; mixture of unlabeled and radiolabeled) over 30 minutes. Eight subjects were enrolled (all male, 50% white race, 50% black race). Matrices collected through 168 hours postdose included blood (intensive sampling for whole blood and plasma concentrations), urine (intervals of six, 12, or 24 hours) and feces (24 hour intervals).

Reviewer's comments: Despite stated sampling through 168 hours postdose, results were reported for 192 h and 216 h timepoints.

The blood-to-plasma ratio of total radioactivity ranged from 0.68 at 15 minutes from the start of infusion to 1.0 (five hour timepoint). Compared to study GS-US-399-1812, plasma RDV and GS-441524 AUC_{inf} values were ~20% lower while GS-704277 AUC_{inf} values were similar.

Cumulative recovery of radioactivity from urine and feces was 92% (Table 9).

Table 9. Remdesivir and metabolites recovery in urine and feces.

Analyte	Percent of dose recovered in urine	Percent recovery in feces	Combined
Remdesivir	10.9	Not determined	
GS-441524	41.0		
GS-704277	3.9		
Total	74.2	18.1	92.3

Source: Prepared by reviewer based on information provided in final study report.

Metabolites were profiled from samples pooled across subjects . The major moieties in plasma were GS-441524 (44% of radioactivity), RDV (14%), and unknown metabolite M27 (11%). The major moieties in urine were GS-441524 (49%) and RDV (10%); six minor unidentified species accounted for 6% of the dose. The major moiety in feces was M14 (12%) with other peaks being <1% each.

In vitro distribution

Study AD-540-2007 evaluated distribution of remdesivir (0.5 µM) and GS-441524 between human cellular and soluble fractions of blood. The mean human blood/plasma concentration ratio was 0.76 for remdesivir and 1.19 for GS-441524. In study AD-540-2016, the mean human blood/plasma ratio of GS-704277 (0.5 µM) was 0.56.

Protein binding of remdesivir (study AD-399-2013) and its metabolites (study AD-399-2031) were evaluated using equilibrium dialysis at analyte concentrations of 2 µM. The free fraction of remdesivir, GS-704277 and GS-441524 were 12%, 99%, and 98%. In a second study (AD-540-2020), RDV protein binding was evaluated using equilibrium dialysis at RDV concentrations of 1-10 µM. Mean RDV fraction unbound was 6.5% at 1 µM and 7.4% at 10 µM.

Reviewer's comments: Remdesivir concentrations in the protein binding study exceeded human C_{max} after a dose of 200 mg IV in AD-540-2020 but not in AD-399-2013. Metabolite concentrations in the protein binding study exceeded human C_{max} after a dose of 200 mg IV in study AD-399-2031 (Table 10).

Table 10. Human C_{max} values after administration of 200 mg IV in study GS-US-399-5505.

Analyte	*Human mean total C_{max} (ng/mL)*	*Human mean total C_{max} (µM)*
Remdesivir	*4378*	*7.3*
GS-704277	*370*	*0.84*
GS-441524	*143*	*0.49*

Source: Reviewer. Analyte molecular weights obtained from the PK Written Summary.

In study AD-540-2008, mean free fractions of RDV (2 µM), GS-441524 (2 µM), and GS-704277 (3 µM) in the presence of human hepatic microsomal fraction were 58%, 89%, and 90%, respectively.

In vitro metabolism of RDV and metabolites

Study AD-540-2022 evaluated metabolic stability of RDV when incubated with human hepatocyte and tissue fractions.. Estimated RDV hepatic fraction metabolized (f_m) values were 0.8 for carboxylesterases, 0.1 for CYP3A, and 0.1 for cathepsin A. RDV can also be metabolized by human plasma and extra hepatic (intestinal) fraction.

Study AD-540-2021 evaluated hydrolysis of RDV (incubated with cathepsin A, CES1b, CES1c, and CES2) and GS-704277 (incubated with HINT1). RDV was metabolized by cathepsin A, CES1b, and CES1c. GS-704277 was metabolized by HINT1.

Study AD-399-2011 evaluated CYP (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) metabolism of RDV . Detectable metabolism was observed for CYP2C8, CYP2D6 and CYP3A4. When normalized to hepatic expression levels, CYP3A4 is expected to have a greater contribution to RDV metabolism compared to CYP2C8 or CYP2D6.

Study AD-540-2018 evaluated CYP (CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5) metabolism of RDV, GS-441524, and GS-704277. As found in AD-399-2011, remdesivir was metabolized by CYP2C8, CYP2D6, and CYP3A4. No metabolism of GS-441524 was observed. Potential metabolism of GS-704277 by CYP3A4 and CYP2C19 was observed; however, the results were inconclusive due to poor analytical sensitivity.

Study AD-540-2019 evaluated UGT (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15) metabolism of RDV, GS-441524, and GS-704277. No metabolism was observed for RDV. Detectable UGT1A3 metabolism was observed for GS-441524 and GS-704277; however, a direct glucuronide metabolite was not detected for either metabolite.

In vitro studies of RDV and metabolites as a substrate of transporters

RDV and metabolites were found to be substrates of several transporters (Table 11).

Table 11. Summary of RDV and metabolite in vitro transporter studies.

Study	Analyte	Transporter	System	Substrate
AD-540-2012[1]	RDV	P-gp	Caco-2	Yes
AD-399-2007[1]	RDV	P-gp BCRP	MDCK	Yes No
AD-399-2008	RDV	OATP1B1 OATP1B3	CHO	Yes No
AD-540-2010	GS-441524	OATP1B1 OATP1B3	HEK293	No
AD-540-2025	GS-441524	OAT1 OAT3 OCT2 MATE1 MATE2K	HEK293	No
AD-540-2010	GS-704277	OATP1B1 OATP1B3	HEK293	Yes
AD-540-2025	GS-704277	OAT1 OAT3 OCT2 MATE1 MATE2K	HEK293	No

[1]Dose-dependent efflux was shown in AD-540-2012 (RDV concentrations of 1, 10, and 100 µM) while a single 1 µM RDV target concentration was evaluated in AD-399-2007.

In vitro inhibition of CYP and non-CYP enzymes by RDV and metabolites

Reversible inhibition

RDV is an inhibitor of several drug metabolizing enzymes (Table 12). GS-441524 and GS-704277 are inhibitors of UGT1A9 (Table 13). For comparison of IC_{50} values with human PK data, RDV and metabolites human plasma C_{max} values after administration of 200 mg IV are shown in Table 10.

Table 12. Summary of RDV reversible enzyme inhibition studies.

Study	Analyte	Concentration (µM)	Enzyme	IC_{50} (µM)
AD-399-2010	RDV	0-100	CYP1A2 (E) CYP2C9 CYP2C19 CYP2D6 CYP3A (M)	>100 63.3 68.3 73.0 >1.6
AD-540-2004	RDV	0-100	CYP1A2 (P) CYP2B6 CYP2C8 CYP3A (T)	>100 77.8 54.9 11.0
AD-540-2005	RDV	0-100	UGT1A1	9.8

Source: Prepared by reviewer. Substrates: E = 7-ethoxyresorufin; M = midazolam; P = phenacetin; T = testosterone.

Table 13. Summary of GS-441524 and GS-704277 reversible enzyme inhibition studies.

Study	Analyte	Concentration (µM)	Enzyme	IC_{50} (µM)
AD-540-2013	GS-441524 GS-704277	Up to 25	CYP1A2 CYP2B6 CYP2C8 CYP2C9 CYP2C19 CYP2D6 CYP3A4	>25
AD-540-2015	GS-441524 GS-704277	0-100	UGT1A1 UGT1A3 UGT1A4 UGT1A6 UGT1B7	>100
AD-540-2015	GS-441524 GS-704277	0-100	UGT1A9 UGT1A9	85.5 88.9

Source: Prepared by reviewer.

Mechanism-based inhibition

RDV (25 µM), GS-441524 (25 µM), and GS-704277 (25 µM) are not mechanism-based inhibitors of CYP (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A) enzymes (AD-540-2004, AD-540-2014).

In vitro induction of CYP enzymes by RDV and metabolites

In study AD-399-2027, induction of CYP (CYP1A2, CYP2B6, CYP3A4) enzymes by RDV (10-50 µM), GS-441524 (25-100 µM), and GS-704277 (10-50 µM) in human hepatocytes was evaluated. For RDV, induction of mRNA (no induction of enzyme activity) was observed in one of three donors for CYP1A2 (24% of positive control) and CYP2B6 (27% of positive control). RDV did not induce CYP3A4. No induction of mRNA or enzyme activity was observed for GS-441524 or GS-704277.

In vitro inhibition of transporters by RDV and metabolites

Inhibition of several transporters by RDV, GS-441524 and/or GS-704277 was observed (Table 14, Table 15, Table 16). The Applicant is planning to conduct an in vitro study to evaluate inhibition of P-gp by GS-441524 and GS-704277.

Table 14. Summary of RDV transporter inhibition studies.

Study	Concentration (µM)	Transporter	System	IC_{50} (µM)
AD-399-2005	0-40	P-gp BCRP OATP1B1 OATP1B3	MDCK MDCK CHO CHO	No inhibition No inhibition 2.8 2.1
AD-399-2029	Up to 100	BSEP MRP2 MRP4 NTCP	Vesicles	22 No inhibition 5.1 72
AD-540-2011	Up to 150 Up to 137 Up to 191	MATE1 MATE2-K OAT3 OCT2 OAT1 OCT1	MDCK MDCK HEK293 HEK293 CHO HEK293	1.74 41.1 11.3 53.5 152 11.3

Source: Prepared by reviewer.

Table 15. Summary of GS-441524 transporter inhibition studies.

Study	Concentration (µM)	Transporter	System	IC_{50} (µM)
AD-540-2009	Up to 241	OATP1B1 OATP1B3	HEK293	241 >241
AD-540-2011	Up to 162 Up to 186 Up to 136	MATE1 MATE2-K OAT3 OCT2 OAT1 OCT1	MDCK MDCK HEK293 HEK293 CHO HEK293	No inhibition No inhibition >186 No inhibition >136 >136
AD-399-2029	Up to 100	BSEP MRP2 MRP4 NTCP	Vesicles	>100
AD-399-2035	Up to 200	BCRP BSEP MRP2 MRP3	Vesicles	>200

Source: Prepared by reviewer.

Table 16. Summary of GS-704277 transporter inhibition studies.

Study	Concentration (µM)	Transporter	System	IC_{50} (µM)
AD-540-2009	Up to 89	OATP1B1 OATP1B3	HEK293	No inhibition >89
AD-540-2011	Up to 88 Up to 74 Up to 98	MATE1 MATE2-K OAT3 OCT2 OAT1 OCT1	MDCK MDCK HEK293 HEK293 CHO HEK293	No inhibition No inhibition >74.3 No inhibition >98 No inhibition
AD-399-2029	Up to 100	BSEP MRP2 MRP4 NTCP	Vesicles	>100
AD-399-2035	Up to 200	BCRP BSEP MRP2 MRP3	Vesicles	>200

Source: Prepared by reviewer.

Predicted clinical significance of in vitro interactions using mechanistic static equations

Study AD-540-2024 used in vitro parameters and equations described in FDA guidance to calculate the potential for significant in vivo inhibition of enzymes or transporters by RDV, GS-441524, and GS-704277.

Using a basic model for reversible inhibition of enzymes (CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A, UGT1A1, UGT2B7), $R_1 \geq 1.02$ indicates a potential interaction. $R_1 \geq 1.02$ was observed for several enzymes for RDV, GS-441524, and GS-704277. Further analysis of reversible inhibition was conducted using a mechanistic static equation where AUCR ≥1.25 indicates a potential interaction. Using RDV day 1 C_{max}, AUCR≥1.25 was observed for RDV regarding inhibition of CYP3A and UGT1A1. However, using RDV day 1 concentration two hours after C_{max}, no effect on CYP3A or UGT1A1 is predicted. AUCR≥1.25 was not observed for any enzyme for GS-441524 or GS-704277.

RDV both inhibited and induced (one of three donors) CYP1A2 and CYP2B6. Using a combined mechanistic static equation, no interaction was predicted (AUCR of 0.91 for CYP1A2 and AUCR of 0.94 for CYP2B6).

A basic model was used to determine potential inhibition of transporters by RDV, GS-441524, and GS-704277. For OATP1B1 and OATP1B3, cutoff values were exceeded for RDV using day 1 C_{max} but not two hours after day 1 C_{max}. Cutoff values were exceeded for inhibition of MATE1 by RDV using day 1 C_{max} but not when using the RDV concentration observed four hours after day 1 C_{max}.

Cutoff values were not exceeded for inhibition of OCT1 by RDV, GS-441524 and GS-704277, and were not exceeded for inhibition of OATP1B1/3 by GS-441524 and GS-704277. Cutoff values were not exceeded for inhibition of OAT1, OAT3, OCT2, or MATE2-K by RDV, GS-441524, or GS-704277.

Reviewer comments: DDI liability reports AD-540-2006 and AD-540-2017 were not reviewed as they were replaced by AD-540-2024 (reviewed above).

4.2 Summary of Bioanalytical Method Validation and Performance

Plasma PK Parameters from study GS-US-399-5505 were included in labeling. We reviewed the method validation and sample analysis reports associated with study GS-US-399-5505 and found the methods to be acceptable (Table 17, Table 18).

Table 17. Assessment of LC-MS/MS method validation reports relevant to study GS-US-399-5505.

Method	Analyte(s)	Matrix	Calibration range	Accuracy and precision values of calibration and QC samples within 15% (20% at LLOQ)	Failed runs	Major deviations	Interference from other analytes	Duration of stability
60-15117	RDV GS-441524 GS-704277	Plasma	4-4000 ng/mL 2-2000 ng/mL 2-2000 ng/mL	Yes	Runs 1-6 failed due to accuracy and precision. May be due to lack of assay ruggedness or stock solutions not fully thawed. After adding an additional injection step and ensuring thawing of solutions, accuaracy and precision was acceptable.	None	Peaks in RDV blanks were up to 7% of PA at LLOQ. No interference in GS-441524 blanks. Peaks in GS-704277 blanks were up to 17% of PA at LLOQ.	RDV and GS-441524 stable for 31 days at -20°C and -70°C GS-704277 stable for 31 days at -70°C
60-15117 amendment 6	RDV GS-441524 GS-704277	Plasma	4-4000 ng/mL 2-2000 ng/mL 2-2000 ng/mL	Yes	None	None	No new chromatograms submitted in this amendment	RDV and GS-441524 stable for 392 days at -20°C and -70°C GS-704277 stable for 257 days at -70°C

Source: Reviewer. PA = peak area. Sample dilution of up to 20-fold was shown to result in acceptable accuracy and precision.

Table 18. Assessment of LC-MS/MS method performance in study GS-US-399-5505.

Analyte	Matrix	Method	Major deviations or failed runs	Accuracy and precision values of calibration and QC samples within 15% (20% at LLOQ)	Max time between sample collection and analysis	Samples measured within the duration of stability	Incurred sample reanalysis pass rate (within 30% of original measurement)	Interference from other analytes	Chromatograms
RDV	Plasma	60-15117	None	Yes	93 days, stored at -70°C	Yes	99%	No interference in blank chromatograms	Chromatograms from study subjects were submitted and appear consistent across samples
GS-441524							99%		
GS-704277							98%		

Source: Reviewer. PA = peak area.

4.3 Physiologically-based Pharmacokinetics Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analysis to predict the plasma PK profiles of remdesivir (RDV) and metabolites (GS-704277 and GS-441524) in pediatric patients 12 years of age and older and weighing at least 40 kg.

The Division of Pharmacometrics has reviewed the final PBPK report, supporting modeling files, and responses to our information requests (submitted on July 24, 2020) to conclude the following:

- The PBPK modeling for RDV was adequate to predict the plasma PK profiles of RDV, GS-704277 and GS-441524 in adults following the proposed dosing regimen (loading dose of 200 mg IV and 100 mg IV daily maintenance dose).
- The changes in the age-depended physiological parameters are not expected to significantly impact the plasma PK profiles of RDV, GS-704277 and GS-441524 for pediatric patients 12 years of age and older and weighing at least 40 kg.
- PBPK analysis can be used to provide supporting evidence for comparable plasma exposure of RDV and metabolites between adults and adolescents (12 years of age and older and weighing at least 40 kg) following the proposed dosing regimen.

Background

The proposed dosing regimen of remdesivir (RDV) is a single loading dose of 200 mg IV on Day 1 followed by once-daily maintenance doses of 100 mg IV from Days 2 for adults and pediatric patients 12 years of age and older and weighing at least 40 kg.

Following a single IV administration of RDV 150 mg, RDV was rapidly eliminated followed by the sequential appearance of GS-704277 and GS-441524 in plasma. The intracellular metabolism of RDV is assumed to be mediated by phosphoramidase cleavage of GS-704277 to GS-441524-MP. GS-441524-MP then converts to the active triphosphate metabolite, GS-443902, via nucleotide kinases. Dephosphorylation of GS-441524-MP results in the nucleoside analog GS-441524 (Figure 6). Both GS-441524-MP and GS-443902 are not detectable in the plasma. The Applicant stated that albumin is likely the main plasma binding protein for RDV, GS-704277 and GS-441524 [PBPK report QP-2020-1041]. The human mass balance study [Study GS-US-399-4231] reported that recovery of RDV was primarily from urine containing approximately 92% of the total dose. The predominant species detected in urine were GS-441524 (49%), followed by RDV (10%) and GS-704277 (2.9%). RDV exhibited a linear PK profile for doses ranging from 3 mg to 225 mg IV].

A PBPK modeling approach for RDV was proposed by the Applicant to support the selection of the proposed dosing regimen for pediatric patients (infants to adolescents) in the Initial Pediatric Study Plan (dated 4/30/2020 under IND 147753). FDA agreed that PBPK modeling approach could be used to support pediatric dose selection in the clinical PK studies; but cited several model limitations and indicated that the model needed to be further optimized for the intended application [FDA DARRTs ID 4593544]. PK data in patients < 18 years of age are not available at the time of NDA submission.

In the current NDA submission, the Applicant proposed the following language in their draft US label regarding PBPK analysis:

Section 8.4	(b) (4)
Section 12.3	

This review evaluates the adequacy of the Applicant's PBPK model to simulate the plasma PK profiles of RDV and metabolites GS-704277 and GS-441524 in adolescent patients (12 years of age and older and weighing at least 40 kg).

Methods

PBPK model structure

The PBPK analysis was performed using the population-based PBPK software Simcyp® (V18, Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). The software's default "Healthy Volunteer" was used for simulating adult exposure of RDV and plasma metabolites. For the adolescent population, the Applicant created a modified "Pediatric" virtual population by sampling from the default pediatric population to compile a pediatric virtual population that is evenly distributed by body weight with an approximately equal proportion of males and females.

The PBPK model of RDV was developed based on in silico derived physicochemical properties, in vitro, and clinical PK data [Studies GS-US-399-5505 and GS-US-399-1812]. Key model parameters are described as follows. In vitro, the unbound fraction of RDV in plasma (fup) ranged from 0.065-0.074 [AD-540-2020] to 0.12 [Study AD-399-2013]. The Applicant set fup as 0.12 and the blood-to-plasma ratio (B/P) as 0.76) [study AD-540-2007] in the PBPK model. A full PBPK distribution model was used for RDV and a Kp scalar of 0.56 was used to characterize RDV volume of distribution after IV administration (Vd= 45-102 L). Although in vitro RDV was a substrate for OATP1B and P-gp transporters, the model assumed that active transport does not mediate the disposition of RDV (perfusion rate-limited). This assumption seemed reasonable because RDV exhibits moderate-to-high hepatic extraction ratio. RDV is rapidly metabolized to GS-704277 by ester hydrolysis. Carboxylesterase 1 (CES1) was identified as the primary esterase responsible for hydrolysis of RDV in vitro [Report AD-540-2021]. In vitro, RDV was also identified as a minor substrate for CYP3A4 and cathepsin A (<10% each). Remdesivir also undergo renal elimination (8.7% of RDV was eliminated unchanged in urine). The observed renal clearance (CLr) of 5.71 L/h was included in the model.

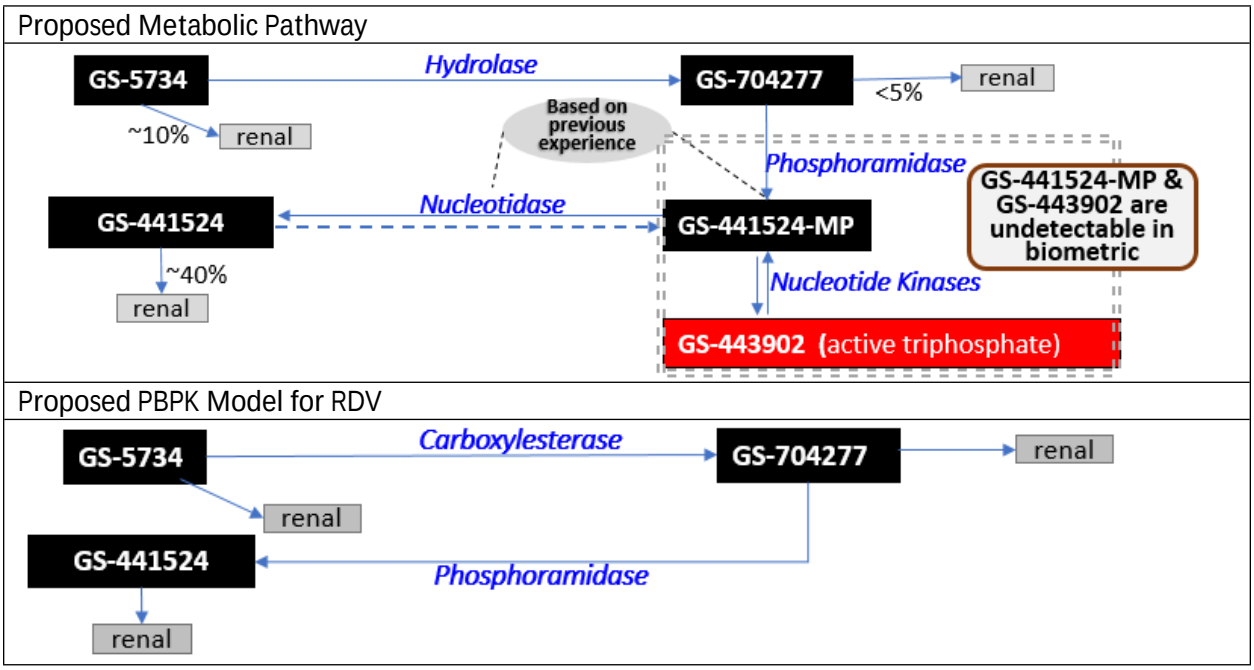
Reviewer's comments: *A two-fold difference in the RDV's fup was reported between two in-vitro studies (see discussion in Section 4.1). Given the intrinsic clearance of RDV is estimated using retrograde method based on clinical PK data, the selection of RDV fup of 0.12 as PBPK model parameters is not expected to significantly impact the simulated plasma PK profiles of RDV and its metabolites.*

The PBPK model of RDV metabolite GS-704277 was developed based on physicochemical properties (in silico estimates), in vitro and clinical PK data [studies GS-US-399-5505 and GS-US-399-1812]. In vitro, the fup of GS-704277 was 0.99. Based on its physiochemical property, GS-704277 is expected to have a low cellular permeability and a minimal B/P value of 0.55 was assumed due to the high hydrophilicity (logP value of -2.31) and ionization at physiologic pH. A minimal PBPK distribution model, with a Kp scalar of 3.3 and single-additional compartment, was used to recover the observed PK profile in plasma. Because the intracellular metabolites of RDV (GS-441524-MP and GS-443902; see below) are not observed in plasma, these metabolites are not incorporated into the current PBPK model. Instead, the model assumed a single non-specific esterase process metabolizes GS-704277 directly to GS-441524 in the liver (See Figure 6).

The PBPK model of RDV metabolite GS-441524 was developed based on physicochemical properties (in silico estimates), in vitro and clinical PK data [studies GS-US-399-5505 and GS-US-399-1812]. In vitro, the fup was 0.98 [study AD-399-2031] and B/P was 1.19 [study AD-399-2007]. A minimal PBPK distribution model, with a volume of distribution of 6.2 L/Kg and single-additional compartment, was used to recover the observed plasma PK profile. GS-441524 undergo renal elimination (35.4 % of RDV dose renally eliminated as GS-441524). The observed CLr value of 9.85 L/h was used in the model. Additional human hepatocyte clearance of GS-441524 was estimated to recover the AUC of GS-441524.

The intracellular metabolism of RDV is assumed to be mediated by phosphoramidase cleavage of the phosphoramidate bond of GS-704277, liberating the nucleoside analog monophosphate, GS-441524-MP. Nucleotide kinases catalyze the intracellular conversion between GS-441524-MP and the active triphosphate metabolite, GS-443902. Dephosphorylation of GS-441524-MP results in the formation of the nucleoside analog GS-441524. The latter metabolite is observable in the plasma (Figure 6).

Figure 6. Scheme of the proposed ADME pathways and PBPK model structure for RDV, GS-704277 and GS-441524.



GS-5734=Remdesivir. Source: Made by the Reviewer based on Figure 1 of the PBPK report QP-2020-1041

Reviewer's comments on the simplified model structure:
The RDV metabolites GS-441524-MP and GS-443902 are produced intracellularly and undetectable in plasma. Since the current model did not include the intracellular metabolism of RDV to the active metabolite GS-443902, it limited the use of this PBPK model to provide pharmacodynamic analysis of RDV. The Reviewer acknowledges that the plasma PK profiles of RDV, GS-704277 and GS-441524 may not be relevant to the PK of the active metabolite in tissues.

PBPK model performance

The predictive performance of the PBPK modeling for RDV and the plasma metabolites GS-704277 and GS-441524 was evaluated by simulation of phase 1 exposure data in healthy adults, following administration of RDV 200 mg IV loading dose (0.5 h infusion) on Day 1, then 100 mg IV daily maintenance doses (0.5 h infusion) starting on Day 2, and continuing through Days 5 or 10 [Study GS-US-399-5505].

PBPK model application

The adult PBPK modeling for RDV was subsequently used to simulate steady-state pediatric exposures accounting for age-dependent changes in organ volume/size (liver and kidney), enzyme expression, plasma protein binding, and organ blood flow.

Reviewer's comments on the clinical applicability of this model:
Given the simplified model structure, the current PBPK modeling for RDV mainly accounted for changes in physiological parameters such as tissue/organ size/volume, blood flow rates, liver and kidney function, and to an extent, CES enzyme expression. Based on the default ontogeny function in the pediatric model (Simcyp V18), CES activity in adolescence (12-18 years of age) is mature by 12 years of age. Based on literature data[1], CES1 and CES2 abundances in adolescence are about 80% and 95% of the adult values in the liver, respectively. While our current understanding of the ontogeny of this enzyme is mainly based on in-vitro information, given our current understanding of enzyme maturation rates in general, CES is likely mature in children over 12 years of age. Therefore, the uncertainty of Applicant's ontogeny function for CES and its impact on the simulated plasma PK profiles can be considered low for adolescents (proposed pediatric population). On the other hand, the uncertainty of other assumptions on the metabolic pathways for 'downstream' metabolites vary. For example, there is high uncertainty of assuming that GS-441524 formation can be simplified by describing it using a single pathway (GS-441524 is directly formed from GS-704277). Reason is this assumption does not consider intracellular metabolic pathways where multiple enzymes and conversions are involved. However, the impact of such assumptions on simulated PK profiles could be lower if the key enzymes involved in the intracellular metabolic pathways are mature in adolescents. Overall, we consider the applicability of the proposed modeling approach to scale from adults to children (birth to < 18 years of age) to be limited when only incorporating changes in physiological parameters and some enzyme ontogeny. However, given the current knowledge about enzyme maturation in adolescents, we consider the current PBPK modeling reasonable to provide support for simulations of plasma PK profiles of RDV and metabolites GS-704277 and GS-441524 in pediatric patients over 12 years of age and weighing over 40 kg.

The Reviewer noted a clinical study in pediatric patients across all age and body weight groups is planned/ongoing.

The Reviewer acknowledged the current PBPK modeling for RDV does not account for the possibility of diminished liver or kidney function in patients due to SARS-CoV-2 infection and/or COVID-19 progression because the impact of infection/disease progression on the PK of RDV and metabolites is currently unknown.

The Reviewer noted the current modeling for RDV is considered adequate for the Applicant's intended purpose - scale plasma PK from adults to adolescents. However, given the current model structure and data limitations, the PBPK modeling for RDV should be further optimized to support future applications, such as evaluation of drug-drug interaction potential, PK/PD analysis and other pediatric age groups.

[1] Boberg et al. Age-Dependent Absolute Abundance of Hepatic Carboxylesterases (CES1 and CES2) by LC-MS/MS Proteomics: Application to PBPK Modeling of Oseltamivir In Vivo Pharmacokinetics in Infants. Drug Metab Dispos. 2017;45(2):216-223.

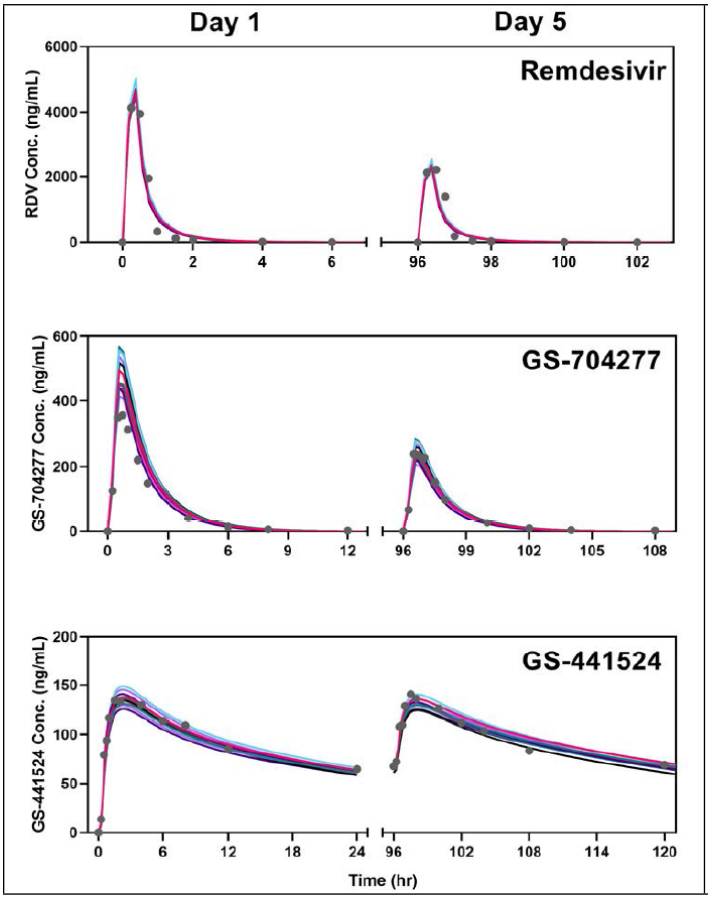
Results

Q1: Can the PBPK modeling for remdesivir describe the plasma PK of remdesivir and its metabolites in adults?

Yes. PBPK simulations reasonably described the observed PK profiles of remdesivir and metabolites GS-704277 and GS-441524 in plasma following a loading dose of 200 mg IV on Day 1, then 100 mg IV daily doses on Days 2 - 5 to adult healthy volunteers, as shown in Figure 7.

The Reviewer noted that simulated PK parameters of remdesivir and metabolites GS-704277 and GS-441524 in plasma have reached steady-stated at Day 5 (result not shown). Thus, there is no difference between the plasma PK profiles simulated following 5-day or 10-day dosing regimens.

Figure 7. Comparison of simulated and observed pharmacokinetics of RDV, GS-704277 and GS-441524 in health adults.



Grey dots: observed Phase 1 mean plasma concentration-time profiles from Study GS-US-399-5505
Colored lines: predicted median plasma concentration-time profiles from 10 simulated trials

Simulation Trial Design: Ten trials of 28 subjects per trial, default age range of 20-50 years, and equal proportion of male and female subjects.

Source: Figure 2 of PBPK report QP-2020-1041

Q2: Are the plasma PK profiles for remdesivir, GS-704277 and GS-441524 comparable between adults and adolescents following the proposed dosing regimen?

Yes. As shown in Table 19, the PK parameters of RDV, GS-704277 and GS-441524 in plasma were comparable between those simulated in adolescents (≥ 12 years of age with body weight ≥ 40 kg) and those observed in adults after the proposed dosing regimen (200 mg IV loading dose on Day 1 followed by 100 mg IV daily maintenance doses) [GS-US-399-5505].

The predictions for RDV and GS-441524 in adolescents were less than 1.20-fold higher than the observed values in adults, for C_{max} and AUC at Day 1 or steady-state (Day 5). While, the predictions for the PK of GS-704277 in adolescents were approximately 1.15 to 1.80- fold higher than the observed values in adults (Table 19).

Table 19. Comparison of observed pharmacokinetics of RDV, GS-704277 and GS-441524 in healthy adults and those predicted for adolescents (≥12 years of age with body weight ≥ 40 kg) following RDV dosing.

RDV	Adult Observed[1]		Adolescent Predicted [4]		Pred/Obs ratio	
	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}
Day 1						
Median	2782.70	4190.00	3106.47	5002.68	1.12	1.19
Geo. Mean	2816.90	4267.20	3168.85	5114.99	1.12	1.20
5th centile	2626.00	3905.10	2490.48	4030.14	-	-
95th centile	3021.70	4663.00	4136.64	6602.58	-	-
Day 5						
Median	1579.30	2335.00	1553.48	2499.88	0.98	1.07
Geo. Mean	1562.40	2189.40	1584.49	2557.38	1.01	1.17
5th centile	1451.00	2024.70	1245.77	2015.57	-	-
95th centile	1682.30	2367.50	2068.78	3297.86	-	-
GS-704277	Adult Observed[2]		Adolescent Predicted		Pred/Obs ratio	
	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}
Day 1						
Median	669.60	362.50	1027.17	636.42	1.53	1.76
Geo. Mean	676.60	355.60	1041.78	647.76	1.54	1.82
5th centile	614.30	317.70	553.47	361.84	-	-
95th centile	745.30	398.00	1884.39	1108.31	-	-
Day 5						
Median	446.70	224.00	513.60	318.21	1.15	1.42
Geo. Mean	438.90	231.80	520.89	323.88	1.19	1.40
5th centile	384.40	201.20	276.77	180.91	-	-
95th centile	501.20	267.10	942.18	554.14	-	-
GS-441524	Adult Observed[3]		Adolescent Predicted[4]		Pred/Obs ratio	
	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}	AUC_{tau}	C_{max}
Day 1						
Median	2167.70	140.00	2375.52	160.42	1.10	1.15
Geo. Mean	2156.20	139.90	2440.21	165.40	1.13	1.18
5th centile	2010.70	129.00	1784.19	120.99	-	-
95th centile	2312.30	151.80	3398.28	230.78	-	-
Day 5						
Median	2158.10	140.50	2267.98	140.10	1.05	1.00
Geo. Mean	2196.20	142.70	2278.62	142.06	1.04	1.00
5th centile	2047.80	132.50	1438.58	98.17	-	-
95th centile	2355.40	153.60	3502.19	205.21	-	-

* Day 1 AUC_{tau}: $AUC_{0\text{-}24hr}$, Day 5 AUC_{tau}: $AUC_{96\text{-}120hr}$;

[1] Table 15.10.1.1.6.1 of Study report# GS-US-399-5505.

[2] Table 15.10.1.1.6.2 of Study report# GS-US-399-5505.

[3] Table 15.10.1.1.6.3 of Study report# GS-US-399-5505.

[4] Summarized by the Reviewer based on submitted model output files.

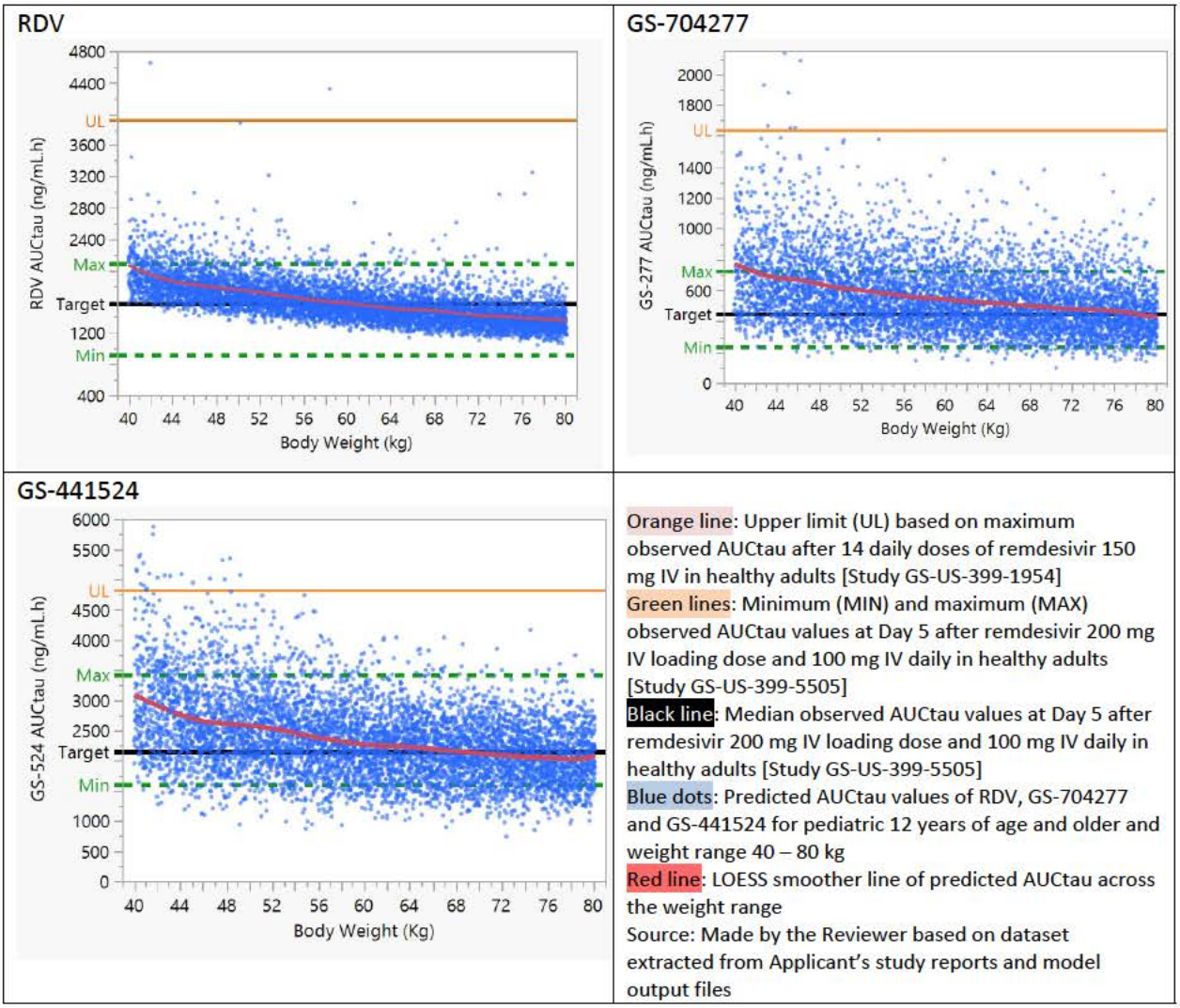
Under the proposed dosing regimen, the PBPK modeling for RDV was used to predict adolescent steady-state AUC (=AUCtau) values for RDV, GS-441524 and GS-704227. For RDV and metabolites, the target AUCtau range was based on a representative range of observed exposures in healthy adults after administration of the therapeutic dosing regimen: 200 mg IV loading dose and 100 mg IV daily maintenance doses [Study GS-US-399-5505]. As shown in Figure 8, the predicted steady-state AUCs for RDV and metabolites in adolescents (red line) were generally comparable to the median adult exposure (black line) and within the maximum and minimum range (green dashed lines), following the therapeutic dosing regimen.

The PBPK model predictions showed that exposures to RDV and metabolites tended to be higher for adolescents in the lower body weight range (Figure 8). Nonetheless, most predicted exposures were within the variability (maximum and minimum range) observed in adults following the therapeutic dosing regimen, and below the pre-defined upper limit of exposure (see below).

The Applicant considered it important to keep RDV and metabolites exposure at or below that previously observed after administration to healthy adults of a higher maintenance dose regimen: 150 mg IV daily for 14 days [Study GS-US-399-1954]. The maximum observed adult steady-state exposures to RDV, GS-704277 and GS-441524 were set as the upper limit of exposure for pediatric dose selection (orange line).

Based on the target exposure ranges for RDV, GS-704277 and GS-441524, the Applicant's proposed dose regimen of RDV for pediatric subjects 12 years of age and older and weighing at least 40 kg is reasonable.

Figure 8. Predicted plasma AUC by bodyweight profile for RDV, GS-704277 and GS-441524 following RDV therapeutic dosage regimen (200 mg IV loading dose and 100 mg IV daily maintenance dose) to pediatric subjects 12 years of age and older and weighing at least 40 kg.



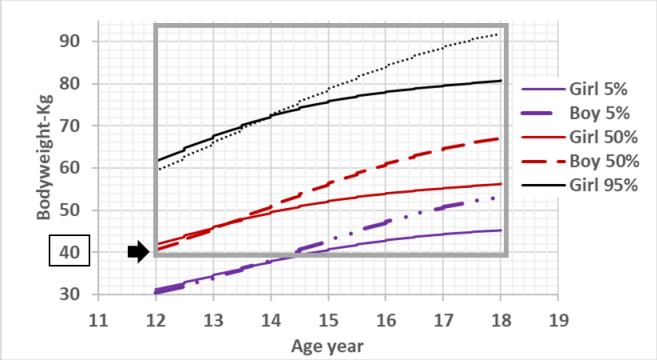
Orange line: Upper limit (UL) based on maximum observed AUCtau after 14 daily doses of remdesivir 150 mg IV in healthy adults [Study GS-US-399-1954]
Green lines: Minimum (MIN) and maximum (MAX) observed AUCtau values at Day 5 after remdesivir 200 mg IV loading dose and 100 mg IV daily in healthy adults [Study GS-US-399-5505]
Black line: Median observed AUCtau values at Day 5 after remdesivir 200 mg IV loading dose and 100 mg IV daily in healthy adults [Study GS-US-399-5505]
Blue dots: Predicted AUCtau values of RDV, GS-704277 and GS-441524 for pediatric 12 years of age and older and weight range 40 – 80 kg
Red line: LOESS smoother line of predicted AUCtau across the weight range
Source: Made by the Reviewer based on dataset extracted from Applicant's study reports and model output files

Reviewer's comment:

The Reviewer noted that 40 kg is the approximate median body weight of a 12-year-old boy or girl[2]. Figure 9 shows the Weight-for-age distribution for adolescents aged 12-18 years. As shown, the proposed minimum body weight threshold of 40 kg includes most adolescents, except those who are under 14 years of age and around the 5th percentile of the population.

[2] https://www.cdc.gov/growthcharts/clinical_charts.htm

Figure 9. Weight-for-age distribution for adolescents aged 12-18 years.



Source: Made by the Reviewer based on CDC growth chart available at https://www.cdc.gov/growthcharts/clinical_charts.htm

Conclusions

The Reviewer acknowledges the current PBPK modeling for RDV has limitations regarding model structure and metabolic pathways involved in RDV and metabolites disposition. However, the model included reasonable assumptions and provided a reasonable description of RDV and plasma metabolites disposition. Thus, the PBPK modeling for RDV was considered adequate to predict the plasma PK profiles of RDV, GS-704277 and GS-441524 in adults following a 200 mg IV loading dose on Day 1 followed by 100 mg IV daily maintenance doses

PBPK analysis showed that the changes in the age-dependent physiological parameters are not expected to significantly impact the plasma PK profiles of RDV, GS-704277 and GS441524 for pediatric patients 12 years of age and older and weighing at least 40 kg. The applicability of the proposed PBPK modeling approach for the intended purpose -scale from adults to adolescents- was considered reasonable. Thus, the modeling is adequate to provide support for simulations of plasma PK profiles of RDV and metabolites GS-704277 and GS-441524 in pediatric patients 12 years of age and older and weighing at least 40 kg.

Based on the target exposure ranges for RDV, GS-704277 and GS-441524 observed in healthy adults [Study GS-US-399-5505], the Applicant's proposed dosing regimen of RDV in this pediatric population is reasonable.

4.4 Pharmacometrics Review

Summary of Pharmcometric Finding

The applicant is seeking a label for Remdesivir (RDV) with approved dosing down to 12 years of age. However, no clinical efficacy and PK data have been collected in adolescents. The approval pathway in pediatrics is extrapolation of efficacy to adults based on exposure matching between adolescents and adults. The applicant performed a Population PK (PPK) analysis to characterize the PK of RDV and its two metabolites in healthy volunteers and performed simulations with this model to determine the expected exposure range of these moieties in adolescents after receiving the same dosing regimen as in adults (200 mg on Day 1 and 100 mg QD thereafter). The reviewer has confirmed the applicant's results and found their model to be a reasonable start for projecting PK into adolescents. A phase 2/3 study is planned, by the applicant, and agreed upon by the agency for children <18 years of age to establish PK and supportive efficacy information. Some pediatric safety data are available from a compassionate use program in patients with Ebola. Data were available for 25 subjects between 5 and 18 years of age and 16 subjects less than 5 years of age.

Results of Sponsors Population PK Analysis

The applicant's PPK Model was developed using healthy adult data from studies GS-US-399-1812, GS-US-399-1954, and GS-US-399-5505. On average 24 samples per subject were included in the analysis from 123 subjects with a total of 2967 samples per analyte included.

Summary statistics of baseline demographics for each study are shown in Table 21 and Table 21. Observed concentrations of RDV and its two metabolites from each study are depicted in Figure 10.

Table 20. Summary Statistics of Continuous Covariates in RDV, GS-704277, and GS-441524 Sequential PPK Analysis.

Covariate	Statistics	GS-US-399-1812 (N = 85)	GS-US-399-1954 (N = 198)	GS-US-399-5505 (N = 179)	Total (N = 477)
Age (years)	Mean (SD)	43.9 (8.52)	42.9 (11.6)	33.5 (6.43)	41.3 (9.54)
	Median [Min, Max]	47.0 [24.0, 55.0]	46.5 [19.0, 55.0]	31.0 [24.0, 44.0]	42.0 [19.0, 55.0]
WT (kg)	Mean (SD)	76.6 (10.6)	74.9 (11.4)	79.9 (11.2)	77.2 (10.9)
	Median [Min, Max]	76.0 [58.7, 101]	73.8 [55.0, 91.0]	80.9 [52.9, 99.6]	76.5 [52.9, 101]
BMI (kg/m^2)	Mean (SD)	26.8 (2.41)	27.1 (2.57)	24.9 (3.17)	26.4 (2.73)
	Median [Min, Max]	27.3 [21.6, 30.2]	28.0 [20.6, 31.8]	24.3 [19.6, 30.4]	26.9 [19.6, 31.8]
BSA (m^2)	Mean (SD)	1.89 (0.170)	1.86 (0.206)	1.99 (0.165)	1.91 (0.178)
	Median [Min, Max]	1.90 [1.57, 2.27]	1.84 [1.48, 2.13]	2.00 [1.54, 2.24]	1.91 [1.48, 2.27]
BCLCR (mL/min)	Mean (SD)	115 (17.3)	116 (21.3)	123 (21.9)	117 (19.1)
	Median [Min, Max]	114 [87.1, 172]	109 [94.4, 166]	122 [88.6, 165]	115 [87.1, 172]

BCLCR = baseline creatinine clearance; BMI = body mass index; BSA = body surface area; max = maximum; min = minimum; N = number of subjects; PopPK = population pharmacokinetic; RDV = remdesivir (GS-5734™); WT = body weight

(Source: Applicant's Population PK Report, Table 5)

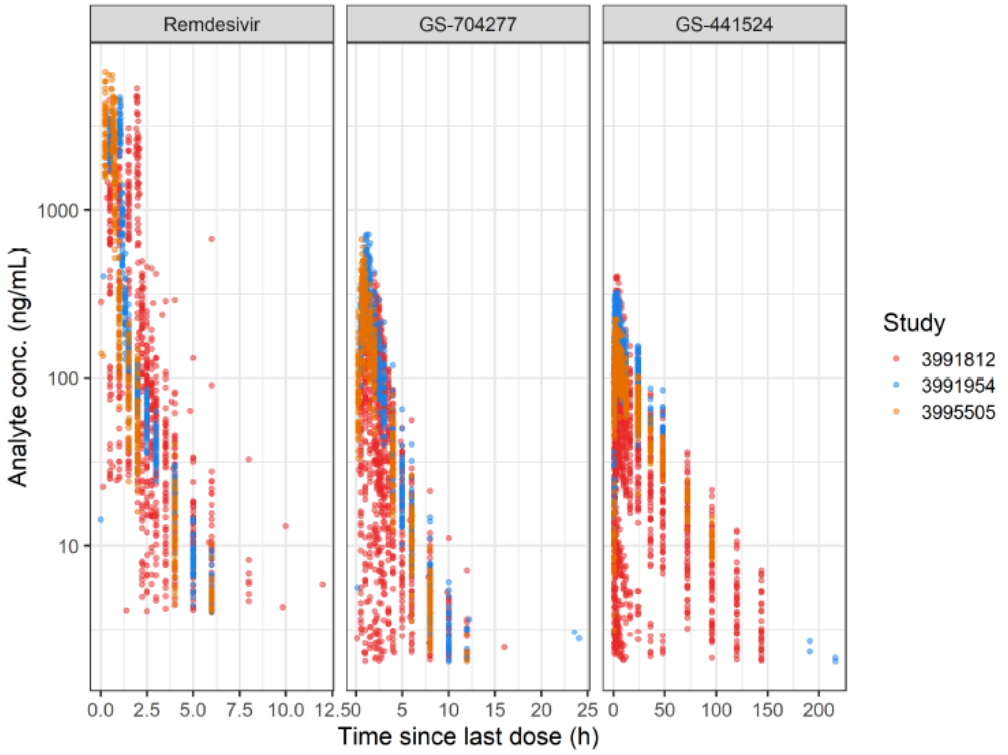
Table 21. Summary Statistics of Categorical Covariates Used in RDV, GS-704277, and GS-441524 Sequential PPK Analysis.

Covariate	Statistics	GS-US-399-1812 N (%)	GS-US-399-1954 N (%)	GS-US-399-5505 N (%)	Total N (%)
Sex	Male	47 (60.3%)	9 (56.2%)	24 (82.8%)	80 (65.0%)
	Female	31 (39.7%)	7 (43.8%)	5 (17.2%)	43 (35.0%)
Race	White	69 (88.5%)	15 (93.8%)	17 (58.6%)	101 (82.1%)
	Black	9 (11.5%)	1 (6.2%)	11 (37.9%)	21 (17.1%)
	Asian	0 (0%)	0 (0%)	1 (3.4%)	1 (0.8%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity	Hispanic	76 (97.4%)	16 (100%)	1 (3.4%)	93 (75.6%)
	Non-Hispanic	2 (2.6%)	0 (0%)	28 (96.6%)	30 (24.4%)

N = number of subjects; PopPK = population pharmacokinetic; RDV = remdesivir (GS-5734™)

(Source: Applicant's Population PK Report, Table 6)

Figure 10. RDV, GS-704277, and GS-441524 Concentration-Time After Dose Profiles for Healthy Volunteers.



conc = concentration; HVs = healthy volunteers; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)
Each circle represents an individual PK observation for RDV (left), GS-704277 (middle), and GS-441524 (right), with red circles for Study GS-US-399-1812, blue circles for Study GS-US-399-1954, and yellow circles for Study GS-US-399-5505.

(Source: Applicant's Population PK Report, Figure 2)

Reviewer's Comments: The applicant's demographics are reasonable for capturing allometric relationships in adults (53 – 101 kg weight range). There is some overlap with the pediatric patient population weight range. Projections down to 12-years old will rely on the consistent use and experience of allometric relationships across pediatric PK in general.

With regards to renal function, Table 20 indicates CRCL generally above 87 mL/min in the pop PK population. Thus, there is not adequate information (i.e. sufficient range of CrCL values) to evaluate the PK in patients with any degree of renal impairment. The lack of significant effect on baseline CrCL is not sufficient to suggest no dosage adjustment in patients with mild renal impairment.

Text that is shaded gray refers to material copied from the applicant's population PK report.

Stepwise Covariate Modeling (SCM)

Based on the covariate screening, the following covariates were included in the stepwise covariate analysis for each sequential model of each analyte:

For RDV:

- CL-RDV: WT, age, sex, race, ethnicity, dose, formulation, infusion duration, and BCLCR
- V1-RDV: WT, age, sex, race, ethnicity, dose, formulation, and infusion duration
- V2-RDV: WT
- Q1-RDV: WT
- F1: formulation

For GS-704277:

- CL-GS-704277: WT, age, sex, race, ethnicity, dose, formulation, infusion duration, and BCLCR
- V1-GS-704277: WT, age, sex, race, ethnicity, dose, formulation, and infusion duration
- V2-GS-704277: WT
- Q1-GS-704277: WT

For GS-441524:

- CL-GS-441524: WT, age, sex, race, ethnicity, dose, formulation, infusion duration, and BCLCR
- V1-GS-441524: WT, age, sex, race, ethnicity, dose, formulation, and infusion duration
- V2-GS-441524: WT
- Q1-GS-441524: WT
- V3-GS-441524: WT
- Q2-GS-441524: WT

Stepwise Forward Addition and Backward Elimination

For RDV, the forward addition resulted in a full model and backward selection did not remove any of the included covariates (Table 22). Next, fixed allometry was explored. Inclusion of fixed allometry was

found to reduce the objective function by 60 points compared to the model selected following SCM. This improvement of the overall fit of the model with no additional df was considered superior and was therefore retained in the model for RDV.

Although deemed significant during the covariate analysis, BCLCR on CL-RDV was found to be insignificant after the inclusion of allometric WT exponents. The BCLCR removal resulted in an objective function increase of 2 OFV points. This reduction in impact is reasonable given the correlation of WT with BCLCR and the relatively narrow range of BCLCR in HVs. The BCLCR was therefore removed from the model. Subject ethnicity impacted CL-RDV by only 12.7% and was therefore removed due to clinical irrelevance (< 20% effect).

Table 22. Summary of Remdesivir SCM.

Reference Model	Covariate Relation	Δdf	OFV	P-Value
Forward model	—	—	10096	(reference)
	−CL-RDV (BCLCR)	−1	10107	0.000638
	−CL-RDV (ETH)	−1	10111	0.000081

Δdf = delta degrees of freedom; BCLCR = baseline creatinine clearance; ETH = ethnicity; CL = clearance; OFV = objective function value; p = p-value between the new model and the reference model; RDV = remdesivir (GS-5734™); SCM = stepwise covariate modeling.

(Source: Applicant's Population PK Report, Table 8)

For GS-704277, after the forward addition step, dose, formulation, and WT were selected as covariates; however, formulation was removed in the backward elimination step (Table 23). After the SCM was completed, fixed allometry was explored. Inclusion of fixed allometry was found to reduce the objective function by 4 points compared to the SCM model, improving the overall fit of the model and reducing the df by 1. Fixed allometry was therefore retained in the model for GS-704277.

Although dose was deemed significant during the covariate analysis, the range (1.3 to 225 mg) explored was broad, expanding outside potential clinical interest. After further exploration, it was found that dose had only a minor effect of approximately 13.6% in the dose range of potential clinical interest (between 30 and 225 mg). Dose was therefore removed from the GS-704277 sequential model as a clinically irrelevant covariate (< 20% effect).

Table 23. Summary of GS-704277 SCM.

Reference Model	Covariate Relation	Δdf	OFV	P-Value
Forward/backward model	—	—	18789	(reference)
	−CL-GS-704277(DOSE)	−1	18828	3.32e-010
	−V1-GS-704277 (WT)	−1	18801	0.000552

Δdf = delta degrees of freedom; BCLCR = baseline creatinine clearance; CL = clearance; OFV = objective function value; p = p-value between the new model and the reference model; SCM = stepwise covariate modeling; V1 = central volume of distribution; WT = body weight

(Source: Applicant's Population PK Report, Table 9)

For GS-441524, during the forward addition step, age, BCLCR, ethnicity, WT, and sex were selected, and backward elimination removed age (Table 24).

Fixed allometry was explored from the SCM model. Inclusion of fixed allometry was found to worsen the objective function by 20 points compared to the SCM model. This was accompanied with a reduction of 1 degree of freedom, making this impact just above the backward elimination criteria. Despite this, the allometric GS-441524 model was accepted based on the following rationale:

1) RDV and GS-704277 models included allometry, and the fits were improved in these model scenarios.
2) The worsening of fit was relatively small utilizing allometry in GS-441524 versus having the model from the SCM in which the WT parameter was selected only on the second intercompartmental clearance parameter. The allometric form of the model has a physiological basis.
3) One of the intended uses of the model is for pediatric scaling simulations to estimate analyte exposures. A broadly accepted parsimonious form of body size in the final PPK model is preferable.

This decision in the GS-441524 model allowed all analytes to be allometrically scaled in the final model.

Once the allometric form of the GS-441524 model was selected, the other covariates selected in the SCM search were found to have reduced significance. The remaining covariates were tested for removal by order of least impact to greatest impact on the PPK model. The significance of BCLCR on CL was reduced to below acceptance criteria (approximately 5 OFV points) and was removed first. After the removal of BCLCR on CL, sex on V1 was next removed due to lack of significance (approximately 6 OFV points). The final non-WT covariate remaining in the model was Hispanic ethnicity. While this parameter had an impact of 24% on elimination CL based on the IIV structure included in the SCM (diagonal matrix), the magnitude of the effect was optimized near approximately 0 upon testing a block structure for IIV. Due to this, the ethnicity parameter was also removed. It is conceded that ethnicity might have some impact on both RDV and GS-441524; the impact is likely no more than 25% and will be re-evaluated when additional data are available.

Table 24. Summary of GS-441524 SCM.

Reference Model	Covariate Relation	Δdf	OFV	P-Value
Forward/backward model	—	—	30643	(reference)
	−CL-GS-441524 (BCLCR)	−1	30665	0.000004
	−CL-GS-441524 (ETH)	−1	30670	2.18e-007
	−Q1- GS-441524(WT)	−1	30684	1.63e-010
	−V1-GS-441524 (SEXF)	−1	30659	0.000090
	−V3- GS-441524(WT)	−1	30674	2.75e-008

Δdf = delta degrees of freedom; BCLCR = baseline creatinine clearance; CL = clearance; ETH = ethnicity; OFV = objective function value; p = p-value between the new model and the reference model; Q1 = apparent intercomparmental clearance; SCM = stepwise covariate modeling; SEXF = sex; V1 = apparent central volume of distribution; V3 = second apparent peripheral compartment; WT = body weight

(Source: Applicant's Population PK Report, Table 10)

Reviewer's Comments: The applicant's decisions to retain fixed allometric exponents versus fitted is critical for extrapolation into pediatrics. For the purposes of extrapolation it is good that the objective function values were lower with the fixed allometric relationships compared to the fitted ones as this is consistent with other pediatric PK and dosing experience in adolescents.

Final Population PK Model

Table 25 provides the final parameter estimates and standard errors associated with the final PPK model. Inclusion of fixed allometry resulted in reduction in IIV between 1% and 9% across analytes or remained unchanged as compared to the base model.

Model diagnostics are shown in Figure 11 and Figure 12. The applicant utilized normalized prediction distribution errors (NPDEs) for the full model that utilized the m3 method for data that were below the limit of quantification, Figure 11. Standard goodness-of-fit plots are shown in Figure 12 for the final model fitting without using the m3 method.

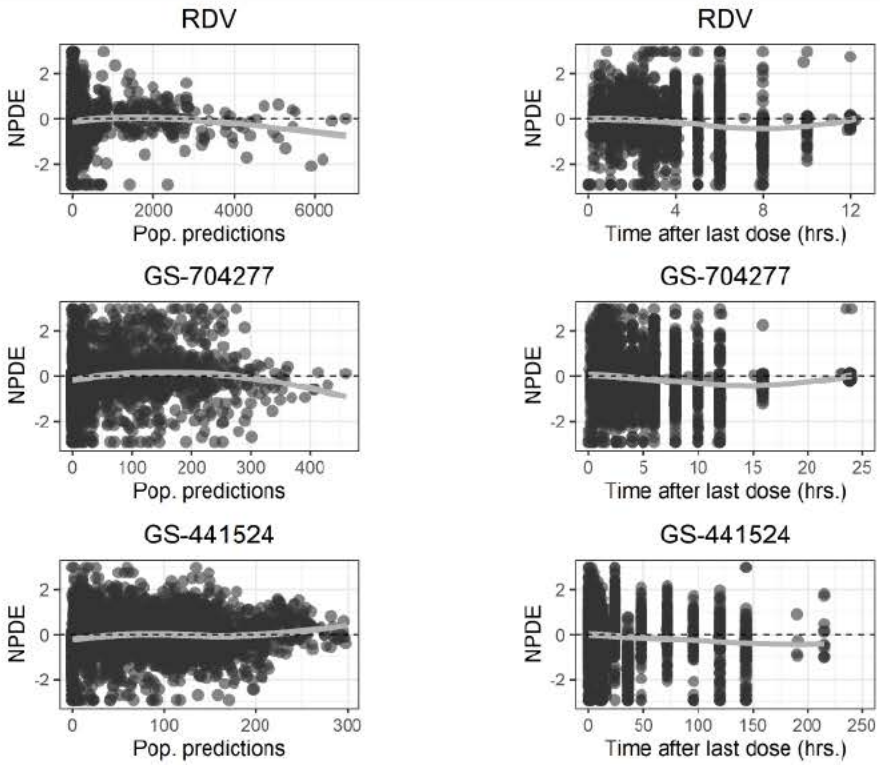
Table 25. Summary of Sequential Final Model PK Parameters for RDV, GS-704277, and GS-441524.

Parameter - Model	Parameter Description	Population Estimate [RSE%]
θ_1 - RDV	Clearance RDV (L/h)	48.2 [2%]
θ_2 - RDV	Central volume RDV (L)	6.34 [3%]
θ_3 - RDV	Peripheral volume RDV (L)	6 [4%]
θ_4 - RDV	Intercompartment clearance RDV (L/h)	5.04 [4%]
θ_1 - GS-704277	Clearance GS-704277 (L/h)	210 [3%]
θ_2 - GS-704277	Central volume GS-704277 (L)	242 [3%]
θ_3 - GS-704277	Peripheral volume GS-704277 (L)	46 [6%]
θ_4 - GS-704277	Intercompartment clearance GS-704277 (L/h)	20.5 [9%]
θ_1 - GS-441524	Clearance GS-441524 (L/h)	17.6 [2%]
θ_2 - GS-441524	Central volume GS-441524 (L)	104 [5%]
θ_3 - GS-441524	First peripheral volume GS-441524 (L)	236 [5%]
θ_4 - GS-441524	Intercompartment clearance to first periph. cmt. GS-441524 (L/h)	379 [6%]
θ_9 - GS-441524	Second peripheral volume GS-441524 (L)	233 [4%]
θ_{10} - GS-441524	Intercompartment clearance to second periph. cmt. GS-441524 (L/h)	31.6 [6%]
ω^2_{11} - RDV	IIV on CL-RDV (%CV)	15% [28%]
ω^2_{22} - RDV	IIV of Vc-RDV (%CV)	32% [69%]

Parameter - Model	Parameter Description	Population Estimate [RSE%]
ω^2_{33} - RDV	IIV of Vp-RDV (%CV)	15% [31%]
ω^2_{11} - GS-704277	IIV on CL-GS-704277 (%CV)	32% [18%]
ω^2_{21} - GS-704277	Correlation CL/Vc GS-704277	0.113 [17%]
ω^2_{22} - GS-704277	IIV of Vc-GS-704277 (%CV)	39% [17%]
ω^2_{33} - GS-704277	IIV of Vp-GS-704277 (%CV)	26% [28%]
ω^2_{11} - GS-441524	IIV on CL-GS-441524 (%CV)	24% [20%]
ω^2_{21} - GS-441524	Correlation CL/Vc GS-441524	0.0527 [36%]
ω^2_{31} - GS-441524	Correlation CL/Vp1 GS-441524	0.0872 [20%]
ω^2_{22} - GS-441524	IIV of Vc-GS-441524 (%CV)	45% [19%]
ω^2_{32} - GS-441524	Correlation Vc/Vp1 GS-441524	0.0356 [75%]
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524 (%CV)	43% [18%]
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524 (%CV)	25% [21%]
sqrt(θ_5) - RDV	Proportional residual error - RDV (%CV)	45% [1%]
θ_6 - RDV	Additive residual error - RDV (ng/mL)	0.884 [11%]
sqrt(θ_5) - GS-704277	Proportional residual error - GS-704277 (%CV)	44% [1%]
θ_6 - GS-704277	Additive residual error - GS-704277 (ng/mL)	0.604 [5%]
sqrt(θ_7) - GS-441524	Proportional residual error - GS-441524 (%CV)	31% [0%]
θ_8 - GS-441524	Additive residual error - GS-441524 (ng/mL)	0.511 [16%]

θ = absolute value of the estimate; %CV = percentage coefficient of variation; IIV = interindividual variability; OFV = objective function value; periph. cmt. = peripheral compartment; PK = pharmacokinetic; RDV = remdesivir (GS-5734™); RSE = relative standard error.
Minimum OFV = 30760.

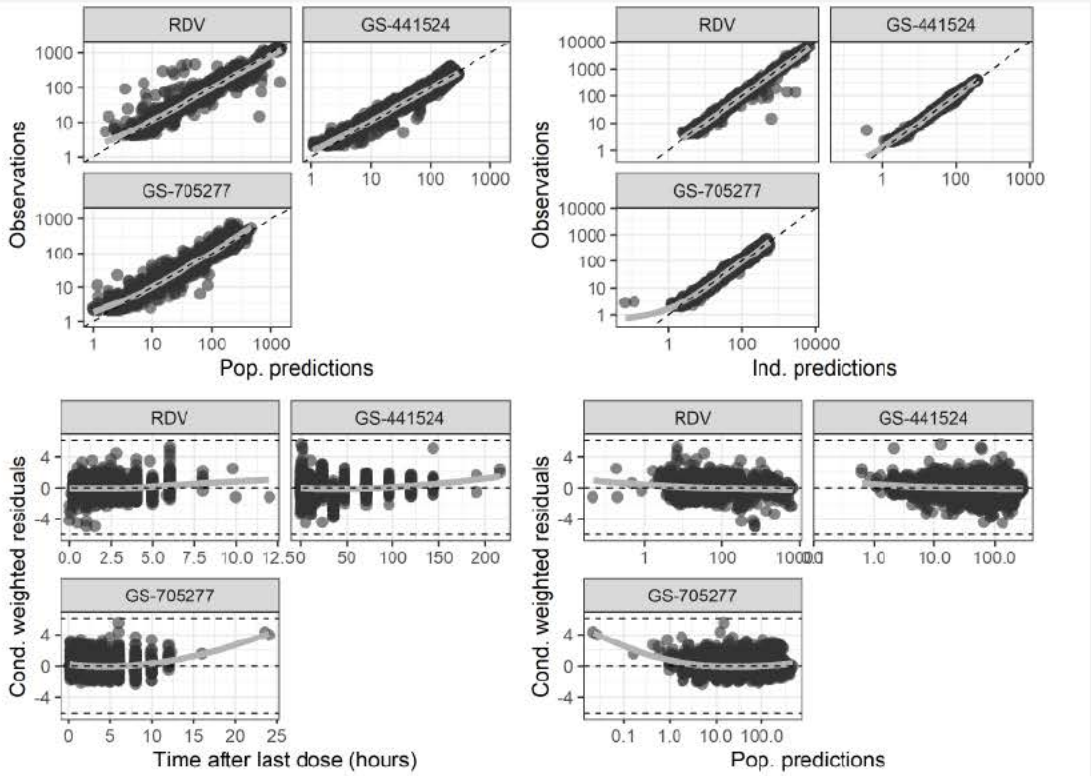
Figure 11. NPDEs of the Final Sequential RDV, GS-704277, and GS-441524 PPK Model.



NPDE = normalized prediction distribution error; Pop. = population; PopPK = population pharmacokinetic; RDV = remdesivir (GS-5734™)
NPDE versus population predictions (left) and time after last dose (right) for RDV (upper), GS-704277 (middle), and GS-441524 (lower) are presented in the plots. Points are individual NPDE. The gray line is the lowess smooth curve.

(Source: Applicant's Population PK Report, Figure 4)

Figure 12. Standard Goodness-of-Fit Plots for Joint Simultaneous Model for RDV, GS-704277, and GS-441524 PPK Model without M3 method.



CWRES = conditional [cond.] weighted residuals; Ind. = individual; Pop. = population; PopPK = population pharmacokinetic; RDV = remdesivir (GS-5734™)
The circles represent individual data points; the gray lines represent lowess smooth curves; and the dashed lines represent either the line of unity (y = x), the unity line at 0 (y = 0), or a CWRES of 6.

(Source: Applicant's Population PK Report, Figure 31)

Reviewer's Comments: The applicant's PPK model for RDV and its two metabolites is acceptable for descriptive labeling and projecting exposures in children down to 12 years of age. Normalized prediction distributions were utilized for diagnostics in place of the standard goodness-of-fit plots for the final model run that utilized M3. These plots and goodness-of-fit plots for the final model without m3 show good distribution about zero or the line of identity suggesting low model misspecification or bias. Additionally, RSE and ETA shrinkage values were generally low (< 10% RSE for fixed effects, <35% RSE for inter-patient variability, and <25% for shrinkage values), providing reassurance in model estimates.

Simulations for Pediatric Patients and Comparison to PBPK Model

The final PPK models were used to simulate the expected exposures (ie, AUCtau, Cmax, and observed drug concentration at the end of the dosing interval [Ctau]) in pediatric subjects for all 3 analytes at Day 1 and Day 5 following the proposed adult and pediatric dosing regimens for RDV. The simulated regimens (with infusion time of 30 minutes) were 200 mg on Day 1 and 100 mg once daily on subsequent days for subjects ≥ 40 kg, or 5 mg/kg on Day 1 and 2.5 mg/kg once daily on subsequent days for subjects < 40 kg. The results of the simulations were compared to observed exposure summaries from Study GS-US-399-5505 in HV and to PBPK predictions {Lutz 2020}. While the PBPK and observed

exposures in Study GS-US-399-5505 were overlaid on the PPK allometric predictions, it should be noted that the population analysis considered exposures from pooled data including Studies GS US-399-1812, GS-US-399-1954, and GS-US- 399-5505.

The results are presented in Figure 3 and Figure 4 and for C_{max} and AUC_{tau} , respectively, for all analytes and in Figure 5 for C_{tau} for GS-441524.

Reviewer's Comments: The population PK model projections to adolescents appear to be in line with those of the PBPK predictions for those subjects ≥40 kg. These projections suggest the exposures are at least that of the adults and mostly within the adult range for subjects ≥40 kg. These data support the approval of RDV from an efficacy perspective.

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