CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	214787
Priority or Standard	Priority
Submit Date(s)	August 7, 2020
Received Date(s)	August 7, 2020
PDUFA Goal Date	April 7, 2021
Division/Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)	Kirk Chan-Tack, MD
Review Completion Date	September 16, 2020
Established Name	Remdesivir (RDV)
(Proposed) Trade Name	Veklury®
Applicant	Gilead Sciences, Inc.
Formulation(s)	Lyophilized formulation for injection, 100 mg Solution formulation for injection, 5 mg/mL
Dosing Regimen	Single intravenous (IV) loading dose of remdesivir 200 mg on Day 1 followed by 100 mg IV once-daily maintenance doses for a total of up to 10 days of dosing
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg hospitalized for coronavirus disease 2019 (COVID-19)

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Glossary

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BRF	Benefit Risk Framework
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
CSR	clinical study report
DAA	direct acting antiviral
DAIDS	Division of AIDS
DSMB	data and safety monitoring board
DDI	drug-drug interaction
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation

eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IND	Investigational New Drug
IMV	invasive mechanical ventilation
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NME	new molecular entity
OR	odds ratio
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PBO	placebo
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamics
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetic
PPI	patient package insert
PREA	Pediatric Research Equity Act
PT	Preferred Term (aka Dictionary Derived Term)
QD	once daily
RDV	remdesivir
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 (2019 novel coronavirus)
SAS	Safety Analysis Set
SBECD	sulfobutylether-β-cyclodextrin sodium salt
SOC	system organ class
SpO2	oxygen saturation
US	United States
WHO	World Health Organization

Executive Summary

1.1. Product Introduction

Veklury® (remdesivir, RDV) is a nucleotide prodrug that is intracellularly metabolized into its active form GS-441524, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis. RDV is a new molecular entity (NME).

The Applicant's proposed indication is (b) (4) The Applicant's recommended dosage for adults and pediatric patients 12 years of age and older and weighing at least 40 kg is a single loading dose of Veklury® 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of Veklury® 100 mg from Day 2 via intravenous infusion.

- The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
- The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or ECMO is 10 days.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from the ACTT-1, GS-US-540-5773 and GS-US-540-5774 Phase 3 trials included in this application provide substantial evidence of effectiveness as required by law 21 CFR 314.126(a)(b) to support approval of RDV for treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg hospitalized for COVID-19.

In ACTT-1, RDV was significantly superior to placebo (PBO) in reducing the time to recovery (median days to recovery: RDV 10 days vs. PBO 15 days) in 1,062 hospitalized subjects with mild, moderate and severe COVID-19. In Study GS-US-540-5773, treatment with 5-day and 10-day regimens of RDV resulted in similar clinical status on Day 14 in 397 hospitalized subjects with severe COVID-19. In Study GS-US-540-5774, treatment with 5-days of RDV resulted in significantly greater odds of improved clinical status on Day 11 compared to standard of care in 584 hospitalized subjects with moderate COVID-19. Cumulatively, these data support RDV for treatment of COVID-19 in hospitalized subjects, irrespective of oxygenation status or oxygen requirement.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Remdesivir (RDV) is an intravenous (IV) antiviral with a proposed indication (b) (4) RDV is a nucleotide prodrug that is intracellularly metabolized into its active form GS-441524, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis.

COVID-19 is a potentially serious or life-threatening disease caused by SARS-CoV-2 virus. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Globally, according to the WHO, 28,584,158 confirmed cases of COVID-19 have been reported as of September 13, 2020, including 916,955 deaths. In the US, according to the Centers for Disease Control and Prevention (CDC), 6,467,481 cases of COVID-19 have been reported with 193,195 deaths as of September 13, 2020. There are no approved treatments for COVID-19.

In ACTT-1, RDV was superior to placebo (PBO) in reducing the time to recovery (median days to recovery: RDV 10 days vs. PBO 15 days). In Study GS-US-540-5773, treatment with 5-day and 10-day regimens of RDV resulted in similar clinical status on Day 14. In Study GS-US-540-5774, treatment with 5-days of RDV resulted in significantly greater odds of improved clinical status on Day 11 compared to standard of care. Cumulatively, these data support RDV for treatment of COVID-19 in hospitalized adults.

The Agency concluded that it was appropriate to include an indication for RDV for the treatment of COVID-19 in hospitalized adolescents ≥ 12 years of age and weighing ≥ 40 kg through extrapolation of efficacy from adults receiving the same dose of RDV as proposed for adolescent patients. This decision was based on the following rationale: (1) adult and pediatric patients with moderate-to-severe COVID-19 display similar symptoms; (2) virologic response to an antiviral drug such as RDV is expected to be similar in adults and pediatric patients; (3) historical concordance of adult and adolescent dosing regimens observed for other drugs; (4) the physiologically based pharmacokinetic model and the population pharmacokinetic model supported use of the adult dose above the 40 kg weight cutoff; and (5) the finding in the RDV Phase 3 clinical trials that the safety in adult subjects weighing 40-50kg (i.e. encompassing weight ranges that are observed in adolescents) was similar to adult subjects weighing >50kg.

Hypersensitivity reactions and hepatotoxicity were the major safety issues identified in this review. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of RDV. Clinical manifestations have included hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and

shivering. The Warnings and Precautions section will provide wording that clearly describes the hypersensitivity reactions that have been observed for RDV.

A hepatotoxicity safety signal was clearly demonstrated in trials in healthy subjects, and transaminase elevations have been reported in patients with COVID-19 in clinical trials, in the EUA population, and in published literature; however, the interpretation of cases in the setting of COVID-19 is challenging. Additionally, pharmacokinetic data in the setting of renal or hepatic impairment are not available, and drug exposures could be elevated in these settings, increasing the potential risk of adverse reactions, including hepatotoxicity. The Warnings and Precautions section will provide wording that clearly describes the hepatotoxicity safety signal that has been observed for RDV.

In ACTT-1, disproportionately higher rates of prothrombin time elevations occurred with RDV compared to PBO. This information will be described in labeling, outlining that prothrombin time should be determined prior to starting RDV and monitored while receiving RDV.

Concomitant use of RDV and chloroquine phosphate (CQ) or hydroxychloroquine sulfate (HCQ) is not recommended based on cell culture data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of RDV. The Warnings and Precautions section will provide wording that clearly describes that concomitant use of RDV with CQ or HCQ is not recommended due to the risk of reduced antiviral activity of RDV.

Approval of RDV for treatment of hospitalized adults and pediatric patients ≥ 12 years of age and weighing ≥ 40 kg is supported by the available efficacy and safety data. The recommended dosage is a single loading dose of RDV 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of RDV 100 mg from Day 2 via intravenous infusion. The duration of therapy should be guided by the severity of the infection and the patient's clinical response as follows:

(1) The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
(2) The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or ECMO is 10 days.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Coronavirus disease 2019 (COVID-19) is a potentially serious or life-threatening disease caused by SARS-CoV-2 virus. COVID-19 can cause severe disease which can result in	The ongoing COVID-19 pandemic is a significant and growing public

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pneumonia, respiratory failure, multi-organ failure, and death. • Globally, 28,584,158 confirmed cases of COVID-19 have been reported as of September 13, 2020, including 6,467,481 people in the United States (US). • Globally, 916,955 deaths due to COVID-19 have been reported as of September 13, 2020, including 193,195 deaths in the United States (US).	health concern, one that affects a large population in the US and worldwide. When infected with SARS-CoV-2, patients can experience symptoms that are severe, debilitating, and can be fatal.
Current Treatment Options	• There are no approved treatments for COVID-19. • Due to the mortality and severe morbidity associated with COVID-19, there is an urgent need to develop effective treatments.	An unmet medical need exists for effective antiviral regimens for patients who develop COVID-19.
Benefit	• The efficacy of RDV was established in three Phase 3 clinical trials which cumulatively evaluated 1322 hospitalized subjects in the RDV treatment arms. The trial populations varied based on disease severity. o ACTT-1: Randomized, double-blind, placebo-controlled, multicenter trial assessing the safety and antiviral efficacy of RDV for treatment of COVID-19 in 1062 adults with mild, moderate, and severe disease. Patients received RDV x 10 days or placebo (PBO) x 10 days. o Study 5773 (Part A): Randomized, open-label trial comparing 5-day and 10-day RDV durations in 397 patients with severe COVID-19. o Study 5774 (Part A): Randomized, open-label trial comparing RDV for 5 days, RDV for 10 days, and standard of care in 584 patients with moderate COVID-19. • ACTT-1 showed that hospitalized patients with COVID-19 and lower respiratory tract involvement who received RDV had a statistically significant faster time to recovery compared to patients who received PBO (10 days vs. 15 days; recovery rate ratio = 1.29; 95% CI: 1.12 to 1.49; p<0.001). Overall, results from this large randomized, double-blinded, placebo-controlled trial provided reliable and statistically persuasive evidence of benefit for RDV for the treatment of patients hospitalized with COVID-19.	Three clinical trials provide substantial evidence of effectiveness of RDV x 5-10 days for treatment of hospitalized adult and pediatric patients (≥ 12 years and ≥ 40 kg) with COVID-19: - The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In Study 5773, the primary efficacy analysis was based on a proportional odds assessment of a 7-point ordinal scale at Day 14, with categories ranging from 1=death to 7=discharged alive. For this endpoint, the proportional odds of improvement in a 7-point ordinal scale at Day 14 yielded an estimated odds ratio (on a scale with values less than 1.00 favoring the 5-day duration) of 0.75, with a 95% confidence interval from 0.51 to 1.12. Thus, the numerical trends in this trial were towards slightly improved outcomes in the 5-day group, although this difference was not statistically significant. These results are suggestive of a similar treatment effect with 5-day and 10-day regimens in this population, with appropriate caveats related to the open-label trial design. • In Study 5774, the primary efficacy analysis was based on a proportional odds assessment of a 7-point ordinal scale at Day 11, with categories ranging from 1=death to 7=discharged alive. For this Day 11 endpoint, results were significantly superior in the RDV 5-day group compared with the standard of care group (OR = 1.65; 95% CI; 1.09 to 2.48; p = 0.02). The RDV 10-day group also had favorable numerical trends compared with the standard of care group, but the difference did not reach statistical significance (p = 0.18). • Limitations of the available data preclude a definite determination of the ideal treatment duration for hospital patients. • Overall, demographic factors did not impact efficacy outcomes in these trials. • The pediatric indication for the treatment of COVID-19 in adolescents ≥ 12 years of age and weighing ≥ 40 kg is based on extrapolation of efficacy from adults receiving the same dose of RDV as proposed for adolescent patients.	- The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation (IMV) and/or ECMO is 10 days. There were insufficient patients enrolled into Study 5773 who required IMV or ECMO at baseline to determine if a 5-day course could be adequate for this patient population. RDV fills an important unmet medical need for patients hospitalized with COVID-19.
Risk	• The safety database for RDV includes 1313 subjects from the three aforementioned Phase 3 clinical trials and is considered adequate. • ACTT-1 included a placebo-controlled comparison for safety. • Study 5774 included a standard-of-care group for safety comparison and compared 5-day and 10-day RDV durations.	RDV demonstrated an overall favorable safety profile. Hypersensitivity reactions and hepatotoxicity were the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Study 5773 compared 5-day and 10-day RDV durations. • Hypersensitivity reactions and hepatotoxicity were the major safety issues. • Nausea was were the most commonly reported adverse drug reaction reported across the trials.	major safety issues identified.
Risk Management	• The RDV prescribing information will include the following safety information: o Section 5 of the RDV label will include a warning regarding the risk of hypersensitivity reactions. EUA safety analyses identified a number of cases of hypersensitivity reactions, including infusion-related and anaphylactic reactions. o A Contraindication will be included to describe that RDV is contraindicated in patients with a history of clinically significant hypersensitivity reactions to RDV or any components of the product. o Although rates of Grade 3/4 transaminase elevations were overall lower for RDV compared to PBO in ACTT-1, Section 5 of the RDV label will include a warning regarding the risk of transaminase elevations because transaminase elevations have been observed in healthy volunteers who received the RDV regimen that has been evaluated in the COVID-19 development program, and have also been reported in patients with COVID-19 who received RDV in the Phase 3 trials. o The hepatic safety profile will also be described in Section 6 of the RDV label. o In ACTT-1, rates of prothrombin time elevations were higher for RDV compared to PBO. Given that these elevations may impact management of patients receiving anticoagulants, this information will be described in labeling, outlining that monitoring is recommended while receiving RDV. o ADRs of interest such as hypersensitivity reactions (including infusion-related and anaphylactic reactions), seizures and rash, will be included under Less Common Adverse Reactions.	Safety concerns associated with RDV will be adequately addressed in product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	o Section 5 will include a warning to describe that concomitant use of RDV with chloroquine phosphate or hydroxychloroquine sulfate is not recommended due to the risk of reduced antiviral activity of RDV.	

1.4. Patient Experience Data

Table 1 contains a summary of Patient Experience Data Relevant to this Application.

Table 1. Patient Experience Data Relevant to this Application

√	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	√ Other: (Expanded Access)	13.4
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Coronavirus disease 2019 (COVID-19) can cause severe disease which can result in pneumonia, respiratory failure, multi-organ failure, and death.[1-7]

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Globally, according to the WHO, 28,584,158 confirmed cases of COVID-19 have been reported as of September 13, 2020, including 916,955 deaths.[2] In the US, according to the Centers for Disease Control and Prevention (CDC), approximately 6,467,481 cases of COVID-19 have been reported with 193,195 deaths as of September 13, 2020.[3]

Due to the substantive disease burden from this ongoing pandemic, a specific unmet medical need exists for effective antiviral regimens for subjects who develop COVID-19 caused by SARS-CoV-2 virus because no approved regimens are available.[8-10] RDV would be the first antiviral drug approved to address this unmet medical need.

2.2. Analysis of Current Treatment Options

There are no approved treatment options for COVID-19 disease caused by SARS-CoV-2 virus.

On May 1, 2020, the Agency granted emergency use authorization (EUA) for the investigational antiviral RDV to treat adults and children hospitalized with severe COVID-19. Based on review of the topline data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (ACTT-1; NCT04280705) and from the Gilead-sponsored open-label trial that evaluated different durations of RDV (Study 5773 [Part A]; NCT04292899), the Agency concluded that it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of adult and pediatric patients hospitalized with severe COVID-19 (defined as SpO2 ≤ 94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation).[12] The following revisions were subsequently made to the EUA:

- June 15, 2020: (1) additional clinical information from the ACTT-1[13] and Study 5773 (Part A)[14] publications was included; (2) Warning and Precautions section was modified to describe hypersensitivity and anaphylactic reactions; (3) an additional Warning and Precautions was added to describe drug interaction information about the risk of reduced antiviral activity when RDV is co-administered with chloroquine phosphate (CQ) or hydroxychloroquine sulfate (HCQ).
- July 27, 2020: Added the conditionally acceptable proprietary name, Veklury®.
- August 28, 2020: Based on the results from GS-US-540-5774 (Part A; NCT04292730)[15] and ACTT-1[13], the Agency concluded that the available data supported revising the EUA to expand the scope of the authorized use to include the treatment of all hospitalized patients with symptomatic suspected or laboratory confirmed COVID-19, irrespective of oxygenation status or oxygen requirement.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This is the first marketing application for any product containing RDV, a new molecular entity.

3.2. Summary of Presubmission/Submission Regulatory Activity

This section will summarize and focus only on the notable events which directly impacted the current RDV NDA.

An Investigational New Drug application (IND) for RDV was submitted on February 24, 2020 by Gilead Sciences, Inc. Fast track designation for RDV for treatment of coronavirus disease 2019 (COVID-19) was granted on March 26, 2020.

Clinical protocols and the development plan were reviewed by the Division throughout the RDV development program, with feedback provided regarding issues of efficacy endpoints, dose selection, treatment duration, treatment regimen, and clinical trial population. The final Phase 3 protocol designs later submitted to the Division were determined to be acceptable.

FDA granted the Applicant's request for a rolling review of this NDA on April 6, 2020. The details of the milestone meetings can be found in the official meeting minutes archived in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). All previous reviews can also be accessed in DARRTS for additional information.

3.3. Foreign Regulatory Actions and Marketing History

At the time this review was finalized, the following regulatory actions had occurred:
Table 2. Summary of Foreign Regulatory Actions

Country	Date of Regulatory Action	Regulatory Mechanism	COVID-19 Patient Population
Japan	May 7, 2020	Exceptional Approval (Article 14 (3) of the Pharmaceuticals and Medical Devices Act)	Suspected or laboratory confirmed COVID-19 in adults and children who are hospitalized with severe disease defined as SpO2 ≤ 94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation, or requiring ECMO
India	June 1, 2020	Grant of Permission to Import New Drug for Sale or for Distribution	Suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease
Taiwan	June 2, 2020	Conditional Approval (Pharmaceutical Affairs Act Article 48-2)	Severe disease, defined as SpO2 ≤ 94% without oxygen inhalation, or requiring oxygen inhalation, or under mechanical ventilation, or under ECMO
United Arab Emirates	June 7, 2020	Emergency Use License	Severe patients with SpO2 ≤ 94% (room air), or requiring oxygen inhalation, or under ECMO, or under IMV
Singapore	June 10, 2020	Conditional Approval	Adult patients with SpO2 ≤ 94% (room air), or those requiring oxygen inhalation, or under IMV, or under ECMO

Qatar	June 29, 2020	Emergency Use Authorization	Severe patients with SpO2 ≤ 94% (room air), or requiring supplemental oxygen, or under ECMO, or under IMV
Saudi Arabia	June 29, 2020	Import Approval for Emergency Use	Severe patients with SpO2 ≤ 94% (room air), or requiring oxygen inhalation, or under ECMO, or under IMV
Switzerland	June 30, 2020	Authorization of Temporary Exemption	Adults and adolescents (≥ 12 years with body weight ≥ 40 kg) with pneumonia requiring supplemental oxygen
European Economic Area*	July 3, 2020	Conditional Marketing Authorization	Adults and adolescents (≥ 12 years with body weight ≥ 40 kg) with pneumonia requiring supplemental oxygen
Australia	July 10, 2020	Provisional Approval	Adults and adolescents (≥ 12 years with body weight ≥ 40 kg) with pneumonia requiring supplemental oxygen
Kuwait	July 15, 2020	Emergency Use Authorization	Severe patients with SpO2 ≤ 94% (room air), or requiring supplemental oxygen, or under ECMO, or under IMV
Hong Kong	July 17, 2020	Emergency Use Authorization (Section 8(5) of the Prevention and Control of Disease Ordinance)	Severe patients with SpO2 ≤ 94% (room air), or requiring supplemental oxygen, or under ECMO, or under IMV
South Korea	July 24, 2020	Conditional Approval (Provision 42 of Korean Pharmaceutical Law)	Confirmed COVID-19 by PCR test, etc.; hospitalized patients with severe disease defined as SpO2 ≤ 94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation or requiring ECMO
Canada	July 27, 2020	Notice of Compliance with Conditions	Adults and adolescents (≥ 12 years with body weight ≥ 40 kg) with pneumonia requiring supplemental oxygen
Israel	July 29, 2020	Conditional Approval (Notice of Compliance with Conditions)	Adults and adolescents (≥ 12 years with body weight ≥ 40 kg) with pneumonia requiring supplemental oxygen

SpO2, oxygen saturation; ECMO, extracorporeal membrane oxygenation: IMV, invasive mechanical ventilation
*Includes Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspection sites were selected from ACTT-1, GS-US-540-5773 and GS-US-540-5774 as these contributed to the proposed indication. A total of 5 sites, 3 from ACTT-1 and 2 with overlapping

enrollment in GS-US-540-5773 and GS-US-540-5774, were selected from the large number of sites per study based on enrollment. All sites were domestic, based on logistical considerations during the ongoing pandemic. The 3 sites from ACTT-1 comprised approximately 20% of all enrollment in that trial.

The final reports from the clinical site inspections were pending at the time this review was finalized.

4.2. Clinical Microbiology

This section includes a brief summary of key RDV nonclinical virology characteristics to support clinical trials evaluating RDV.

- RDV is a nucleotide prodrug that is intracellularly metabolized into its active form GS-443902, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis.
- The GS-443902 adenosine nucleotide analog is incorporated into the nascent RNA chain by the coronavirus viral RNA polymerase (nsp12) and evades proofreading by the coronavirus exoribonuclease, resulting in a decrease in coronavirus RNA production (Agostini et al., 2018).[16]
- GS-443902, the active triphosphate form of RDV (RDV-TP), is efficiently incorporated into the nascent RNA strand, and termination of RNA synthesis occurs at position i+3 (PC-540-2005). RDV-TP has a unique property resulting in its high selectivity over incorporation of its natural nucleotide counterpart adenosine triphosphate (PC-540-2005).
- The ratio of Michaelis-Menten steady-state kinetic parameters V_{max}/K_m for a single incorporation of a natural nucleotide over a nucleotide analogue, where a selectivity value lower than 1 indicates the analogue is incorporated more efficiently than the natural NTP and greater than 1 indicates less efficient incorporation than a natural NTP, was used to assess selectivity for RDV-TP incorporation by recombinant SARS-CoV-2 RdRp for single nucleotide incorporations in comparison with ATP. Steady-state kinetic parameters for single nucleotide incorporations of RDV-TP where performed in comparison with ATP. Previously, a selectivity value of 0.35 for RDV-TP incorporation with MERS-CoV RdRp was reported (Gordon et al., 2020).[17] SARS-CoV-2 and SARS-CoV showed selectivity values of 0.26 and 0.32, respectively, indicating that RDV-TP is incorporated more selectively than ATP (PC-540-2005).
- The active site of the betacoronavirus RdRp (nsp12) is conserved despite sequence variations with SARS-CoV and SARS-CoV-2 sharing 96% identity compared to 71% for MERS-CoV-2 compared to SARS-CoV-2 (PC-540-2005).
- The catalytic metal ions in SARS-CoV-2 nsp12 are coordinated by a trio of aspartates, D618, D760, and D761, and the substrate β-phosphate is stabilized by R555. Amino acid residues D623, S682, and N691 are involved in 2'OH recognition of the incoming nucleotide, and these amino acids are conserved across betacoronavirus RdRps (PC-540-2005).
- No amino acid substitutions were observed at any of the conserved amino acid residues in nsp12 that directly interact with the metal ions or RDV-TP or may contribute to the inhibitor's delayed chain termination. Furthermore, a larger set of residues were also considered that are located within 5Å and 10Å from the active site and residues that are located within 7Å of the

primer RNA C1' positions. Only one substitution (A547V) within 10 Å of the active site was observed in one sequence of 1993 clinical isolates investigated (PC-540-2006).

- In the presence of increasing concentrations of UTP the signal at i+3 decreases concomitantly with an increase in the full-length product. UTP concentrations that are ~100-fold higher than RDV-TP can cause significant reductions in delayed chain-termination (PC-540-2005).
- RDV exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment (PC-540-2001). The EC_{50} values of RDV against SARS-CoV-2 in Vero cells was 137 nM at 24 hours and 750 nM at 48 hours post-treatment (PC-540-2001).
- An EC_{50} value of 770 nM in Vero cells has been reported for RDV against SARS-CoV-2 by the Wuhan Institute of Virology (Wang et al., 2020).[18]
- RDV inhibited a recombinant chimeric virus expressing the RdRp gene (nsp12) of SARS-CoV-2 in a backbone of SARS-CoV with a fluorescent reporter protein in Huh7 cells with an EC_{50} value = 3.0 nM (PC-540-2002).
- Cell culture antiviral assessments against other human and animal coronaviruses are summarized below:
    - RDV and GS-466547 (an opposite diastereomer) were tested in cell culture antiviral activity assessments against SARS-CoV and MERS-CoV. RDV and GS-466547 inhibited replication of MERS-CoV in Vero E6 cells with mean EC_{50} values of 0.52 and 0.42 μM, respectively. No cytotoxicity was observed at 10 μM, the highest concentration tested, indicating selective inhibition of virus replication with selectivity indices of >19 and >24, respectively.
    - GS-466547 inhibited SARS-CoV and MERS-CoV replication in human airway epithelial (HAE) cultures as measured by the reduction in the expression of a fluorescent reporter protein at compound concentrations ranging from 0.1 to 1.1 μM.
    - The activity of RDV against SARS-CoV and MERS-CoV was assessed using recombinant viruses expressing a fluorescent reporter protein in a continuous human lung epithelial cell line, 2B4 (Calu-3; MERS-CoV only) and primary HAE cells (SARS-CoV and MERS-CoV). RDV inhibited MERS-CoV replication in Calu-3 cells, with a mean EC_{50} value of 0.025 μM (Sheahan et al., 2017).[19] In HAE cells, RDV inhibited both SARS-CoV and MERS-CoV replication with EC_{50} values of 0.069 and 0.074 μM, respectively. In both HAE and Calu-3 cells, no cytotoxicity was observed at 10 μM of RDV, the highest concentration tested, indicating that RDV has selectivity indices >100 in these cell culture systems (Sheahan et al., 2017).[19]
    - RDV showed cell culture antiviral activity against human betacoronavirus OC43 and alphacoronavirus 229E as well as the animal betacoronavirus murine hepatitis virus and the genetically divergent porcine deltacoronavirus with submicromolar EC_{50} values ranging from 0.02 to 0.15 μM in various cell types (Agostini et al., 2018; Sheahan et al., 2017; Brown et al., 2019).[16, 19, 20]
    - RDV inhibited the replication of SARS-CoV-2 and SARS-CoV with EC_{50} values of 0.0099 μM and 0.0066 μM, respectively, in HAE cells after 48 hours of treatment. No cytotoxicity has been observed for RDV in HAE cells at concentrations up to 10 μM (CC_{50}

value >10μM) (PC-540-2002). The dose response curve of RDV against SARS-CoV-2 exhibited a shallow dose-dependent increase in inhibition compared to the response against SARS-CoV, indicating that RDV may be more active against SARS-CoV. Alternatively, there could be a lag in formation of the active diphosphate partially overcome by higher concentrations due to slow uptake by the cells, slow metabolism of the prodrug to the monophosphate, or a slow phosphorylation step.

- The development of resistance to RDV in coronaviruses has been assessed by cell culture passaging of murine hepatitis virus (MHV), a coronavirus, in the presence of the RDV parent nucleoside, GS-441524. After 23 passages, two substitutions were selected in the nsp12 polymerase at residues conserved across coronaviruses: F476L and V553L (Agostini et al., 2018).[16]
- Compared to wild-type virus, recombinant MHV containing the F476L substitution showed 2.4-fold reduced susceptibility to RDV, and MHV containing the V553L substitution demonstrated 5-fold reduced susceptibility, while the double mutant conferred 5.6-fold reduced susceptibility to RDV in cell culture (Agostini et al., 2018).[16] The potential relevance of this finding to SARS-CoV-2 is unknown.

- The antiviral activity of RDV against RSV in HEp-2 cells was antagonized in a CQ-dose-dependent manner when CQ was co-incubated in the cultures at clinically relevant concentrations ranging from 10 to 2,560 nM with EC_{50} value increases ranging from 1.19- to 4.43-fold (PC-540-2009).
  - Based on these findings, the Warnings and Precautions section of the EUA outlined that coadministration of RDV and CQ/HCQ is not recommended based on in vitro data demonstrating an antagonistic effect of CQ on the intracellular metabolic activation and antiviral activity of RDV. This information will also be included in the approved labeling.
- Co-incubation of RDV and CQ resulted in a CQ dose-dependent reduction in formation of intracellular RDV-TP, indicating an antagonistic effect of CQ on RDV metabolism to its active triphosphate. Significant CQ antagonism of RDV-TP formation was observed at 8 hours post treatment with 1 and 10 μM CQ concentrations resulting in >2-fold reductions of RDV-TP, respectively. RDV-TP reductions persisted for the 48-hour duration of the assay.
- There are no directly relevant animal studies showing that RDV inhibits SARS-CoV-2 or improves outcomes in an animal model of SARS-CoV-2 to date.
- RDV showed antiviral activity in SARS-CoV-2-infected rhesus monkeys. Administration of RDV at 10/5 mg/kg (10 mg/kg first dose, followed by 5 mg/kg once daily thereafter) using IV bolus injection initiated 12 hours post-inoculation with SARS-CoV-2 resulted in a reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and lung viral RNA levels compared with vehicle-treated animals (Williamson et al., 2020).[21]
- In a non-lethal mouse model of SARS-CoV pathogenesis, administration of 25 mg/kg RDV subcutaneously twice daily beginning 1 day before or 1 day after SARS-CoV inoculation resulted in reduced lung viral load and improved clinical signs of disease and lung function (Sheahan et al., 2017).[19]
- In a mouse model of MERS-CoV pathogenesis, administration of 25 mg/kg RDV subcutaneously twice daily beginning 1 day before or 1 day after MERS-CoV inoculation improved pulmonary function and reduced lung viral loads and lung pathology (Sheahan et al., 2020).[22] Of note, this

mouse model was not uniformly lethal at the challenge doses used in these studies, which resulted in ~50% mortality by Day 6. Treatment with RDV did not improve survival.

- In MERS-CoV-infected rhesus monkeys, administration of RDV at 10 mg/kg or 5 mg/kg once daily for 7 days using IV bolus injection beginning 1 day prior to MERS-CoV inoculation resulted in a reduction of clinical scores, clinical signs of respiratory disease, and viral RNA levels compared to vehicle-treated animals (De Witt et al., 2020).[23]

Please refer to Dr. Eric Donaldson's Clinical Virology review for additional details.

4.3. Product Quality

The commercial RDV drug product is summarized below:

- Lyophilized Powder: Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and diluted into 0.9% saline prior to administration by intravenous infusion. Remdesivir for injection, 100 mg, is supplied in a single-dose clear glass vial. The appearance of the lyophilized powder is white to off-white to yellow.
- Remdesivir injection, 5 mg/mL, is a sterile, preservative-free, clear, colorless to yellow, aqueous-based concentrated solution that is to be diluted into 0.9% saline prior to administration by intravenous infusion. Remdesivir injection, 5 mg/mL, is supplied in a single-dose clear glass vial.

The inactive ingredients are sulfobutylether-β-cyclodextrin sodium salt (SBECD), Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment. Remdesivir for injection, 100 mg, contains 3 g SBECD and remdesivir injection, 5 mg/mL contains 6 g SBECD. RDV clinical supplies and stability lots were manufactured at the designated commercial manufacturing sites, (b) (4)

Please refer to the CMC Reviews by Dr. Shalini Anand, Dr. Katherine Windsor, Dr.Erika Pfeiler, Dr. Ying Zhang, and Dr. Erika Englund for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for RDV. The final report from the inspection of the production facilities was not available at the time this review was finalized.

4.4. Nonclinical Pharmacology/Toxicology

This section summarizes the key outcomes of the pharmacology/toxicology discipline review. Please see the Pharmacology/Toxicology review by Dr. John Dubinion for full details.

- Nonclinical safety studies were conducted in rats and cynomolgus monkeys for 2 weeks.
- The kidney was identified as the target organ of toxicity, mainly driven by the SBECD excipient. Findings included increased serum creatinine, proteinuria, increased kidney weight, and proximal tubular epithelial necrosis.
- Additional adverse effects were noted on appetite, body weight gain, and (increased) respiration rate.
- RDV was not assessed as a potential mutagen or clastogen.

- In vitro examinations also showed little to no potential of cytotoxicity or mitochondrial toxicity of RDV or its major metabolites.
- A complete reproductive and development toxicity program has not identified any risks for pregnant mothers or their off-spring.

4.5. Clinical Pharmacology

This section summarizes the key outcomes of the clinical pharmacology discipline review, including highlights of pharmacokinetics (PK), pharmacodynamics (PD), and dose-response relationships that support dose selection. Please see the Clinical Pharmacology review by Dr. Mario Sampson for full details.

4.5.1. Mechanism of Action

RDV is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase, which is essential for viral replication.

4.5.2. Human Dose Selection

The antiviral activity data demonstrated in animal models with SARS-CoV[19] and MERS-CoV[23] (related coronaviruses that are similar to SARS-CoV-2), cell culture activity against SARS-CoV-2[18], and results from the Phase 1 studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231 and GS-US-399-5505 formed the basis for selecting the dose and durations studied in ACTT-1, GS-US-540-5773 and GS-US-540-5774. Additional safety data was available from patients with Ebola Virus Disease.[24]

No PK data was collected in the Phase 3 studies. For these studies, the study sponsors and investigators assessed that PK would not be collected due to logistical challenges and potential risks to health care providers.

<u>Pediatric dosing</u>
Two PK modeling approaches were used to predict plasma exposures of RDV and metabolites in adolescents:

- Physiologically-Based Pharmacokinetic (PBPK): mechanistic approach that incorporates age-dependent physiology and drug physicochemical properties. PBPK model development was based on the adult Phase 1 exposure data in healthy volunteers administered a 200 mg loading dose of RDV IV over 0.5 hours on Day 1, then 100 mg daily maintenance doses of RDV IV over 0.5 hours starting on Day 2 and continuing through Days 5 or 10 (Study GS-US-399-5505).
- Population pharmacokinetic (popPK): compartmental model fit to observed PK data in healthy adults (n=123). Median (min, max) body weight was 77 kg (53, 101) in this dataset. The popPK model includes body weight. Allometric scaling was used to simulate exposures in patients weighing ≥40 kg.

Analyses of the PBPK model and popPK model indicate that in children weighing ≥ 40 kg, administration of the proposed clinical regimen results in exposures of RDV, GS-704277, and GS-441524 that are generally within the range of exposures observed in adults, therefore supporting extrapolation of clinical trial results observed in adults to pediatrics weighing ≥ 40 kg. The Agency concluded that, using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of RDV and metabolites in children 12 years of age and older and weighing at least 40 kg as observed in healthy adults.

The Agency has also determined that the available data do not adequately support an indication for children weighing < 40 kg. At present, there are no PK data in children and the ability of the PBPK model and popPK model to accurately predict exposures of RDV and metabolites in these lower weight bands is uncertain. In a future submission, the results from a dedicated pediatric trial will be provided to support an indication in pediatric patients < 12 years of age or weighing less than 40 kg.

4.5.3. Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination

- RDV is a prodrug that is metabolized to metabolites GS-704277 and GS-441524.
- GS-441524 is a nucleoside analog that is intracellularly phosphorylated to the active nucleoside triphosphate GS-443902.
- Carboxylesterase 1 is thought to primarily metabolize RDV. However, RDV is also a substrate of CYP2C8, CYP2D6, and CYP3A4.
- RDV is a substrate of transporters P-gp and OATP1B1.
- In a human mass balance study, 74% of the dose was recovered from urine.
- Mean half-lives of RDV, GS-441524 and GS-443902 are 1.0 hours, 27 hours and 43 hours.

Intrinsic Factors

- The impact of COVID-19 on the PK of RDV and metabolites is unknown.
- Renal Impairment: The pharmacokinetics of RDV have not been evaluated in patients with renal impairment. A renal impairment study will be conducted as a PMR.
- Hepatic Impairment: The pharmacokinetics of RDV have not been evaluated in patients with hepatic impairment. A hepatic impairment study will be conducted as a PMR.
- In a popPK analysis of RDV, GS-704277 and GS-441524 PK data from healthy adults, body weight affected exposure while demographic factors such as age, gender, and race did not have an effect on PK.

Extrinsic Factors: Drug Interactions

- No human drug interaction studies have been conducted. The in vitro studies with RDV are summarized below:
    - Effect of RDV on other drugs: 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. In vitro, RDV is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1. Due to the short term (up to 10 day) 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 UGT or MATE-1 substrates is not generally clinically significant, no additional DDI studies are recommended to evaluate the effect of RDV on other drugs.

- Effect of other drugs on RDV: In vitro studies were conducted to evaluate RDV and metabolites as a substrate of various drug metabolizing enzymes and transporters. RDV is primarily metabolized by carboxylesterases (CES) 1 and 2 and is a substrate of OATP1B1 and P-gp transporters. The metabolite GS-704277 is a substrate of OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established. DDI trials of RDV and other concomitant medications have not been conducted, however, the Applicant will conduct a drug interaction trial of RDV with rifampin (broad spectrum inducer of enzymes/transporters) as a postmarketing requirement. The planned human DDI study with rifampin will evaluate the clinical relevance of P-gp/OATP induction on RDV.

Exposure-response
PK data was not collected in Phase 3 studies. Exposure-response relationships are unknown.

Please see Section 10 of this review (Labeling) and the clinical pharmacology review for complete details.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 contains a summary of the three Phase 3 trials and other pertinent trials that were submitted with this application.

Table 3. Summary of Relevant Clinical Trials

Trial Identity	NCT No.	Phase	Trial Design	Regimen	Study Population	No. of patients enrolled	Study Endpoint	No. of Centers and Countries
Studies to Support Efficacy and Safety								
ACTT-1 (Trial 20-0006)	04280705	3	Randomized, double-blind, placebo-controlled trial with 1:1 randomization	RDV 10 days* or placebo (PBO) 10 days	Hospitalized adults with COVID-19	1062 in total: 541 RDV_{10} 521 PBO	Time to recovery through Day 29 and Safety	66 sites, 11 countries
GS-US-540-5773 (Part A)	04292899	3	Randomized, open-label trial with 1:1 randomization	RDV 5 days[§] or RDV 10 days*	Hospitalized adults and adolescents with severe COVID-19	397 in total: 200 RDV_5 197 RDV_{10}	Clinical status on Day 14 and Safety	55 sites, 8 countries
GS-US-540-5774 (Part A)	04292730	3	Randomized, open-label trial with 1:1:1 randomization	RDV 5 days[§] or RDV 10 days* or Standard of care	Hospitalized adults and adolescents with moderate COVID-19	584 in total: 191 RDV_5 193 RDV_{10} 200 Standard of care	Clinical status on Day 11 and Safety	105 sites, 12 countries
Other Studies Pertinent to the Review of Efficacy and Safety								
GS-US-399-1812	N/A	1	Randomized, blinded, placebo-controlled, first-in-human, single-ascending dose study, with 4:1 randomization	RDV 3, 10, 30, 75, 150, and 225 mg or PBO	Healthy adults	96 in total: 78 RDV 18 PBO	Safety and PK	1 site (in US)
GS-US-399-1954	N/A	1	Randomized, blinded, placebo-controlled, multiple-dose study, with 2:1 randomization	RDV 150 mg IV QD x 7 days or 14 days or PBO	Healthy adults	24 in total: 16 RDV 8 PBO	Safety and PK	1 site (in US)
GS-US-399-4231	N/A	1	Open-label, mass-balance study	150 mg IV single dose	Healthy adults	8 in total: 8 RDV	Safety and PK	1 site (in US)

Trial Identity	NCT No.	Phase	Trial Design	Regimen	Study Population	No. of patients enrolled	Study Endpoint	No. of Centers and Countries
GS-US-399-5505	N/A	1	Randomized, blinded, placebo-controlled, multiple-dose study, with 4:1 randomization	RDV 5 days[§] or RDV 10 days* or PBO	Healthy adults	36 in total: 29 RDV 7 PBO	Safety and PK	1 site (in US)

*RDV_{10}, RDV for 10 days (200 mg IV on Day 1, followed by 100 mg IV QD Days 2-10)
[§]RDV_5, RDV for 5 days (200 mg IV on Day 1, followed by 100 mg IV QD Days 2-5)
PBO, placebo; PK, pharmacokinetics; IV, intravenous; QD, once daily; N/A, not applicable
In the Phase 3 trials, subjects were not required to remain hospitalized to receive the entire treatment course that they were randomized to receive.
- In ACTT-1, study drug was given daily for up to a total of 10 days of treatment. Study drug was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.
- In Study 5773 and Study 5774: subjects in the RDV_5 group received RDV daily for up to a total of 5 days; subjects in the RDV_{10} group received RDV daily for up to a total of 10 days. Treatment with RDV was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

5.2. Review Strategy

The clinical efficacy review is based on the Phase 3 trials ACTT-1, GS-US-540-5773 and GS-US-540-5774. The clinical reviewer along with the statistical reviewer collaborated extensively during the review process, and a number of analyses included in this review were performed by the statistical reviewer, Dr. Daniel Rubin. In addition, there were significant interactions with the clinical pharmacology, pharmacometrics, virology, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

The primary efficacy endpoint (i.e. time to clinical recovery in ACTT-1; clinical status assessed by a 7-point ordinal scale on Day 14 in GS-US-540-5773; clinical status assessed by a 7-point ordinal scale on Day 11 in GS-US-540-5774) will be discussed in detail in this review. A summary of mortality findings is also discussed; however, it is important to note that mortality was neither the pre-specified primary nor key secondary endpoint in these trials, and that the subgroup mortality assessments by ordinal scale were not prespecified and no adjustments for multiple comparisons were performed on confidence intervals or p-values.

Detailed analyses of other secondary endpoints such as treatment-related improvements in the ordinal scale (i.e., from death to not hospitalized, no limitations on activities), will not be discussed here but are presented in Dr. Rubin's statistics review.

The clinical safety review was primarily based on ACTT-1, GS-US-540-5773 and GS-US-540-5774. Due to differences in study design (double-blinded, placebo controlled vs. open-label studies evaluating different durations, one with a standard of care group, one without a standard of care group), data from these three Phase 3 trials were not pooled. Python software was used to conduct the safety analyses presented in this review; any analyses performed by the Applicant or other members of the FDA review team will be labeled as such.

Overall, clinical efficacy and safety were primarily based on ACTT-1 given its design as a large randomized, double-blind, placebo-controlled, multicenter trial. GS-US-540-5773 and GS-US-540-5774 provided supportive evidence of clinical efficacy and safety of RDV for treatment of COVID-19.

6 Review of Relevant Individual Trials Used to Support Efficacy

Compliance with Good Clinical Practices
Each of the three pivotal Phase 3 trials was conducted under a US IND application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization (ICH) guideline for Good Clinical

Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The trial protocols, amendments and informed consent forms were reviewed and approved by independent ethics committees (IEC) or institutional review boards (IRB) before trial initiation. Investigators (or designees) were responsible for obtaining written informed consent from each individual prior to undertaking any study-related procedures. The FDA OSI inspected selected clinical sites but the inspection reports were not available at the time this review was finalized (See Section 4.1). A detailed discussion of the OSI audit will be available in the Clinical Inspection Summary.

Data Quality and Integrity: Sponsor's Assurance
The review team considered the Applicant's methods for assuring data quality and integrity to be adequate. These methods included investigator and study center staff training on the trial protocols and study-specific procedures, study site monitoring in accordance with ICH GCP guidelines, compliance audits of investigative sites, use of electronic case report forms (eCRFs), and use of data validation specifications along with manual data review. The Applicant reviewed eCRF data to verify protocol and GCP adherence, and to verify the data against source documentation. The Applicant confirmed that missing data, selected protocol deviations and other data inconsistencies were addressed prior to database finalization. Clinical laboratory data were transferred electronically to the Applicant using defined transfer specifications. The Applicant's lead clinical data associate completed the database.

6.1. ACTT-1 (Trial 20-0006)

6.1.1. Study Design

Overview and Objectives
Trial 20-0006 (Adaptive COVID-19 Treatment Trial, ACTT-1) is a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial assessing the safety and antiviral efficacy of RDV for the treatment of COVID-19 in hospitalized adults. The primary objective of the trial is to evaluate the efficacy of treatment with 10 days of RDV relative to placebo (PBO) in adults hospitalized with COVID-19.

Enrollment began on February 21, 2020 and ended on April 19, 2020. The last subject observation included in the NDA submission was made on May 21, 2020, at which point the database was finalized for analysis. Subjects were enrolled across 66 study sites in the US, Denmark, the United Kingdom, Greece, Germany, North Macedonia, Spain, Mexico, Japan, Singapore, and South Korea.

Trial Design

Hospitalized adults with laboratory-confirmed SARS-CoV-2 infection were randomized in a 1:1 ratio in a double-blind manner to receive either RDV or matching placebo (PBO) for 10 days. A placebo-controlled trial design was chosen because no approved regimens exist for this patient population. Study drug was given daily for up to a total of 10 days of treatment. Study drug was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

Inclusion criteria specified that patients were to be males and non-pregnant females aged ≥18 years who had laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR or other public health assay in any specimen. Patients could have illness of any duration, and at least one of the following:
• Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
• SpO2 ≤ 94% on room air, OR
• Requiring supplemental oxygen, OR
• Requiring mechanical ventilation

Exclusion criteria disallowed patients with ALT/AST >5 times the upper limit of normal or eGFR <30 mL/min.

Patients in this trial could have either mild-to-moderate or severe COVID-19. Severe disease was defined as hospitalization requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), or peripheral oxygen saturation (SpO2) ≤ 94% on room air, or tachypnea (respiratory rate ≥ 24 breaths/minute). Mild-to-moderate disease was defined as having SpO2 > 94% on room air and respiratory rate < 24 breaths/minute without supplemental oxygen. Randomization was stratified on this baseline classification of mild/moderate versus severe disease, as well as by study site.

Study Endpoints
The primary efficacy endpoint was time to recovery through Day 29. Recovery was defined by being in category 1, 2, or 3 in the 8-point ordinal scale listed below. Patients who died before recovering were censored in the analysis at Day 29, corresponding to failing to recover through the entire follow-up period. The time to recovery analysis was to be based on an estimated hazard ratio from a Cox proportional hazards model, log-rank test, and comparison of median days to recovery between RDV and PBO.

<u>8-Point Ordinal Scale:</u>
8. Death;
7. Hospitalized, on invasive mechanical ventilation or ECMO;
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
5. Hospitalized, requiring supplemental oxygen;
4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care;
2. Not hospitalized, limitation on activities and/or requiring home oxygen;
1. Not hospitalized, no limitations on activities

The pre-specified primary efficacy analysis was to be conducted in an intention-to-treat (ITT) population of all randomized patients.

A pre-specified key secondary efficacy analysis was an analysis of the above ordinal scale at Day 15 using a proportional odds model.

Because the primary efficacy endpoint was a time to event endpoint, this trial was powered as an event driven study that would reach the final analysis after 400 patients had met recovery criteria. This was planned to provide 85% power for detecting a hazard ratio of 1.35 (on a scale where values greater than 1.00 corresponded to faster recovery in the RDV group). Enrollment ended on April 19, 2020 after 1063 subjects had been randomized.

Statistical Analysis Plan
The primary hypothesis was that time-to-recovery does not differ between the experimental and control arms. The statistical analysis plan pre-specified an interim analysis to be conducted by the data and safety monitoring board (DSMB) after 200 of the 400 recoveries had been observed. This meeting was scheduled for April 27, 2020. However, due to rapid enrollment there had already been over 400 recoveries in the analysis set presented to the DSMB at this meeting. Because this exceeded the originally planned final number of recoveries in the trial, no interim adjustment to significance tests or confidence intervals was applied for the DSMB analysis.

The analysis population is the full analysis set (FAS). Subgroup analyses of the primary endpoint were planned for exploratory purposes only. Subgroups included baseline severity and baseline ordinal scale category.

Please refer to Dr. Daniel Rubin's statistics review for complete details.

Protocol Amendments
Two protocol amendments were made, neither of which significantly impact the conduct of this double-blinded trial. Key changes in these amendments are summarized below.

Amendment 1 (dated March 1, 2020)
• Primary endpoint was revised from a comparison of the seven-category ordinal scale scores on Day 15 to a comparison of the eight-category ordinal scale scores on Day 15.
- From the original seven-category ordinal scale (7-Death; 6-Hospitalized, on invasive mechanical ventilation or ECMO; 5-Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4-Hospitalized, requiring supplemental oxygen; 3-Hospitalized, not requiring supplemental oxygen; 2-Not hospitalized, limitation on activities; 1-Not hospitalized, no

limitations on activities), the ordinal scale was increased to 8 categories to address the concern that "Hospitalized not requiring oxygen" comprised 2 separate categories, i.e., patients requiring medical care and those no longer requiring ongoing medical care (e.g. kept in hospital for infection control).
• Sample size was increased from 394 to 440.

Amendment 2 (dated April 1, 2020)
• Primary endpoint was revised from a comparison of the eight-category ordinal scale scores on Day 15 to a comparison of time to recovery up to Day 29.
• The endpoint (clinical status [8-point ordinal scale] at Day 15) was revised to be a key secondary end point.
• Sample size was increased to ensure there was a sufficient number of patients (400) who achieved a "recovered" status for the primary objective. The target of 400 recoveries corresponds to a sample size that depends on the proportion of subjects who recover by Day 29. This proportion will be evaluated on pooled (i.e., blinded) data to evaluate the total sample size required. The preliminary estimate, based on a 70% recovery probability, was 572 patients. Additionally, enrollment was permitted after 400 recoveries were observed up until midnight 19 April 2020, to provide additional data for important subgroups of interest.

Reviewer Comment: These amendments were assessed as reasonable for the following reasons: (1) limitations in knowledge about the natural clinical history of COVID-19 when the trial was designed in February 2020; (2) subsequent, emerging data suggested that COVID-19 has a more protracted course than was previously known, which generated concern that a difference in clinically meaningful outcomes after Day 15 would have been missed by a single assessment at Day 15; (3) timing that these changes were made during the study; (4) double-blinded study design.

Amendment 2 was proposed on March 22, 2020 by NIAID trial statisticians who were blinded to treatment assignment and to outcome data. At that time, 72 patients (approximately 7% of the overall study population) had been enrolled. The original primary outcome (clinical status [8-point ordinal scale] at Day 15) became the key secondary end point. As detailed in Dr. Rubin's review, outcomes for both primary and key secondary end points were significantly different between RDV and PBO.

6.1.2. Study Results

Patient Disposition
Of the 1107 subjects who were screened, 1062 were randomized to treatment groups and received at least one dose of study medication and were included in the FAS: 541 in the RDV group and 521 in the PBO group (Table 4).

Table 4. ACTT-1 Treatment Duration, FAS

	RDV	Placebo

	(N=541) n (%)	(N=521) n (%)
Treatment receipt status		
Received treatment	531* (98.2%)	517§ (99.2%)
Did not receive treatment	10 (1.8%)	4 (0.8%)
Study completion status		
Completed study (including death or recovery)	517 (95.6%)	508 (97.5%)
Discontinued study	14 (2.6%)	9 (1.7%)
Reason for study discontinuation		
SAE or AE other than death	4 (0.7%)	0 (0%)
Transferred to another hospital	1 (0.2%)	1 (0.2%)
Voluntary withdrawal by subject	6 (1.1%)	5 (1.0%)
Voluntary withdrawal by subject and transition to comfort care	3 (0.6%)	2 (0.4%)
Withdrawal by investigator	0 (0%)	1 (0.2%)
Completed all 10 doses of treatment	208 (38.4%)	226 (43.4%)
Discontinued treatment	323 (59.7%)	291 (55.9%)
Reason for treatment discontinuation		
Recovered	223 (41.2%)	158 (30.3%)
Death	15 (2.8%)	19 (3.6%)
SAE or AE other than death	52 (9.6%)	70 (13.4%)
Intermittent missed doses	18 (3.3%)	26 (5.0%)
Withdrawal by investigator	4 (0.7%)	1 (0.2%)
Voluntary withdrawal by subject	6 (1.1%)	8 (%)
Voluntary withdrawal by subject and transition to comfort care	4 (0.7%)	6 (1.2%)
Transferred to another hospital	1 (0.2%)	1 (0.2%)
Became ineligible after enrollment	0 (0%)	1 (0.2%)
Protocol deviation	0 (0%)	1 (0.2%)

*For the RDV group, 531 denotes the subjects who were allocated to RDV and treated.; §For the PBO group, 517 denotes the subjects who were allocated to PBO and treated (including 1 subject who incorrectly received RDV).
Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: A total of 434 subjects (RDV [n=208], PBO [n=226]) received all 10 doses of study drug.

A total of 614 subjects (RDV [n=323], PBO [n=291]) received fewer than 10 doses of study drug. The four most common reasons for receiving fewer than 10 doses of study drug were as follows:

- *381 subjects (RDV [n=223], PBO [n=158]) due to discharge*
- *34 subjects (RDV [n=15], PBO [n=19]) due to death*
- *112 subjects (RDV [n=52], PBO [n=70]) due to non-fatal AE/SAE*
- *44 subjects (RDV [n=18], PBO [n=26]) due to any missed doses*

Protocol Violations/Deviations

A total of 81 important protocol deviations occurred in 80 subjects (RDV [n=43], PBO [n=37]) during the study. One subject had 2 deviations and the remainder had a single deviation. Violations of inclusion/exclusion criteria were the most common deviations (RDV [n=33], PBO [n=26]), followed by management not according to protocol (RDV [n=6], PBO [n=9]), study

medication dosing (RDV [n=2], PBO [n=1]), and study medication not given according to schedule (RDV [n=2], PBO [n=2]). These protocol violations had no bearing on the interpretability of the trial results.

Baseline Characteristics
Tables 5 and 6 summarize the baseline demographic and disease characteristics.

Table 5. ACTT-1 Baseline Demographic Characteristics, FAS

Demographic Parameters	RDV (N=541) n (%)	Placebo (N=521) n (%)	Total (N=1062) n (%)
Sex			
Male	352 (65.1%)	332 (63.7%)	684 (64.4%)
Female	189 (34.9%)	189 (36.3%)	378 (35.6%)
Age			
Mean years (SD)	58.7 (14.6)	59.2 (15.5)	58.9 (15.0)
Median (years)	59.0	60.0	59.0
Min, max (years)	21.0, 94.0	21.0, 95.0	21.0, 95.0
Age Group			
18 - 39 years	59 (10.9%)	60 (11.5%)	119 (11.2%)
40 - 64 years	295 (54.5%)	264 (50.7%)	559 (52.6%)
≥ 65 years	187 (34.6%)	197 (37.8%)	384 (36.2%)
Race			
White	279 (51.6%)	287 (55.1%)	566 (53.3%)
Black or African American	109 (20.1%)	117 (22.5%)	226 (21.2%)
Asian	79 (14.6%)	56 (10.7%)	135 (12.7%)
Other[1]	74 (13.7%)	61 (11.7%)	135 (12.7%)
Ethnicity: Hispanic/Latino			
Yes	134 (24.8%)	116 (22.3%)	250 (24.5%)
No	382 (70.6%)	373 (71.6%)	755 (71.1%)
Not disclosed	25 (4.6%)	32 (6.1%)	57 (5.4%)
BMI			
Mean (SD)	30.7 (7.5)	30.5 (7.5)	30.6 (7.5)
Region			
United States	427 (78.9%)	410 (78.7%)	837 (78.8%)
Great Britain	25 (4.6%)	21 (4%)	46 (4.3%)
Denmark	22 (4.1%)	21 (4%)	43 (4.0%)
Spain	16 (3%)	12 (2.3%)	28 (2.6%)
Greece	10 (1.8%)	12 (2.3%)	22 (2.1%)
South Korea	9 (1.7%)	12 (2.3%)	21 (2.0%)
Singapore	9 (1.7%)	7 (1.3%)	16 (1.5%)
Japan	8 (1.5%)	7 (1.3%)	15 (1.4%)
Germany	7 (1.3%)	6 (1.2%)	13 (1.2%)
North Macedonia	4 (0.7%)	7 (1.3%)	11 (1.0%)
Mexico	4 (0.7%)	6 (1.2%)	10 (0.9%)

[1]Includes American Indian/Alaska Native, Hawaiian or Pacific Islander, Multi-Racial, and Unknown
Source: ADSL, ACTT-1 dataset

Reviewer Comment: The treatment arms are well balanced with respect to age, race, sex, weight, and region. The majority (approximately 80%) of the study population is from the US, which makes the data readily applicable to the US population. Additionally, the multinational nature of the study enabled more rapid study enrollment and helped ensure that the findings are relevant to the US and ex-US populations as a global unmet medical need exists for effective antiviral regimens for subjects with COVID-19. Virologic response to an antiviral drug such as RDV is expected to be the same both in US and ex-US sites. The preponderance of subjects aged 40-64 (53%) and ≥ 65 years (36%) in the study population reflect the epidemiology of COVID-19.

Table 6. ACTT-1 Baseline Disease Characteristics

Baseline Disease Characteristics	RDV (N=541) n (%)	Placebo (N=521) n (%)	Total (N=1062) n (%)
Days from symptom onset to enrollment			
≤6	158 (29.2%)	124 (23.8%)	282 (26.6%)
7-9	148 (27.4%)	152 (29.2%)	300 (28.2%)
10-12	113 (20.9%)	108 (20.7%)	221 (20.8%)
≥13	121 (22.4%)	135 (25.9%)	
Median (interquartile range), days	9 (6, 12)	9 (7, 13)	9 (6, 12)
Disease severity			
Mild-to-moderate	55 (10.2%)	50 (9.6%)	105 (9.9%)
Severe	486 (89.8%)	471 (90.4%)	957 (90.1%)
Baseline ordinal scale			
4. Hospitalized - not requiring supplemental oxygen - requiring ongoing medical care	75 (13.9%)	63 (12.1%)	138 (13.0%)
5. Hospitalized - requiring supplemental oxygen	232 (42.9%)	203 (39%)	435 (41.0%)
6. Hospitalized - on noninvasive ventilation or high-flow oxygen	95 (17.6%)	98 (18.8%)	193 (18.2%)
7. Hospitalized - on invasive mechanical ventilation or ECMO	131 (24.2%)	154 (29.6%)	285 (26.8%)
Missing	8 (1.5%)	3 (0.6%)	11 (1.0%)
Summary of co-morbidities			
None	97 (17.9%)	97 (18.6%)	194 (18.3%)
One	138 (25.5%)	137 (26.3%)	275 (25.9%)
Two or more	296 (54.7%)	283 (54.3%)	579 (54.5%)
Missing	10 (1.8%)	4 (0.8%)	14 (1.3%)
Co-morbidities*			
Hypertension	269 (49.7%)	264 (50.7%)	533 (50.1%)
Obesity	242 (44.7%)	234 (44.9%)	476 (44.8%)
Type 2 diabetes	164 (30.3%)	158 (30.3%)	323 (30.4%)
Coronary artery disease	69 (12.8%)	57 (10.9%)	126 (11.9%)

Asthma	63 (11.6%)	57 (10.9%)	120 (11.3%)
Chronic respiratory disease	37 (6.8%)	41 (7.9%)	78 (7.3%)
Cancer	43 (7.9%)	37 (7.1%)	80 (7.5%)
Immune deficiency	32 (5.9%)	41 (7.9%)	73 (6.9%)
Chronic kidney disease	38 (7.0%)	29 (5.6%)	67 (6.3%)
Congestive heart failure	31 (5.7%)	28 (5.4%)	59 (5.6%)
Chronic liver disease	14 (2.6%)	12 (2.3%)	26 (2.4%)
Chronic oxygen requirement	15 (2.8%)	4 (0.8%)	19 (1.8%)
Type 1 diabetes	7 (1.3%)	3 (0.6%)	10 (0.9%)

*Subjects can have more than one comorbidity; n (%) is based on the number of cases divided by N.
Source: Table created by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: The treatment arms are overall balanced with respect to baseline disease characteristics. A total of 957 subjects (90% in both treatment groups) had severe disease at baseline, defined a requirement for mechanical ventilation, oxygen requirement, SpO_2 ≤94% on room air, or respiratory rate ≥24 breaths/minute.

The median number of days between symptom onset and randomization was 9 days for both treatment arms.

Most subjects had 1 (26%) or 2 or more (55%) of the 13 prespecified coexisting conditions at enrollment. The most commonly reported comorbidities were hypertension (50%), obesity (45%), and type 2 diabetes mellitus (30%). The distribution of comorbidities was similar between the two treatment groups.

Baseline clinical status (8-point ordinal scale) also reflected the severity of baseline disease:

- *285 subjects (27%) had a clinical status of 7 (hospitalized, receiving invasive mechanical ventilation or ECMO)*
  - *A lower proportion of subjects in the RDV group had baseline ordinal scale of 7 compared to the PBO group (24% vs. 30%)*
- *193 subjects (18%) had a clinical status of 6 (hospitalized, receiving noninvasive ventilation or high-flow oxygen devices)*
  - *The proportion of subjects with baseline ordinal scale of 6 was overall similar between the RDV and PBO groups (18% vs. 19%)*
- *435 subjects (41%) had a clinical status of 5 (hospitalized, requiring supplemental oxygen)*
  - *A higher proportion of subjects in the RDV group had baseline ordinal scale of 5 compared to the PBO group (43% vs. 39%)*
- *138 subjects (13%) had a clinical status of 4 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19-related or otherwise])*
  - *A higher proportion of subjects in the RDV group had baseline ordinal scale of 5 compared to the PBO group (14% vs. 12%)*

Efficacy Results – Primary Endpoint

Tables 7 provides a summary of overall primary efficacy results as well as the primary efficacy outcomes by baseline severity.

Table 7. ACTT-1 Primary Efficacy Results

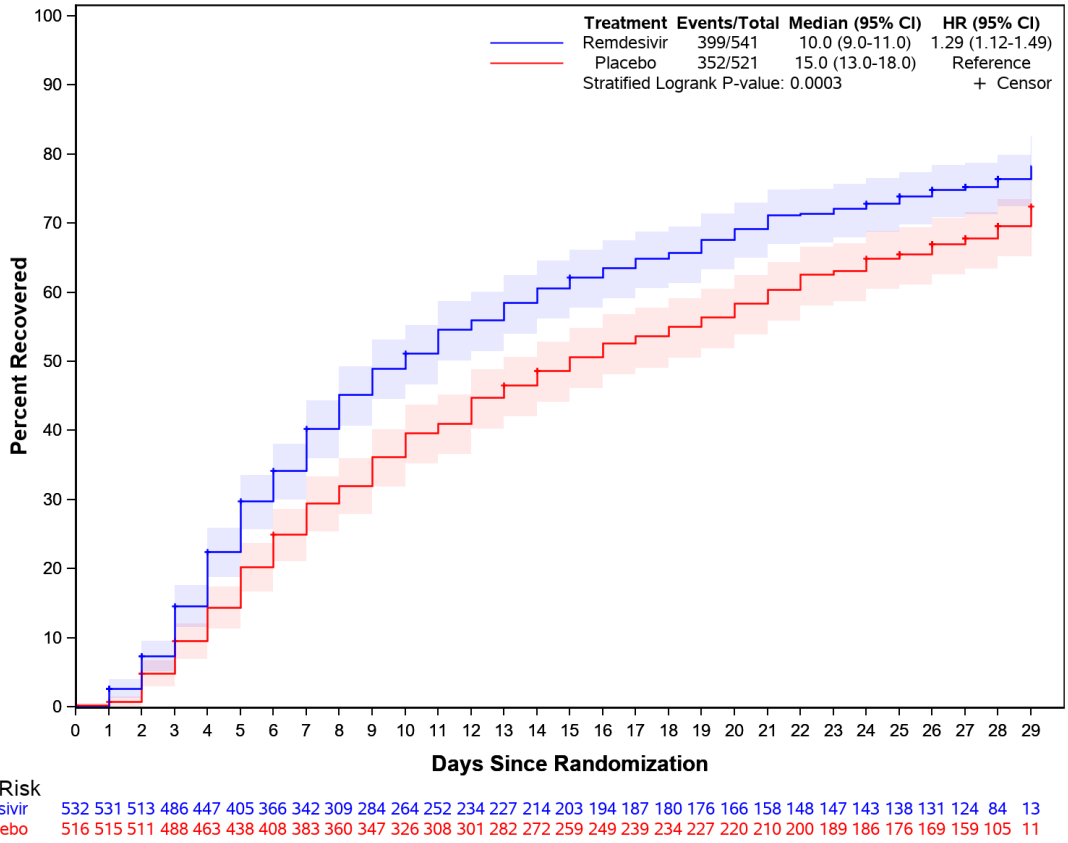
	Overall (N=1062)		Mild-to-moderate (N=105)		Severe (N=957)	
Days to recovery	RDV (N=541)	PBO (N=521)	RDV (N=55)	PBO (N=50)	RDV (N=486)	PBO (N=471)
Number of recoveries	399	352	52	46	345	306
Median (95% CI)	10 (9, 11)	15 (13, 18)	5 (4, 6)	5 (4, 7)	11 (10, 14)	18 (15, 20)
Recovery rate ratio (95% CI); p-value*	1.29 (1.12, 1.49); p < 0.001		1.22 (0.82, 1.81)		1.31 (1.12, 1.52)	

*Recovery rate ratio and HR calculated from the stratified Cox model for the analysis of the overall study population; an unstratified Cox model was used for the analysis of each baseline disease severity stratum. Recovery rate ratio and HR p-values calculated using the stratified log-rank test. Recovery rate ratios > 1 indicate benefit for RDV. Hazard ratios < 1 indicate benefit for RDV.

Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

The results for the primary efficacy analysis of time to recovery are also illustrated in Figure 1.

Figure 1 ACTT-1 Primary efficacy analysis of time to recovery through Day 29 (ITT population)



Abbreviations: ITT = intent-to-treat; CI = confidence interval; HR = recovery rate ratio.
Notes: The plot is based on a Kaplan-Meier analysis. The recovery rate ratio is based on a proportional hazards model that stratifies for baseline disease severity (mild-to-moderate versus severe). A recovery rate ratio <1 favors placebo (PBO) and a recovery rate ratio >1 favors remdesivir (RDV).
Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: In the intent-to-treat population of all randomized patients, the time to recovery was significantly faster for RDV compared to PBO. The median time to recovery was 10 days in the RDV group vs. 15 days in the PBO group (Figure 1). The estimated hazard ratio (on a scale with values greater than 1.00 favoring RDV) was 1.29 with a 95% confidence interval for the hazard ratio from 1.12 to 1.49, and a two-sided p-value <0.001.

In subjects with mild/moderate disease at enrollment (n=105), the median time to recovery was 5 days in both the RDV and PBO groups (recovery rate ratio, 1.22; [95% CI 0.82 to 1.81]).

In patients with severe disease at enrollment (n=957), the median time to recovery was 11 days in the RDV group compared to 18 days in the PBO group (recovery rate ratio, 1.31; [95% CI, 1.12 to 1.52]; p<0.001).

Key Secondary Endpoint
Table 8 describes the pre-specified key secondary efficacy analysis of the ordinal scale at Day 15 using a proportional odds model.

Reviewer Comment: Results for the key secondary endpoint of the ordinal scale at Day 15 also favored RDV: odds ratio = 1.54 from a proportional odds model; 95% CI: 1.25 to 1.91; p<0.001.

Subgroup Analyses
Table 8 also summarizes the time to recovery by baseline ordinal score.

Table 8. ACTT-1 Treatment Outcomes
by Baseline Ordinal Score

	Ordinal Baseline Score 4		Ordinal Baseline Score 5		Ordinal Baseline Score 6		Ordinal Baseline Score 7	
	RDV 10 Days (N = 75)	Placebo (N = 63)	RDV 10 Days (N = 232)	Placebo (N = 203)	RDV 10 Days (N = 95)	Placebo (N = 98)	RDV 10 Days (N = 131)	Placebo (N = 154)
Time to recovery through Day 29								
Number of recoveries	73	58	206	156	57	61	63	77
Median days (95% CI)	5.0 (4.0 , 6.0)	6.0 (4.0 , 9.0)	7.0 (6.0 , 8.0)	9.0 (7.0 , 11.0)	15.0 (11.0 , 28.0)	19.5 (15.0 , 27.0)	29.0 (25.0 , NE)	28.0 (24.0 , NE)
Recovery rate ratio[1] (95% CI)	1.29 (0.91 , 1.83)	-	1.45 (1.18 , 1.79)	-	1.09 (0.76 , 1.57)	-	0.98 (0.70 , 1.36)	-
Ordinal scale at Day 15 n(%) in each category								
Total with Baseline and Day 15 ordinal score data	75	63	232	203	95	98	131	154
(1) Not hospitalized, no limitations on activities	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
(2) Not hospitalized, limitation on activities and/or requiring home oxygen	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
(3) Hospitalized, not requiring supplemental oxygen, no longer requires ongoing medical care	8 (10.7)	4 (6.3)	6 (2.6)	4 (2)	-	-	-	-
(4) Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	3 (4)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
(5) Hospitalized, requiring supplemental oxygen	3 (4)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)

(6) Hospitalized, on non-invasive ventilation or high flow oxygen devices	1 (1.3)	-	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
(7) Hospitalized, on invasive mechanical ventilation or ECMO	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
(8) Death	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio[2] (95% CI)	1.46 (0.78 , 2.72)	-	1.64 (1.17 , 2.31)	-	1.40 (0.85 , 2.3)	-	1.22 (0.79 , 1.86)	-
Day 28 all-cause mortality								
Number of deaths by 28 days	3	3	9	25	19	20	28	29
Kaplan-Meir estimate % (95% CI)	4.1 (0.0 , 8.5)	4.8 (0.0 , 10.0)	4.0 (1.4 , 6.5)	12.7 (7.9 , 17.3)	21.2 (12.2 , 29.2)	20.4 (12.0 , 28.0)	21.9 (14.4 , 28.7)	19.3 (12.7 , 25.3)
Hazard ratio[3] (95% CI)	0.82 (0.17 , 4.07)	-	0.30 (0.14 , 0.64)	-	1.02 (0.54 , 1.91)	-	1.13 (0.67 , 1.89)	-

Abbreviations: RDV = Remdesivir; CI=Confidence Interval
[1] Recovery rate ratio is from an unstratified Cox proportional hazards model. Recovery rate ratios > 1 indicate benefit for RDV.
[2] Proportional odds models are unadjusted.
[3] Hazard ratio is from an unstratified Cox proportional hazards model. Hazard ratios < 1 indicate benefit for RDV.

Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: Subgroup analyses demonstrated the strongest benefit of RDV in subjects with a baseline ordinal score of 5 (requiring low flow oxygen). That this subgroup comprised the largest proportion (approximately 41%) of the study population could have facilitated the detection of this effect.

For subjects with baseline ordinal score of 4 (hospitalized, not requiring supplemental oxygen), results for the time to recovery analysis in this subgroup numerically favored RDV and were consistent with the overall study results: recovery rate ratio = 1.29; 95% CI; 0.91 to 1.83. These findings were not unexpected given that it seems biologically plausible that initiating antiviral treatment earlier in the disease course could result in improved clinical outcomes.

For subjects with baseline ordinal scores of 6 (requiring noninvasive ventilation or high-flow oxygen) or 7 (requiring invasive mechanical ventilation/ECMO), it is possible that the sample size and the duration of follow-up may not have been sufficient to potentially demonstrate efficacy in these subgroups. Additionally, because the relative contribution of ongoing viral infection vs. secondary hyperinflammatory immune response to the development of severe COVID-19 is not completely understood at this time, the findings in these subgroups do not exclude the possibility for some benefit in subjects with higher ordinal scores.

Impact on Mortality

Of note, mortality was neither the pre-specified primary nor key secondary endpoint of this trial. The subgroup mortality assessments by ordinal scale were also not prespecified and no adjustments for multiple comparisons were made for confidence intervals or p-values (Table 8).

Overall, 29-day mortality was 11% in the RDV group vs. 15% in the PBO group (hazard ratio, HR 0.73 [95% CI 0.52, 1.02], p=0.066). Therefore, ACTT-1 did not show a statistically significant decrease in mortality with RDV compared to PBO.

Regarding HR by subgroup, while the subgroups for the ordinal scale were pre-defined, separate analyses of 29-day mortality by baseline ordinal score were not. These post-hoc analyses and the p-values associated with these comparisons were not pre-specified and adjustments for multiple comparisons were not made:

- Baseline ordinal score of 4 (hospitalized, not on oxygen): mortality was 4% in the RDV group vs. 5% in the PBO group (HR 0.82; 95% CI: 0.17, 4.07)
- Baseline ordinal score of 5 (hospitalized, on low-flow oxygen): mortality was 4% in the RDV group vs. 13% in the PBO group (HR 0.30; 95% CI: 0.14, 0.64)
- Baseline ordinal score of 6 (hospitalized, on high-flow oxygen or non-invasive mechanical ventilation): mortality was 21% in the RDV group vs. 20% in the PBO group (HR 1.02; 95% CI: 0.54, 1.91)
- Baseline ordinal score of 7 (hospitalized, on invasive mechanical ventilation or ECMO): mortality was 22% in the RDV group vs. 19% in the PBO group (HR 1.13; 95% CI: 0.67, 1.89)

Reviewer Comment: For Day 29 all-cause mortality, there was a numerical trend towards lower mortality in the RDV group [59/541 (11%)] than the PBO group [77/521 (15%)], with a two-sided p-value of 0.07.

These subgroup analyses by baseline ordinal score should be interpreted with caution because no adjustments were made for multiple comparisons and the sample size in some of the subgroups was small. Acknowledging the caveats in these post-hoc subgroup analyses, the data indicate a mortality benefit with RDV in the subgroup of hospitalized patients with disease advanced enough to require low flow oxygen, but not advanced enough to require intubation and ventilation/ECMO.

Although no mortality benefit was observed with RDV in patients requiring high-flow oxygen or noninvasive mechanical ventilation or invasive mechanical ventilation or ECMO, given that the relative contribution of ongoing viral infection vs. secondary hyperinflammatory immune response to the development of severe COVID-19 is not completely understood at this time, it is unclear whether an antiviral drug could achieve a statistically significant mortality benefit in these subgroups, or whether detecting such a treatment effect may require larger sample sizes.

Readmissions
A total of 41 subjects (4%) were readmitted during study follow-up: 26 subjects (5%) in the RDV group and 15 subjects (3%) in the PBO group. Baseline immunodeficiency was associated with readmission.

- Immunodeficient at baseline:
    - RDV: 8/32 (25%)
    - Placebo: 4/41 (9.8%)
- Not immunodeficient at baseline:
    - RDV: 18/509 (3.5%)
    - Placebo: 11/480 (2.3%)

Reviewer Comment: The low readmission rates provide additional evidence of clinically meaningful benefit, especially given the high proportion of patients with severe disease in this trial and its large sample size. Baseline immunodeficiency is associated with a significantly increased risk of severe disease.[7] Consequently, it was not surprising that subjects with baseline immunodeficiency had higher rates of readmission.

Overall Assessment: The results from this large randomized, double-blind, placebo-controlled, multicenter trial provided reliable and statistically persuasive evidence of benefit for RDV in hospitalized patients with COVID-19.

6.2. GS-US-540-5773

6.2.1. Study Design

Overview and Objectives
GS-US-540-5773 (Part A) is Phase 3, randomized, open-label, multicenter trial assessing the safety and antiviral efficacy of 5-day and 10-day RDV durations for the treatment of patients with severe COVID-19. There was no placebo or standard of care group. The primary objective of the trial is to evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14.

Enrollment began on March 6, 2020 and ended on March 26, 2020. The last subject observation included in the NDA submission was made on April 27, 2020, at which point the database was finalized for analysis. Subjects were enrolled across 55 study sites in the US, Germany, Italy, Spain, Hong Kong, Singapore, South Korea, and Taiwan.

Trial Design
Hospitalized adults and adolescents (≥12 years) with laboratory-confirmed SARS-CoV-2 infection were randomized in a 1:1 ratio to receive RDV for either 5-days or 10-days.
- In the RDV 5-day group, RDV was given daily for up to a total of 5 days.
- In the RDV 10-day group, RDV was given daily for up to a total of 10 days.
- Treatment with RDV was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

Inclusion criteria specified that patients were to be males and non-pregnant female patients aged ≥12 years with SARS-CoV-2 infection confirmed by RT-PCR testing, current hospitalization, radiographic evidence of pulmonary infiltrates, and SpO_2 ≤94% on room air or requirement for supplemental oxygen.

Exclusion criteria disallowed patients with any of the following: mechanical ventilation for ≥5 days, ECMO, patients with multiorgan failure, ALT/AST >5 times the upper limit of normal, creatinine clearance <50 mL/min, or concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing.

Study Endpoints
The pre-specified primary efficacy analysis was to examine results on a 7-point ordinal scale at Day 14 using a proportional odds model.

<u>7-Point Ordinal Scale:</u>
1. Death;
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring low flow supplemental oxygen;

5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration);
7. Not hospitalized.

Statistical Analysis Plan
The null hypothesis was that the odds of improvement for the RDV 5-day group was the same as the odds of improvement for the RDV 10-day group with respect to clinical status assessed by a 7-point ordinal scale on Day 14, with the alternative hypothesis being that the odds of improvement with respect to clinical status assessed by a 7-point ordinal scale on Day 14 was different for the 2 treatment groups. The odds ratio, 95% CI, and p-value for comparing treatment groups were provided. The analysis population is the FAS.

Subgroup analyses of the primary endpoint were planned for exploratory purposes only. Subgroups included age, sex, country, and oxygen support status based on the 7-point ordinal scale (invasive mechanical ventilation; high flow oxygen; low flow oxygen; room air).

The open-label design and primary endpoint choice may have favored the 5-day group compared with the 10-day group. Subjects in the 10-day group may have had a lower chance of achieving discharge (the best category in the ordinal scale) between Day 6 and Day 10 because they were still assigned to receive intravenous therapy during this period of time.

There was an issue with pre-specification in this trial, as the statistical analysis plan was not provided to the FDA or otherwise made public until after release of topline results. Specifically, the adjustment for baseline ordinal score in the proportional odds model was not included in the protocol or documented with FDA prior to dissemination of results.

Please refer to Dr. Daniel Rubin's statistics review for complete details.

Protocol Amendments
Three protocol amendments were made and are summarized below.

<u>Amendment 1 (dated March 15, 2020)</u>
• Primary endpoint was revised as follows:
- From: Proportion of participants in each group with normalization of fever and oxygen saturation [criteria for normalization: temperature < 36.6°C (armpit), < 37.2°C (oral), < 37.8°C (rectal); and SpO2 > 94%, sustained for at least 24 hours] through Day 14.
- To: Clinical status assessed by a 7-point ordinal scale on Day 14 consisting of the following categories: 1, death; 2, hospitalized, receiving invasive mechanical ventilation or ECMO; 3, hospitalized, receiving noninvasive ventilation or high-flow oxygen devices; 4, hospitalized, requiring low-flow supplemental oxygen; 5, hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to Covid-19); 6, hospitalized,

requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for RDV administration); and 7, not hospitalized.
• Study was revised to 2 parts: Part A (randomized) and newly added Part B (non-randomized)
• Sample size was increased from 400 (Part A) to up to 2400 (Part A [n=400], Part B [up to 2000]).
- In Part B, the number of mechanically ventilated patients was capped at 500.
• Number of study sites was revised from 50 to up to 100.
• Inclusion criteria was revised as follows:
- Allowed enrollment of adolescents age ≥12 to 18 years.
- Removed the requirement to have fever (defined as temperature ≥ 36.6°C armpit, ≥ 37.2°C oral, ≥ 37.8°C rectal).
- Changed from SpO2 ≤ 94% on room air at screening to SpO2 ≤ 94% on room air at screening or requiring supplemental oxygen at screening.
• Exclusion criteria was revised as follows:
- From: Mechanical ventilation at screening.
- To: Mechanically ventilated (including veno-venous [V-V] extracorporeal membrane oxygenation [ECMO]) ≥ 5 days, or any duration of veno-arterial (V-A) ECMO.
• Revised the statistical methodology and analysis due to changes in endpoints and study design.

Amendment 2 (dated March 20, 2020)
• Revised informed consent language to include informed consent with a legal representative and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions.

Amendment 3 (dated April 12, 2020)
• Sample size was increased from 2400 to up to 6000 (Part A [n=400], Part B [up to 5600]).
• Number of study sites was revised from 100 to up to 160.
• Removed the enrollment limit for the mechanically ventilated treatment group in Part B.

Reviewer Comment: The primary endpoint was changed during this open-label trial. Although the Applicant stated that the decision to change the primary endpoint was made before any subjects were enrolled, there were 35 subjects randomized before 03-15-2020 and 6 subjects randomized on 03-15-2020. Hence, approximately 10% of subjects in this trial were enrolled at or before the day of protocol amendment finalization. Of note, the amended protocol was not submitted to the FDA until 03-17-2020, and the dates are unclear when IRBs had reviewed and implemented the protocol changes. The primary endpoint change is a possible source of bias because the change was made after nontrivial enrollment and with knowledge of unblinded data. As detailed in Dr. Rubin's review, the outcomes were overall similar before (OR = 0.75 [favors 5 days]; 95% CI: 0.33 to 1.67; p-value: 0.48) and after (OR = 0.80 [favors 5 days]; 95% CI: 0.50 to 1.26; p-value: 0.33) the time of the primary endpoint change.

The other amendments were assessed as not to have significantly impact the conduct of this trial.

6.2.2. Study Results

Patient Disposition

A total of 407 subjects were screened for participation, of whom 401 were randomized: 201 subjects in the RDV 5-day group and 200 subjects in the RDV 10-day group. A total of 397 randomized subjects (200 subjects in the RDV 5-day group and 197 subjects in the RDV 10-day group) received at least one dose of study drug and were included in the FAS (Table 9).

Table 9. GS-US-540-5773 Treatment Duration, FAS

	RDV 5 Days (N=200) n (%)	RDV 10 Days (N=197) n (%)
Treatment completion status		
Completed	172 (86%)	86 (43.7%)
Discontinued	28 (14%)	111 (56.3%)
Reason for treatment discontinuation		
Hospital discharge	16 (8%)	67 (34%)
Death	0 (0%)	12 (6.1%)
Non-fatal AE	9 (4.5%)	22 (11.2%)
Protocol violation	1 (0.5%)	1 (0.5%)
Withdrawal by subject	2 (1%)	4 (2%)
Investigator decision	0 (0%)	5 (2.5%)
Number of doses		
1	2 (1%)	4 (2%)
2	6 (3%)	9 (4.6%)
3	8 (4%)	11 (5.6%)
4	11 (5.5%)	10 (5.1%)
5	171 (85.5%)	19 (9.6%)
6	2 (1%)	11 (5.6%)
7	0 (0%)	17 (8.6%)
8	0 (0%)	16 (8.1%)
9	0 (0%)	13 (6.6%)
10	0 (0%)	85 (43.1%)
11	0 (0%)	0 (0%)
12	0 (0%)	1 (0.5%)
13	0 (0%)	0 (0%)
14	0 (0%)	1 (0.5%)

Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: Of the 397 subjects, 139 subjects (35%) prematurely discontinued RDV: 28 subjects (14%) in the RDV 5-day group and 111 subjects (56%) in the RDV 10-day group.

The most common reasons for premature discontinuation of RDV were:
• Hospital discharge: 16 subjects (8%) in the RDV 5-day group and 67 subjects (34%) in the RDV 10-day group.

• *Adverse event: 9 subjects (5%) in the RDV 5-day group and 22 subjects (11%) in the RDV 10-day group.*
• *Death: zero subjects in the RDV 5-day group and 12 subjects (6%) in the RDV 10-day group.*

Protocol Violations/Deviations

A total of 103 important protocol deviations occurred among 77 subjects during the study. Of the 77 subjects, 59 subjects had a single deviation, 12 subjects had 2 deviations, 4 subjects had 3 deviations, and 2 subjects had 4 deviations. The majority of deviations (54 of 103) were for SAEs reported beyond 24 hours of identification. The second largest category (28 of 103) was for subjects who did not meet the eligibility criteria; of these 28 deviations, 16 were for subjects who did not receive a PCR test ≤ 4 days before randomization. These protocol violations had no bearing on the interpretability of the trial results.

Baseline Characteristics

Tables 10 and 11 summarize the baseline demographic and disease characteristics for subjects in the FAS.

Table 10. GS-US-540-5773 Baseline Demographic Characteristics

Demographic Parameters	RDV 5 Days (N=200) n (%)	RDV 10 Days (N=197) n (%)	Total (N=397) n (%)
Sex			
Male	120 (60%)	133 (68%)	253 (64%)
Female	80 (40%)	64 (32%)	144 (36%)
Age			
Mean years (SD)	60 (15.1)	60 (14.4)	57 (8.3)
Median (years)	61	62	58
Min, max (years)	20, 98	21, 93	24, 85
Age Group			
< 40 years	23 (11.5%)	18 (9%)	41 (10%)
40 - 64 years	93 (46.5%)	95 (48%)	188 (47%)
65 - 74 years	52 (26%)	53 (27%)	105 (26%)
≥ 75 years	32 (16%)	31 (16%)	63 (16%)
Race			
White	142 (71%)	134 (68%)	276 (70%)
Black or African American	21 (10.5%)	23 (12%)	44 (11%)
Asian	20 (10%)	25 (13%)	45 (11%)
American Indian/Alaska Native	2 (1%)	0 (0%)	2 (0.5%)
Native Hawaiian/Other Pacific Islander	1 (0.5%)	0 (0%)	1 (<0.5%)
Other	14 (7%)	10 (5%)	24 (6%)
Not Permitted	0 (0%)	5 (3%)	5 (1%)
Ethnicity: Hispanic/Latino			
Yes	47 (23.5%)	38 (19%)	85 (21%)
No	152 (76%)	150 (76%)	302 (76%)
Not Permitted	1 (0.5%)	9 (5%)	10 (3%)

Region			
United States	118 (59%)	111 (56.3%)	229 (58%)
Germany	3 (1.5%)	1 (0.5%)	4 (1%)
Spain	31 (15.5%)	30 (15.2%)	61 (15%)
Hong Kong	2 (1%)	2 (1%)	4 (1%)
Italy	39 (19.5%)	38 (19.3%)	77 (19%)
South Korea	6 (3%)	6 (3%)	12 (3%)
Singapore	1 (0.5%)	8 (4.1%)	9 (2%)
Taiwan	0 (0%)	1 (0.5%)	1 (<0.5%)

Source: ADSL, Study 5773 dataset

Reviewer Comment: The treatment arms are overall balanced with respect to age, race, and region. There was higher proportion of male subjects in the RDV 10-day group compared to the RDV 5-day group (68% vs. 60%).

The majority (approximately 58%) of the study population is from the US, which makes the data readily applicable to the US population. Additionally, the multinational nature of the study enabled more rapid study enrollment and helped ensure that the findings are relevant to the US and ex-US populations as a global unmet medical need exists for effective antiviral regimens for subjects with COVID-19. Virologic response to an antiviral drug such as RDV is expected to be the same both in US and ex-US sites. The preponderance of subjects aged 40-64 (47%) and ≥ 65 years (42%) in the study population reflect the epidemiology of COVID-19.

Although a protocol amendment allowing enrollment of subjects aged 12-17 was implemented, no subjects aged 12-17 were enrolled in the randomized portion (Part A) of this clinical trial.

Table 11. GS-US-540-5773 Baseline Disease Characteristics

Baseline Disease Characteristics	RDV 5 Days (N=200) n (%)	RDV 10 Days (N=197) n (%)	Total (N=397) n (%)
Days from symptom onset to first dose			
≤6	52 (26%)	45 (22.8%)	97 (45.1%)
7-9	62 (31%)	62 (31.5%)	124 (31.2%)
10-12	48 (24%)	51 (25.9%)	99 (24.9%)
≥13	36 (18%)	36 (18.3%)	72 (18.1%)
Median (interquartile range), days	9 (6, 11)	9 (7, 12)	9 (7, 11)
Baseline ordinal scale			
2. Hospitalized with invasive mechanical ventilation or ECMO	4 (2%)	9 (4.6%)	13 (3.3%)
3. Hospitalized with noninvasive ventilation or high-flow oxygen	49 (24.5%)	59 (29.9%)	108 (27.2%)
4. Hospitalized with low-flow supplemental oxygen	113 (56.5%)	108 (54.8%)	221 (55.7%)
5. Hospitalized without supplemental oxygen	34 (17%)	21 (10.7%)	55 (13.9%)

but requiring ongoing medical care			
Co-morbidities			
Hypertension	101 (50.5%)	98 (49.7%)	199 (50.1%)
Type 2 diabetes	46 (23%)	42 (21.3%)	88 (22.1%)
Obesity	83 (41.5%)	80 (40.6%)	163 (41.1%)
Asthma	37 (18.5%)	28 (14.2%)	65 (16.4%)
Immunodeficiency	2 (1%)	1 (0.5%)	3 (0.8%)
Cancer	27 (13.5%)	18 (9.1%)	45 (11.3%)

Source: Table created by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: The most commonly reported comorbidities were hypertension (50%), obesity (41%), and type 2 diabetes mellitus (22%). The distribution of comorbidities was similar between the two treatment groups.

The treatment arms are well balanced with respect to median duration of symptoms prior to first dose of RDV (9 days).

Baseline clinical status (7-point ordinal scale) differed across treatment groups and could have contributed to the efficacy outcomes that were observed:

- *A higher proportion of subjects in the RDV 10-day group had a clinical status of 2 (hospitalized, on invasive mechanical ventilation or ECMO) compared to the RDV 5-day group PBO group (5% vs. 2%).*
- *A higher proportion of subjects in the RDV 10-day group had a clinical status of 3 (hospitalized, on noninvasive ventilation or high-flow oxygen) compared to the RDV 5-day group PBO group (30% vs. 25%).*

There was a statistically significant difference in baseline clinical status (7-point ordinal scale) between treatment groups, with a better clinical status in the RDV 5-day group compared with the RDV 10-day group (p = 0.0230). There was also a statistically significant difference between treatment groups in baseline oxygen support status, which was derived from the 7-point ordinal scale used to assess clinical status, with a better clinical status in the RDV 5-day group compared to the RDV 10-day group (p = 0.0175).

Efficacy Results - Primary Endpoint
Primary analysis of the primary endpoint with adjustment for differences in baseline clinical status demonstrated that treatment with RDV for 5 days and treatment with RDV for 10 days resulted in similar clinical status at Day 14 (p = 0.14).

Table 12 summarizes overall primary endpoint results (at Day 14) and also provides the primary efficacy outcomes at Day 28.

Table 12. GS-US-540-5773 Overall Primary Efficacy Results (Day 14) and Day 28 Outcomes

Ordinal Scale	Day 14 (Primary)		Day 28	
	RDV 5-Days (N=200)	RDV 10-Days (N=197)	RDV 5-Days (N=200)	RDV 10-Days (N=197)
7 (Not hospitalized)	120 (60.0%)	103 (52.3%)	151 (75.5%)	127 (64.5%)
6 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, other than per protocol RDV administration)	8 (4.0%)	3 (1.5%)	2 (1.0%)	2 (1.0%)
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	12 (6.0%)	12 (6.1%)	12 (6.0%)	8 (4.1%)
4 (Hospitalized, requiring low-flow supplemental oxygen)	19 (9.5%)	15 (7.6%)	3 (1.5%)	9 (4.6%)
3 (Noninvasive ventilation or high-flow oxygen devices)	8 (4.0%)	10 (5.1%)	3 (1.5%)	6 (3.0%)
2 (Invasive mechanical ventilation or ECMO)	17 (8.5%)	33 (16.8%)	6 (3.0%)	17 (8.6%)
1 (Death)	16 (8.0%)	21 (10.7%)	23 (11.5%)	28 (14.2%)
Proportional odds model (adjusted for baseline score)	OR = 0.74 (favors 5 days) 95% CI: 0.50 to 1.10 p-value = 0.14		OR = 0.69 (favors 5 days) 95% CI: 0.44 to 1.10 p-value = 0.12	

Notes: The odds ratio and p-value are based on a proportional odds model that adjusts for the baseline ordinal scale score. An odds ratio <1 favors the 5-day group and an odds ratio >1 favors the 10-day group.
Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: Primary analysis results of the proportional odds model at Day 14 yielded an estimated odds ratio (on a scale with values less than 1.00 favoring the RDV 5-day group) of 0.74, with a 95% confidence interval from 0.50 to 1.10. Thus, the numerical trends in this trial were towards slightly improved outcomes in the RDV 5-day group, although this difference was not statistically significant. These findings were sustained at Day 28.

Subgroup Analyses

Subgroup analyses were also conducted to evaluate differences in treatment response based on baseline disease characteristics (Table 13) and baseline demographics (Table 14).

Table 13: GS-US-540-5773 Subgroup Analysis: Day 28 recovery by selected baseline disease characteristics

Baseline Disease Characteristics	RDV 5-Days (N=200)	RDV 10-Days (N=197)
Days from symptom onset		
< 10	89/114 (78.1%)	74/107 (69.2%)
≥ 10	62/84 (73.8%)	55/87 (63.2%)
Ordinal scale		
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	31/34 (91.2%)	14/21 (66.7%)
4 (Hospitalized, requiring low-flow supplemental oxygen)	93/113 (82.3%)	93/108 (86.1%)
3 (Noninvasive ventilation or high-flow oxygen devices)	29/49 (59.2%)	21/59 (35.6%)
2 (Invasive mechanical ventilation or ECMO)	0/4 (0%)	1/9 (11.1%)

Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: The apparent trend toward better outcomes in the RDV 5-day group compared to the RDV 10-day group may have several causes, including the significantly higher proportion of patients in the RDV 10-day group having the most severe disease categories (i.e. requiring invasive mechanical ventilation or high-flow oxygen).

Table 14: GS-US-540-5773 Subgroup Analysis: Day 28 recovery by Baseline Demographic Characteristics

	RDV 5-Days (N=200)	RDV 10-Days (N=197)
Age at baseline (years)		
< 65 years	81.9% (95/116)	80.5% (91/113)
≥ 65 years	69.0% (58/84)	45.2% (38/84)
Sex		
Male	71.7% (86/120)	61.7% (82/133)
Female	83.8% (67/80)	73.4% (47/64)
Race		
White	76.8% (109/142)	61.9% (83/134)
Black or African American	85.7% (18/21)	82.6% (19/23)
Asian	60.0% (12/20)	72.0% (18/25)
Other or unknown	82.4% (14/17)	60.0% (9/15)
Region		
US	82.2% (97/118)	71.2% (79/111)
Italy	64.1% (25/39)	42.1% (16/38)
Other	72.1% (31/43)	70.8% (34/48)

Source: Analysis Performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: There was a lower proportion of men in the RDV 5-day group compared to the RDV 10-day group (60% vs. 68%). Given that worse outcomes have been reported in male subjects[1-5], this imbalance may have contributed toward the apparent trend toward better outcomes in the RDV 5-day group compared to the RDV 10-day group.

Overall, for these demographic subgroups, Day 28 recovery rates were either numerically higher in the RDV 5-day group compared to the RDV 10-day group, or comparable across treatment groups. For some subgroups (such as Black/African Americans and Asian), the sample sizes are too small to make reliable conclusions. Overall, these results support the comparable efficacy of both RDV treatment groups in all demographic subgroups evaluated.

Other Subgroups of Interest

Invasive Mechanical Ventilation or ECMO at Day 5

For subjects who were on invasive mechanical ventilation or ECMO at Day 5, those in the RDV 10-day group appeared to have better outcomes than those in the RDV 5-day group, as suggested by the following:

- The proportion of subjects on IMV/ECMO at Day 5 who died on or before Day 14 was lower in the RDV 10-day group (7 out of 41 subjects [17%]) than the RDV 5-day group (10 out of 25 subjects [40%]).
- A higher proportion of subjects in the RDV 10-day group showed improvements in oxygen support status at Day 14 (3 subjects [7%] improved to high-flow oxygen; 3 subjects [7%] improved to low-flow oxygen; 5 3 subjects [12%] were discharged on or before Day 14) compared to the RDV 5-day group (2 subjects [8%] improved to low-flow oxygen, 1 subject [4%] improved to room air; 2 subjects [8%] were discharged on or before Day 14).

Reviewer Comment: These subgroup analyses reflect the uncertainty surrounding the optimal treatment duration in patients who progress to mechanical ventilation. These patients may benefit from 10 days of RDV. For this subgroup, it is possible that the small sample size and the pre-specified duration of follow-up may not have been sufficient to potentially demonstrate efficacy in this subgroup.

Readmissions

Readmissions were not recorded for this study.

Impact on Mortality

Of note, mortality was neither the pre-specified primary nor key secondary endpoint of this trial, and that the subgroup mortality assessments by ordinal scale were not prespecified and no adjustments for multiple comparisons were performed on confidence intervals or p-values.

Overall, 28-day mortality was 12% in the RDV 5-day group vs. 14% in the RDV 10-day group, a non-statistically significant difference.

Reviewer Comment: For Day 28 all-cause mortality, there was a numerical trend towards lower mortality in the RDV 5-day group [23/200 (12%)] than the RDV 10-day group [28/197 (14%)].

Virology

Limited virologic data were available, precluding meaningful assessment of virologic outcomes such as effect of RDV on SARS-CoV-2 viral load.

Overall Assessment: In this open-label, randomized, multicenter trial in subjects with severe COVID-19 pneumonia, primary efficacy analyses showed numerical trends towards slightly improved outcomes in the RDV 5-day group compared to the RDV 10-day group, although this difference was not statistically significant. These results are suggestive of a similar treatment effect with 5-day and 10-day regimens in this population, with appropriate caveats related to the open-label trial design. Due to the absence of a control arm, the magnitude of benefit cannot be determined from this trial.

It is noteworthy that subjects randomly assigned to the RDV 10-day group had significantly worse baseline clinical status (i.e. higher proportions required invasive mechanical ventilation/ECMO and high-flow oxygen at baseline) than those assigned to the RDV 5-day group (p=0.02). After adjusting for baseline imbalances in disease severity, outcomes were similar across treatment groups as measured by several endpoints, including clinical status at Day 28, time to clinical improvement, recovery at Day 28, and all-cause mortality at Day 28. However, due to the small proportion of subjects who were receiving invasive mechanical ventilation (IMV) or ECMO at baseline, these findings cannot be extrapolated to the IMV/ECMO subpopulation.

Although the number of subjects on IMV/ECMO at baseline were relatively small (RDV 10-day group [n=9] vs. RDV 5-day group [n=4]), those in the RDV 10-day group appeared to have better outcomes than those in the RDV 5-day group, as suggested by lower Day 28 recovery rates (11% vs. 0%). In addition, subjects who progress to mechanical ventilation while on treatment may benefit from 10 days of RDV.

Overall, the study findings add to the totality of the data supporting the efficacy of RDV in hospitalized patients with COVID-19. There were no significant differences in recovery rates or mortality rates across treatment groups once adjusted for group differences at baseline. The uncertainty about the optimal duration of treatment for patients requiring invasive mechanical ventilation or ECMO will be addressed in labeling by providing flexibility in the treatment duration, guided by the severity of the infection and the patient's clinical response.

6.3. GS-US-540-5774

6.3.1. Study Design

Overview and Objectives
GS-US-540-5774 (Part A) is Phase 3, randomized, open-label, multicenter trial assessing the safety and antiviral efficacy of RDV for 5 days, RDV for 10 days, and standard of care for the treatment of patients with moderate COVID-19. The primary objective of the trial is to evaluate the efficacy of 2 RDV regimens compared to standard of care, with respect to clinical status assessed by a 7-point ordinal scale on Day 11.

Enrollment began on March 15, 2020 and ended on April 18, 2020. The last subject observation included in the NDA submission was made on April 29, 2020, at which point the database was finalized for analysis. Subjects were enrolled across 105 study sites in the US, United Kingdom, France, Germany, Italy, Netherlands, Spain, Switzerland, Hong Kong, Singapore, South Korea, and Taiwan.

Trial Design
Hospitalized adults and adolescents (≥12 years) with laboratory-confirmed SARS-CoV-2 infection were randomized in a 1:1:1 ratio to receive RDV for 5-days, RDV for 10-days, or standard of care.
- In the RDV 5-day group, RDV was given daily for up to a total of 5 days.
- In the RDV 10-day group, RDV was given daily for up to a total of 10 days.
- Treatment with RDV was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

Inclusion criteria specified that patients were to be males and non-pregnant female patients aged ≥12 years with SARS-CoV-2 infection confirmed by RT-PCR testing, current hospitalization, radiographic evidence of pulmonary infiltrates, and SpO_2 >94% on room air.
Exclusion criteria disallowed patients with any of the following: mechanical ventilation at screening, ALT/AST >5 times the upper limit of normal, creatinine clearance <50 mL/min, or concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing.

Study Endpoints
The pre-specified primary efficacy analysis was to examine results on a 7-point ordinal scale at Day 11 using a proportional odds model.

<u>7-Point Ordinal Scale:</u>
1. Death;
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring low flow supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration);
7. Not hospitalized.

Statistical Analysis Plan
The null hypothesis was that the odds of improvement for either the RDV 5-day group or 10-day group is the same as the odds of improvement for the standard of care only group with respect to clinical status assessed by a 7-point ordinal scale on Day 11. The alternative hypothesis was that the odds of improvement for the RDV 5-day group or 10-day group is

different from the odds of improvement for the standard of care only group with respect to clinical status assessed by a 7-point ordinal scale on Day 11. The odds ratio, 95% CI, and p-value for comparing treatment groups were provided. The analysis population is the FAS.

Subgroup analyses of the primary endpoint were planned for exploratory purposes only. Subgroups included age, sex, country, and oxygen support status based on the 7-point ordinal scale (invasive mechanical ventilation; high flow oxygen; low flow oxygen; room air).

The open-label design and primary endpoint choice may have favored the RDV 5-day group compared with the RDV 10-day group. Subjects in the RDV 10-day group may have had a lower chance of achieving discharge (the best category in the ordinal scale) between Day 6 and Day 10 because they were still assigned to receive intravenous therapy during this period of time.

One issue in this trial related to pre-specification. Specifically, the statistical analysis plan was not submitted to FDA or otherwise made public until after study completion. The preceding protocol did not discuss the specific multiplicity correction that would be applied for the primary analyses, nor the form of the proportional odds model.

Please refer to Dr. Daniel Rubin's statistics review for complete details.

Protocol Amendments
Two protocol amendments were made and are summarized below.

Amendment 1 (dated March 15, 2020)
• Primary endpoint was revised as follows:
- From: Proportion of participants discharged by Day 14.
- To: Clinical status assessed by a 7-point ordinal scale on Day 11 consisting of the following categories: 1, death; 2, hospitalized, receiving invasive mechanical ventilation or ECMO; 3, hospitalized, receiving noninvasive ventilation or high-flow oxygen devices; 4, hospitalized, requiring low-flow supplemental oxygen; 5, hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to Covid-19); 6, hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for RDV administration); and 7, not hospitalized.
• Study was revised to 2 parts: Part A (randomized) and newly added Part B (non-randomized)
• Sample size was increased from 600 (Part A) to up to 1600 (Part A [n=400], Part B [up to 1000]).
• Number of study sites was revised from 50 to up to 100.
• Inclusion criteria was revised as follows:
- Allowed enrollment of adolescents age ≥12 to 18 years.
- Removed the requirement to have fever (defined as temperature ≥ 36.6°C armpit, ≥ 37.2°C oral, ≥ 37.8°C rectal).
• Revised the statistical methodology and analysis due to changes in endpoints and study design.

Amendment 2 (dated April 29, 2020)

• Revised informed consent language to include informed consent with a legal representative and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions.
• Number of study sites was revised from 100 to up to 160.
• Exclusion criteria was revised as follows:
- From: Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing.
- To: Concurrent treatment or planned concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2.

Reviewer Comment: The primary endpoint was changed during this open-label trial. The Applicant stated that the decision to change the primary endpoint was made before any subjects were enrolled. No subjects were randomized before 03-15-2020 and one subject was randomized on 03-15-2020. Hence, the endpoint change may have had limited impact for this trial. Of note, the amended protocol was not submitted to the FDA until 03-17-2020, and the dates are unclear when IRBs had reviewed and implemented the protocol changes.

The other amendments were assessed as not to have significantly impact the conduct of this trial.

6.3.2. Study Results

Patient Disposition

A total of 612 subjects were screened for participation, of whom 596 were randomized: 197 subjects in the RDV 5-day group, 199 subjects in the RDV 10-day group, and 200 subjects in the standard of care group. A total of 584 randomized subjects (191 subjects in the RDV 5-day group, 193 subjects in the RDV 10-day group, and 200 subjects in the standard of care group) received at least one dose of study drug and were included in the FAS (Table 15).

Table 15. GS-US-540-5774 Treatment Duration, FAS

	RDV 5 Days (N=191) n (%)	RDV 10 Days (N=193) n (%)	Standard of care (N=200) n (%)
Treatment completion status			
Completed	145 (75.9%)	73 (37.8%)	N/A
Discontinued	46 (24.1%)	120 (62.2%)	N/A
Reason for treatment discontinuation			
Hospital discharge	35 (18.3%)	98 (50.8%)	N/A
Death	0 (0%)	1 (0.5%)	N/A
Non-fatal AE	4 (2.1%)	8 (4.1%)	N/A
Protocol violation	0 (0%)	2 (1%)	N/A
Withdrawal by subject	5 (2.6%)	6 (3.1%)	N/A
Investigator decision	1 (0.5%)	4 (2.1%)	N/A

Lost to follow-up	1 (0.5%)	0 (0%)	N/A
Non-compliance with study drug	0 (0%)	1 (0.5%)	N/A
Number of doses			
1	7 (3.7%)	8 (4.1%)	N/A
2	11 (5.8%)	18 (9.3%)	N/A
3	18 (9.4%)	26 (13.5%)	N/A
4	10 (5.2%)	20 (10.4%)	N/A
5	143 (74.9)	18 (9.3%)	N/A
6	1 (0.5%)	10 (5.2%)	N/A
7	1 (0.5%)	10 (5.2%)	N/A
8	0 (0%)	7 (3.6%)	N/A
9	0 (0%)	3 (1.6%)	N/A
10	0 (0%)	73 (37.8%)	N/A

Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: Of the 384 subjects treated with RDV, 166 subjects (43%) prematurely discontinued study treatment: 46 subjects (24%) in the RDV 5-day group and 120 subjects (62%) in the RDV 10-day group.

The most common reasons for premature discontinuation of RDV were:
• Hospital discharge: 35 subjects (18%) in the RDV 5-day group and 98 subjects (51%) in the RDV 10-day group.
• Adverse event: 4 subjects (2%) in the RDV 5-day group and 8 subjects (4%) in the RDV 10-day group.
• Subject decision to withdraw from study: 5 subjects (3%) in the RDV 5-day group and 6 subjects (3%) in the RDV 10-day group.

Protocol Violations/Deviations
A total of 37 important protocol deviations occurred among 35 subjects during the study:
• RDV 5-day group: 8 subjects had 9 protocol deviations
• RDV 10-day group: 11 subjects had 11 protocol deviations
• Standard of care group: 16 subjects had 17 protocol deviations

Of these 35 subjects, 33 subjects had a single deviation, and 2 subjects had 2 deviations. A total of 18 deviations were for subjects who did not meet the eligibility criteria. The second largest category (8 of 37) was for SAEs that were reported beyond 24 hours of identification. These protocol violations had no bearing on the interpretability of the trial results.

Baseline Characteristics
Tables 16 and 17 summarize the baseline demographic and disease characteristics for subjects in the FAS.

Table 16. GS-US-540-5774 Baseline Demographic Characteristics

Demographic Parameters	RDV 5 Days (N=191) n (%)	RDV 10 Days (N=193) n (%)	Standard of care (N=200) n (%)
Sex			
Male	114 (60%)	118 (61%)	125 (62.5%)
Female	77 (40%)	75 (39%)	75 (37.5%)
Age			
Mean years (SD)	56 (14.6)	55.3 (15.5)	55.3 (15.1)
Median (years)	58	56	57
Min, max (years)	12, 90	20, 94	23, 95
Age Group			
< 40 years	24 (12.6%)	31 (16.1%)	37 (18.5%)
40 - 64 years	118 (61.8%)	110 (57%)	105 (52.5%)
65 - 74 years	31 (16%)	26 (13.5%)	38 (19%)
≥ 75 years	18 (9%)	26 (13.5%)	20 (10%)
Race			
White	109 (57%)	107 (55%)	112 (56%)
Black or African American	35 (18%)	37 (19%)	27 (13.5%)
Asian	34 (18%)	31 (16%)	37 (18.5%)
American Indian/Alaska Native	2 (1%)	0 (0%)	1 (0.5%)
Native Hawaiian/Other Pacific Islander	1 (0.5%)	1 (0.5%)	1 (0.5%)
Other	5 (3%)	12 (6%)	15 (7.5%)
Not Permitted	5 (3%)	5 (3%)	7 (3.5%)
Ethnicity: Hispanic/Latino			
Yes	25 (13.1%)	42 (21.8%)	34 (17%)
No	162 (84.8%)	144 (74.6%)	152 (76%)
Not Permitted	4 (2.1%)	7 (3.6%)	13 (6.5%)
Missing	0 (0%)	0 (0%)	1 (0.5%)
Region			
United States	76 (39.8%)	99 (51.3%)	85 (42.5%)
France	2 (1%)	1 (0.5%)	0 (0%)
Germany	8 (4.2%)	6 (3.1%)	8 (4%)
Italy	30 (15.7%)	23 (11.9%)	26 (13%)
Netherlands	3 (1.6%)	0 (0%)	1 (0.5%)
Spain	37 (19.4%)	28 (14.5%)	31 (15.5%)
Switzerland	4 (2.1%)	5 (2.6%)	6 (3%)
United Kingdom	7 (3.7%)	9 (4.7%)	17 (8.5%)
Hong Kong	9 (4.7%)	11 (5.7%)	7 (3.5%)
South Korea	7 (3.7%)	4 (2.1%)	10 (5%)
Singapore	3 (1.6%)	6 (3.1%)	9 (4.5%)
Taiwan	5 (2.6%)	1 (0.5%)	0 (0%)

Source: ADSL, Study 5774 dataset

Reviewer Comment: The treatment arms are generally similar with respect to age, race, and sex.

Approximately 45% of the overall study population is from the US, which makes the data readily applicable to the US population. Additionally, the multinational nature of the study enabled more rapid study enrollment and also provided valuable data to ensure that the results are relevant to the US and ex-US populations as a global unmet medical need exists for effective antiviral regimens for subjects with COVID-19. Virologic response to an antiviral drug such as RDV is expected to be the same both in US and ex-US sites. The preponderance of subjects aged 40-64 (57%) and ≥ 65 years (27%) in the study population reflect the epidemiology of COVID-19.

Although a protocol amendment allowing enrollment of subjects aged 12-17 was implemented, only one subject aged 12-17 was enrolled in the randomized portion (Part A) of this clinical trial.

Table 17. GS-US-540-5774 Baseline Disease Characteristics

Baseline Disease Characteristics	RDV 5 Days (N=191) n (%)	RDV 10 Days (N=193) n (%)	Standard of care (N=200) n (%)
Days from symptom onset to first dose			
≤6	73 (38.2%)	80 (41.5%)	54 (27%)
7-9	53 (27.7%)	49 (25.4%)	63 (31.5%)
10-12	34 (17.8%)	31 (16.1%)	43 (21.5%)
≥13	31 (16.2%)	29 (15%)	37 (18.5%)
Median (interquartile range), days	8 (5, 11)	8 (5, 11)	9 (6, 11)
Baseline ordinal scale			
3. Hospitalized with noninvasive ventilation or high-flow oxygen	2 (1%)	1 (0.5%)	2 (1%)
4. Hospitalized with low-flow supplemental oxygen	29 (15.2%)	23 (11.9%)	36 (18%)
5. Hospitalized without supplemental oxygen but requiring ongoing medical care	160 (83.8%)	163 (84.5%)	160 (80%)
6. Hospitalized without supplemental oxygen or ongoing medical care	0 (0%)	6 (3.1%)	2 (1%)
Co-morbidities			
Hypertension	82 (42.9%)	85 (44%)	81 (40.5%)
Type 2 diabetes	71 (37.2%)	85 (44%)	76 (38%)
Obesity	53 (27.7%)	59 (30.6%)	55 (27.5%)
Asthma	22 (11.5%)	31 (16.1%)	28 (14%)
Immunodeficiency	7 (3.7%)	6 (3.1%)	2 (1%)
Cancer	36 (18.8%)	26 (13.5%)	33 (16.5)

Source: Table created by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: The most commonly reported comorbidities were hypertension (43%), type 2 diabetes mellitus (40%), and obesity (29%). The distribution of comorbidities was generally similar across treatment groups.

The treatment arms are well balanced with respect to median duration of symptoms prior to first dose of RDV (8 days).

Baseline clinical status (7-point ordinal scale) was generally similar across treatment groups. The following differences were not statistically significant:

- *Among subjects with a clinical status of 4 (hospitalized with low-flow supplemental oxygen), the rates were slightly higher in the standard of care group compared to the RDV 5-day group and RDV 10-day group, respectively (18% vs. 15% vs. 12%).*
- *Among subjects with a clinical status of 5 (hospitalized without supplemental oxygen but requiring ongoing medical care), the rates were slightly lower in the standard of care group compared to the RDV 5-day group and RDV 10-day group, respectively (80% vs. 84% vs. 85%).*

Efficacy Results - Primary Endpoint

Table 18 provides a summary of overall primary efficacy results.

Table 18. GS-US-540-5774 Overall Primary Efficacy (Day 11)

Ordinal Scale	RDV 5-Days (N=191)	RDV 10-Days (N=193)	Standard of care (N=200)
7 (Not hospitalized)	134 (70.2%)	125 (64.8%)	120 (60%)
6 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, other than per protocol RDV administration)	7 (3.7%)	9 (4.7%)	8 (4%)
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	38 (19.9%)	44 (22.8%)	46 (23%)
4 (Hospitalized, requiring low-flow supplemental oxygen)	7 (3.7%)	12 (6.2%)	11 (5.5%)
3 (Noninvasive ventilation or high-flow oxygen devices)	5 (2.6%)	0 (0%)	7 (3.5%)
2 (Invasive mechanical ventilation or ECMO)	0 (0%)	1 (0.5%)	4 (2%)
1 (Death)	0 (0%)	2 (1%)	4 (2%)
Proportional odds model (adjusted for baseline score)	OR = 1.65 (favors RDV) 95% CI: 1.09 to 2.48 p = 0.02	OR = 1.31 (favors RDV) 95% CI: 0.88 to 1.95 p = 0.18	

Notes: Odds ratios and p-values are based on proportional odds models that are not adjusted for baseline covariates. An odds ratio <1 favors standard of care and an odds ratio >1 favors RDV.
Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: The primary efficacy analysis was based on a proportional odds assessment of a 7-point ordinal scale at Day 11, with categories ranging from 1=death to 7=discharged alive. For this Day 11 endpoint, results were statistically significantly superior in the RDV 5-day group compared with the standard of care group: OR = 1.65; 95% CI; 1.09 to 2.48; p = 0.02. The RDV 10-day group also had favorable numerical trends compared with the standard of care group, but the difference did not reach statistical significance (p = 0.18).

Subgroup analyses
Although all subjects had SpO_2 >94% on room air at screening, 31 subjects (16%) in the RDV 5-day group, 24 subjects (12%) in the RDV 10-day group, and 38 subjects (19%) in the standard care group used supplemental oxygen on Day 1 because of deteriorating clinical status or for breathing comfort. Subgroup analyses were conducted to evaluate differences in treatment response based on subjects without any baseline oxygen supplementation (Table 19).

Table 19. GS-US-540-5774 Day 11 ordinal scale results in subjects without any baseline oxygen supplementation

Ordinal Scale	RDV 5-Days (N=160)	RDV 10-Days (N=169)	Standard of care (N=162)
7 (Not hospitalized)	114 (71.2%)	109 (64.5%)	100 (61.7%)
6 (Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care, other than per protocol RDV administration)	7 (4.4%)	8 (4.7%)	7 (4.3%)
5 (Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise])	33 (20.6%)	42 (24.9%)	42 (25.9%)
4 (Hospitalized, requiring low-flow supplemental oxygen)	3 (1.9%)	7 (4.1%)	8 (4.9%)
3 (Noninvasive ventilation or high-flow oxygen devices)	3 (1.9%)	0 (0%)	4 (2.5%)
2 (Invasive mechanical ventilation or ECMO)	0 (0%)	1 (0.6%)	1 (0.6%)
1 (Death)	0 (0%)	2 (1.2%)	0 (0%)
Proportional odds model (not adjusted for baseline score)	OR = 1.59 (favors RDV)	OR = 1.15 (favors RDV)	

	95% CI: 1.00 to 2.51 p = 0.05	95% CI: 0.75 to 1.79 p = 0.52	

Source: Analysis performed by Dr. Daniel Rubin, Statistics Reviewer

Reviewer Comment: In subjects with moderate COVID-19 disease who did not require oxygen baseline, results were statistically superior in the RDV 5-day group compared with the standard of care group: OR = 1.59; 95% CI; 1.00 to 2.51; p = 0.05. The trends in the RDV 10-day group were overall comparable with the standard of care group.

Readmissions
Readmissions were not recorded for this study.

Impact on Mortality
Of note, mortality was neither the pre-specified primary nor key secondary endpoint of this trial, and that the subgroup mortality assessments by ordinal scale were not prespecified and no adjustments for multiple comparisons were performed on confidence intervals or p-values.

Overall, 28-day mortality was 1% (2 subjects) in the RDV 5-day group vs. 2% (3 subjects) in the RDV 10-day group vs. 2% (4 subjects) in the standard care group; these differences were not statistically significant.

Reviewer Comment: All-cause mortality rates at Day 28 in moderate COVID-19 disease were low (1-2%) and comparable across treatment groups.

Virology
Limited virologic data were available, precluding meaningful assessment of virologic outcomes such as effect of RDV on SARS-CoV-2 viral load.

Overall Assessment: In this open-label, multicenter trial of patients with moderate COVID-19 pneumonia, the RDV 5-day group achieved a statistically significant difference in clinical status by Day 11 compared to the standard of care group. Patients receiving up to 10 days of RDV had favorable numerical trends compared to standard of care, but the differences were not statistically significant at Day 11.

Limitations of this trial included the open-label design and its possible influence on the timing of discharge decisions between groups assigned different therapy durations, and uncertainty regarding whether the Day 11 ordinal scale was the most appropriate primary endpoint for a trial in moderate disease.

Overall, the study findings add to the totality of the data supporting the efficacy of RDV in hospitalized patients with COVID-19. For a substantive proportion of patients not requiring supplemental oxygen, a 5-day treatment duration appears sufficient. However, the uncertainty about the optimal duration of treatment for patients will be addressed in labeling by providing

flexibility in the treatment duration guided by the severity of the infection and the patient's clinical response.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

In ACTT-1, the time to recovery was significantly faster with RDV compared to PBO. The median time to recovery was 10 days in the RDV group compared to 15 days in the PBO group (recovery rate ratio = 1.29; 95% CI: 1.12 to 1.49; p<0.001).

In GS-US-540-5773, treatment with 5-day and 10-day regimens of RDV resulted in similar clinical status on Day 14 in 397 hospitalized subjects with severe COVID-19.

In GS-US-540-5774, treatment with 5-days of RDV resulted in significantly greater odds of improved clinical status on Day 11 compared to standard of care in 584 hospitalized subjects with moderate COVID-19.

7.1.2. Subpopulations

Overall, demographic factors did not impact efficacy outcomes in in ACTT-1, GS-US-540-5773 and GS-US-540-5774. Please refer to the Statistics review by Dr. Daniel Rubin for complete details.

7.1.3. Dose and Dose-Response

Dose-ranging studies were not conducted as part of the Phase 3 development program. In GS-US-540-5773 and GS-US-540-5774, as well as in Phase 1, RDV was evaluated for different durations.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

The goal of treatment of COVID-19 in hospitalized patients is reduction in morbidity and mortality. Therefore, the Phase 3 studies were designed to evaluate clinically meaningful primary endpoints, consistent with the Guidance for Industry COVID-19: Developing Drugs and Biologic Products for Treatment or Prevention.[10]

Statistically significant treatment benefit over placebo for the primary endpoint of time to recovery was observed in ACTT-1 when RDV was administered to hospitalized adults with mild-to-moderate or severe COVID-19. There was a numerical trend towards lower mortality with RDV group [59/541 (11%)] vs. PBO [77/521 (15%)], with a two-sided p-value of 0.07. Evidence of clinically meaningful benefit was also supported by the low (4%) readmission rate, despite the preponderance of patients with severe disease.

Data from GS-US-540-5773 in hospitalized subjects with severe COVID-19 pneumonia showed numerical trends towards improved outcomes in the RDV 5-day group compared to the RDV 10-day group, although this difference was not statistically significant. These results are suggestive of a similar treatment effect with 5-day and 10-day regimens in this population, with appropriate caveats related to the open-label trial design. Of note, there were insufficient patients enrolled into GS-US-540-5773 who required IMV or ECMO at baseline to determine whether a 5-day course could be adequate for that subgroup.

Data from GS-US-540-5774 in hospitalized subjects with moderate COVID-19 pneumonia showed that the RDV 5-day group achieved a statistically significant difference in clinical status by Day 11 compared to the standard of care group. Patients receiving up to 10 days of RDV had favorable numerical trends compared to standard of care, but the differences were not statistically significant at Day 11. Limitations of this trial included the open-label design and its possible influence on the timing of discharge decisions between groups assigned different therapy durations, and uncertainty regarding whether the Day 11 ordinal scale was the most appropriate primary endpoint for a trial in moderate disease. Overall, the study findings add to the totality of the data supporting the efficacy of RDV in hospitalized patients with COVID-19.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

RDV would be the first FDA approved drug for patients who are hospitalized with COVID-19.

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

The efficacy of RDV for the treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg hospitalized for COVID-19 has been established by the results from the Phase 3 trials discussed in Section 6.

Data from ACTT-1 demonstrate that, for hospitalized adults with mild-to-moderate or severe COVID-19, treatment with up to 10 days of RDV yields improved clinical outcomes compared to placebo (PBO). The key findings from ACTT-1 are as follows:

- The primary efficacy analysis in the overall study population strongly favored RDV:
  - The time to recovery was significantly faster in the RDV group than the PBO group. Median time to recovery was 10 days in the RDV group compared to 15 days in the PBO group.
  - Recovery rate ratio = 1.29; 95% CI: 1.12 to 1.49; p<0.001.
- There was an interaction observed by baseline disease severity:
  - In patients with mild/moderate disease at enrollment (n=105), the median time to recovery was 5 days in both the RDV and PBO groups (recovery rate ratio, 1.22; [95% CI 0.82 to 1.81]).
  - In patients with severe disease at enrollment (n=957), the median time to

recovery was 11 days in the RDV group compared to 18 days in the PBO group (recovery rate ratio, 1.31; [95% CI, 1.12 to 1.52]; p<0.001).

- Results for the key secondary endpoint of the ordinal scale at Day 15 also favored RDV: odds ratio = 1.54 from a proportional odds model; 95% CI: 1.25 to 1.91; p<0.001.
- For Day 29 all-cause mortality, there was a numerical trend towards lower mortality in the RDV group [59/541 (11%)] than the PBO group [77/521 (15%)], with a two-sided p-value of 0.07.
- Despite the majority of patients having severe disease, a low (4%) readmission rate occurred in ACTT-1. Readmissions occurred in 26 subjects (5%) in the RDV group and 15 subjects (3%) in the PBO group.

Overall, results from this large, randomized, double-blind, placebo-controlled, multicenter trial in 1062 patients with mild-to-moderate or severe COVID-19 provided reliable and statistically persuasive evidence of benefit for RDV in a broad hospitalized patient population.

Although clear treatment benefit was not apparent in the subgroup of patients requiring mechanical ventilation or ECMO, the trial was not designed to robustly assess efficacy by ordinal scale level, and the findings do not exclude the possibility of benefit in these subjects. It is possible that the sample size and the duration of follow-up may not have been sufficient to potentially demonstrate efficacy in this subgroup.

With respect to patients who were hospitalized but did not have an oxygen requirement at enrollment, data from two randomized Phase 3 trials, GS-US-540-5774 (Part A) and ACTT-1, provide statistical evidence supporting the use of RDV:

- The main source of standalone evidence was Study GS-US-540-5774 (Part A): randomized, open-label trial comparing RDV for 10 days, RDV for 5 days, and standard of care in 584 patients with moderate COVID-19.
  - Study GS-US-540-5774 was restricted to moderate COVID-19 by requiring SpO_2 >94% on room air at screening.
  - The primary efficacy analysis was based on a proportional odds assessment of a 7-point ordinal scale at Day 11, with categories ranging from 1=death to 7=discharged alive.
  - For this Day 11 endpoint, results were significantly superior in the RDV 5-day group compared with the standard of care group: OR = 1.65; 95% CI; 1.09 to 2.48; p = 0.02. The RDV 10-day group also had favorable numerical trends compared with the standard of care group, but the difference did not reach statistical significance (p = 0.18).
  - Limitations of this trial included the open-label design and its possible influence on the timing of discharge decisions between groups assigned different therapy durations, and uncertainty regarding whether the Day 11 ordinal scale was the most appropriate primary endpoint for a trial in moderate disease.
- Additional evidence supporting RDV for the treatment of mild-to-moderate disease came from the aforementioned ACTT-1 randomized, double-blind trial comparing RDV for 10

days vs. PBO in 1062 patients with mild-to-moderate or severe COVID-19.

- ACTT-1 provided evidence for the treatment of mild-to-moderate COVID-19 because there were 138 randomized patients with a NIAID ordinal score of 4 at baseline, meaning they were hospitalized but did not require supplemental oxygen.
  - Results for the time to recovery analysis in this subgroup numerically favored RDV (recovery rate ratio = 1.29; 95% CI; 0.91 to 1.83) and were consistent with the overall study results.
  - Numerical trends favored RDV in this subgroup for the key secondary endpoint of the Day 15 ordinal scale (odds ratio = 1.48 from a proportional odds model; 95% CI: 0.80 to 2.77) and were consistent with overall study results.
  - Numerical trends favored RDV in this subgroup for the secondary endpoint of incidence of new oxygen use (36% [95% CI, 26% to 47%] in the RDV group compared to 44% in the PBO group [95% CI, 33% to 57%]).

From a clinical perspective, based on the results from the Phase 3 trials, the available data support the proposed indication for the treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg hospitalized for COVID-19.

8 Review of Safety

8.1. Safety Review Approach

The safety review focused on ACTT-1, GS-US-540-5773 and GS-US-540-5774 as these three Phase 3 studies will be described in labeling. Due to differences in study design (double-blinded, placebo controlled vs. open-label studies evaluating different durations, one with a standard of care group, one without a standard of care group), data from these three Phase 3 trials were not pooled.

Because ACTT-1 is a large, randomized, double-blind, placebo-controlled, multicenter trial in 1062 patients with mild-to-moderate or severe COVID-19, these data comprise the basis of the safety evaluation detailed below. GS-US-540-5773 and GS-US-540-5774 provided supportive safety data toward the overall safety assessment.

Unless otherwise specified, the analyses presented in this section were performed using the analysis datasets for ACTT-1, GS-US-540-5773 (Part A) and GS-US-540-5774 (Part A). Data were analyzed with Python software. Discrepancies between the FDA analyses and the Applicant's analyses were relatively minor and attributable to variable methods of pooling and subgroup analyses.

Hepatotoxicity was noted in early Phase 1 clinical development and led to dosing restrictions due to drug-related toxicity. Transaminase elevations were also observed in healthy volunteers

who received 200 mg of RDV followed by 100 mg doses for 5 to 10 days. Of note, transaminase elevations have been reported in patients with COVID-19 which complicates the safety assessment.[4-7, 25-28] A thorough hepatic safety review was conducted by FDA reviewers and compared to that of the Applicant.

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of RDV. Hypersensitivity reactions were a focus of scrutiny during the safety review, prompted by the emergence of additional cases through the EUA. The safety review also focused on adverse drug reactions of interest, including rash, renal events, hemorrhagic events, seizure events, pancytopenia, rhabdomyolysis, and pancreatitis.

Given the close temporal proximity of the finalized Phase 3 data and the timing of the original NDA submission, the Agency agreed with the Applicant's assessment that a safety update report (SUR) was not needed.

The Emergency Use Authorization (EUA) outlines mandatory reporting of all medication errors and adverse events (death, serious adverse events) considered to be potentially related to RDV. EUA safety data were reviewed by the Office of Surveillance and Epidemiology (OSE) and key findings are highlighted in the relevant safety sections of this report.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 20 describes the overall exposure to RDV in the studies that contribute to the primary safety database. The maximum duration of exposure to RDV was 14 days.

Table 20. Safety Population, Size and Denominators

Primary Safety Database for RDV Individuals exposed to RDV for the indication under review N= 1443			
Clinical Trial Groups	New Drug (RDV)[a] (n=1443)	Standard of care (n=200)	Placebo (PBO) (n=550)
Phase 1: Healthy Volunteers	131[b]	N/A	33
Phase 3: COVID-19 infected	1313	200	517

[a] The total numbers include subjects who received lower than the to-be-marketed dose of RDV, as well as subjects who received longer than the to-be-marketed duration of RDV.

[b] The Phase 1 studies include dose-ranging studies evaluating RDV.

8.2.2. Relevant characteristics of the safety population

Baseline characteristics for ACTT-1, GS-US-540-5773 and GS-US-540-5774 are described individually in Section 6.

Reviewer Comment: The bulk of the safety database is comprised of white men 50 years and older, including approximately 31% greater than 65 years of age. Subgroup analyses based on demographic factors will be presented in Section 8.6 of this review.

8.2.3. Adequacy of the safety database

The safety database for both products is adequate to assess the safety of RDV for the proposed indication, dosage regimen, duration of treatment, and patient population. ACTT-1 evaluated 532 subjects treated with the proposed dose and duration of RDV. Combined with supportive data from GS-US-540-5773 and GS-US-540-5774, these three Phase 3 trials provide an adequate safety database for treatment of adults and pediatric patients 12 years of age and older and weighing at least 40 kg hospitalized for COVID-19.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No data quality or data integrity issues were identified. For ACTT-1, GS-US-540-5773 and GS-US-540-5774, all narratives for deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment.

8.3.2. Categorization of Adverse Events

No issues were identified with respect to recording, coding, and categorizing AEs. The Applicant categorized AEs and SAEs in accordance with standard regulatory definitions.

In ACTT-1, GS-US-540-5773 and GS-US-540-5774, AEs were graded using the Division of AIDS (DAIDS) toxicity grading criteria. The Clinical Data Scientist (CDS) reviewer verified the Applicant's translation of verbatim terms to preferred terms for events reported in these Phase 3 trials.

8.3.3. Routine Clinical Tests

In ACTT-1, GS-US-540-5773 and GS-US-540-5774, routine clinical evaluation and laboratory testing occurred at pre-specified intervals:

- ACTT-1: Screening, Day 1 (Baseline), Daily until discharge; Follow-Up on Days 15, 22, and 29.
- GS-US-540-5773: Screening, Day 1 (Baseline), Days 2-14; Follow-Up on Day 28.
- GS-US-540-5774: Screening, Day 1 (Baseline), Days 2-14; Follow-Up on Day 28.

For these Phase 3 trials, the frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurement, physical examinations, and standard laboratory safety tests. Of note, prothrombin time (PT) was only collected in ACTT-1. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

In ACTT-1, all Grade 3 and 4 AEs, all SAEs, all AEs leading to study drug discontinuation, any Grade 2 or higher hypersensitivity reactions, and all laboratory abnormalities were recorded.

In GS-US-540-5773 and GS-US-540-5774, all AEs, all SAEs, all AEs leading to study drug discontinuation, and all laboratory abnormalities were recorded.

8.4. Safety Results

Each subsection in this section presents the results from ACTT-1, GS-US-540-5773 and GS-US-540-5774.

The Safety Analysis Set (SAS) was used for all analyses unless otherwise specified; all subjects who received at least one dose of study medication were included in the SAS. Treatment-emergent events were defined in the Phase 3 trials and in this review as any AE with onset date on or after study drug start date and no later than 30 days after permanent study drug discontinuation, or any AE leading to premature study drug discontinuation. For all analyses, subjects who experienced the same treatment-emergent AE on more than once occasion are counted only once, at the highest toxicity grade reported. When a "total" value is included for a column, it represents the total number of subjects included the analysis, rather than the total number of events.

An overall summary of safety events in ACTT-1, GS-US-540-5773 and GS-US-540-5774 is presented in Tables 21-23. The reviewer assessments and conclusions are overall similar to the Applicant's.

Table 21. Overview of Adverse Events, ACTT-1

Subjects Experiencing Event n (%)	RDV 10 Days N=532	PBO 10 Days N=516
Any AE*	305 (57.3%)	323 (62.6%)
Related AE*	41 (7.7%)	47 (9.1%)
Any Grade 3 or 4 AE	273 (51.3%)	295 (57.2%)
Related Grade 3 or 4 AE	41 (7.7%)	46 (8.9%)
SAE	131 (24.6%)	163 (31.6%)
Related SAE	2 (0.4%)	3 (0.6%)
Death	60 (11.3%)	77 (14.9%)
Related deaths	0 (0%)	0 (0%)
Discontinuation of study drug due to AE	57 (10.7%)	77 (14.9%)
D/c of study drug due to related AEs	11 (2.1%)	15 (2.9%)
Dose interruption due to AE	32 (6.0%)	49 (9.5%)
Interruption of study drug due to related AEs	14 (2.6%)	20 (3.9%)

*Any Grade 2 or higher suspected drug-related hypersensitivity reactions and all Grade 3 or higher AEs.

Reviewer Comment: Higher rates of deaths, SAEs, AEs, Grade 3/4 AEs, AEs leading to discontinuation, and AEs leading to dose interruption were observed with PBO compared to RDV.

Table 22. Overview of Adverse Events, GS-US-540-5773

Subjects Experiencing Event n (%)	RDV 5 Days N=200	RDV 10 Days N=197
Any AE	143 (71.5%)	148 (75.1%)
Related AE	33 (16.5%)	40 (20.3%)
Grade 3 or 4 AE	53 (26.5%)	71 (36.0%)
Related Grade 3 or 4 AE	8 (4.0%)	10 (5.1%)
SAE	43 (21.5%)	68 (34.5%)
Related SAE	3 (1.5%)	4 (2.0%)
Death	24 (12.0%)	28 (14.2%)
Related deaths	0 (0%)	0 (0%)
Discontinuation of study drug due to AE	9 (4.5%)	22 (11.2%)
D/c of study drug due to related AEs	5 (2.5%)	11 (5.6%)
Dose interruption due to AE	0 (0%)	4 (2.0%)
Interruption of study drug due to related AEs	0 (0%)	4 (2.0%)

Source: ADAE dataset, Study 5773

Reviewer Comment: Higher rates of deaths, SAEs, AEs, and AEs leading to discontinuation were observed in the RDV in 10-day group compared to the RDV 5-day group.

Table 23. Overview of Adverse Events, GS-US-540-5774

Subjects Experiencing Event n (%)	RDV 5 Days N=191	RDV 10 Days N=193	Standard of care N=200
Any AE	97 (50.8%)	106 (54.9%)	90 (45.0%)
Related AE	36 (18.8%)	25 (13.0%)	N/A
Grade 3 or 4 AE	20 (10.5%)	19 (9.8%)	20 (10.0%)
Related Grade 3 or 4 AE	6 (3.1%)	5 (2.6%)	N/A
SAE	8 (4.2%)	7 (3.6%)	18 (9.0%)
Related SAE	1 (0.5%)	0 (0%)	N/A
Death	2 (1.0%)	2 (1.0%)	4 (2.0%)
Related deaths	0 (0%)	0 (0%)	N/A
Discontinuation of study drug due to AE	4 (2.1%)	7 (3.6%)	N/A
D/c of study drug due to related AEs	4 (2.1%)	5 (2.6%)	N/A
Dose interruption due to AE	4 (2.1%)	0 (0%)	N/A
Interruption of study drug due to related AEs	4 (2.1%)	0 (0%)	N/A

Source: ADAE dataset, Study 5774

Reviewer Comment: Higher rates of AEs were observed in the RDV groups compared to the standard of care group. Rates of Grade 3/4 AEs were generally similar across all treatment groups. Lower rates of SAEs were observed in the RDV groups compared to the standard of care group.

8.4.1. Deaths

In ACTT-1, GS-US-540-5773 and GS-US-540-5774, deaths were overall consistent with those observed in a hospitalized patient population.

ACTT-1

Deaths occurred in 11% of subjects in the RDV group and 15% of subjects in the PBO group (Table 24).

Table 24. Deaths, ACTT-1

Preferred Term	RDV 10 Days N=532	PBO 10 Days N=516
Cardiac arrest	7 (1.3%)	4 (0.8%)
Hypotension	2 (0.4%)	0 (0%)
Intestinal ischaemia	2 (0.4%)	0 (0%)
Pneumonia aspiration	2 (0.4%)	0 (0%)
Multiple organ dysfunction syndrome	4 (0.8%)	3 (0.6)
Arrhythmia	1 (0.2%)	0 (0%)
Chronic respiratory failure	1 (0.2%)	0 (0%)
Pulmonary haemorrhage	1 (0.2%)	0 (0%)
Pulseless electrical activity	1 (0.2%)	0 (0%)
Small intestinal perforation	1 (0.2%)	0 (0%)
Hypoxia	1 (0.2%)	1 (0.2%)
Shock	1 (0.2%)	1 (0.2%)
Septic shock	4 (0.8%)	5 (1.0%)
Acute respiratory distress syndrome	4 (0.8%)	5 (1.0%)
COVID-19	2 (0.4%)	3 (0.6%)
COVID-19 pneumonia	1 (0.2%)	2 (0.4%)
Death	0 (0%)	1 (0.2%)
Oxygen saturation decreased	0 (0%)	1 (0.2%)
Respiratory disorder	0 (0%)	1 (0.2%)
Respiratory distress	2 (0.4%)	4 (0.8%)
Cardio-respiratory arrest	1 (0.2%)	3 (0.6%)
Cardiogenic shock	0 (0%)	2 (0.4%)
Myocardial infarction	0 (0%)	3 (0.6%)
Pulmonary embolism	0 (0%)	4 (0.8%)
Acute respiratory failure	2 (0.4%)	6 (1.2%)
Respiratory failure	20 (3.8%)	28 (5.4%)
TOTAL SUBJECTS	60 (11.3%)	77 (14.9%)

Source: ADAE dataset, ACTT-1

Reviewer Comment: Higher rates of deaths occurred in the PBO group compared to the RDV group. All of the deaths were assessed as unrelated to study drug by the study investigators. The clinical narratives were reviewed and I agree with the investigators' assessments that these deaths were unrelated to study medication. Higher rates of deaths were observed in PBO compared to RDV.

GS-US-540-5773

Deaths occurred in 12% of subjects in the RDV 5-day group and 14% of subjects in RDV 10-day group (Table 25).

Table 25. Deaths, GS-US-540-5773

Preferred Term	RDV 5 Days N=200	RDV 10 Days N=197
Respiratory failure	5 (2.5%)	3 (1.5%)
Corona virus infection	3 (1.5%)	1 (0.5%)
Acute kidney injury	1 (0.5%)	0 (0%)
Death	1 (0.5%)	0 (0%)
Pneumonia	1 (0.5%)	0 (0%)
Sepsis	1 (0.5%)	0 (0%)
Thrombocytopenia	1 (0.5%)	0 (0%)
Ventricular tachycardia	1 (0.5%)	0 (0%)
Pneumonia viral	2 (1.0%)	2 (1.0%)
Pulmonary embolism	1 (0.5%)	1 (0.5%)
Septic shock	2 (1.0%)	3 (1.5%)
Cardiac arrest	0 (0%)	1 (0.5%)
Gastrointestinal haemorrhage	0 (0%)	1 (0.5%)
Haemodynamic instability	0 (0%)	1 (0.5%)
Hypoxia	0 (0%)	1 (0.5%)
Respiratory distress	0 (0%)	1 (0.5%)
Shock haemorrhagic	0 (0%)	1 (0.5%)
Thrombosis	0 (0%)	1 (0.5%)
Multiple organ dysfunction syndrome	2 (1.0%)	4 (2.0%)
Acute respiratory distress syndrome	1 (0.5%)	3 (1.5%)
Pneumothorax	1 (0.5%)	3 (1.5%)
Acute respiratory failure	3 (1.5%)	6 (3.0%)
TOTAL SUBJECTS	24 (12.0%)	28 (14.2%)

Source: ADAE dataset, Study 5773

Reviewer Comment: Slightly higher rates of deaths occurred in the RDV 10-day group compared to the RDV 5-day group. All of the deaths were assessed as unrelated to study drug by the study investigators. The clinical narratives were reviewed and I agree with the investigators' assessments that these deaths were unrelated to study medication.

GS-US-540-5774

Deaths occurred in 1% of subjects in the RDV 5-day group, 1% of subjects in the RDV 10-day

group, and 2% of subjects in the standard of care group (Table 26).

Table 26. Deaths, GS-US-540-5774

Preferred Term	RDV 5 Days N=191	RDV 10 Days N=193	Standard of care N=200
Respiratory failure	1 (0.5%)	0 (0%)	1 (0.5%)
Acute respiratory distress syndrome	1 (0.5%)	0 (0%)	0 (0%)
Atrioventricular block complete	0 (0%)	1 (0.5%)	0 (0%)
Haemodynamic instability	0 (0%)	1 (0.5%)	0 (0%)
Cardiac arrest	0 (0%)	0 (0%)	2 (1.0%)
TOTAL SUBJECTS	2 (1.0%)	2 (1.0%)	4 (2.0%)

Source: ADAE dataset, Study 5774

Reviewer Comment: There were low rates of deaths (1-2%) across treatment groups. All of the deaths were assessed as unrelated to study drug by the study investigators. The clinical narratives were reviewed and I agree with the investigators' assessments that these deaths were unrelated to study medication.

Overall Assessment: No specific drug-related safety concern has been identified from the broad range of deaths reported in ACTT-1, GS-US-540-5773 and GS-US-540-5774. There were no treatment-related deaths.

8.4.2. Serious Adverse Events

In ACTT-1, GS-US-540-5773 and GS-US-540-5774, SAEs were overall consistent with those observed in a hospitalized patient population.

ACTT-1

SAEs occurred in 25% of subjects in the RDV group and 32% of subjects in the PBO group. The majority of these SAEs were assessed by investigators as not related to study drug. Table 27 provides a summary of SAEs by system organ class (SOC) and Preferred Term (PT).

Table 27. Treatment-emergent SAEs by System Organ Class (SOC) and Preferred Term (PT), ACTT-1

SOC PT	RDV 10 Days N=532	PBO 10 Days N=516
Gastrointestinal disorders (SOC)	7 (1.3%)	3 (0.6%)
Intestinal ischaemia	3 (0.6%)	0 (0%)
Diarrhoea	1 (0.2%)	0 (0%)
Duodenal perforation	1 (0.2%)	0 (0%)
Gastrointestinal haemorrhage	1 (0.2%)	0 (0%)
Small intestinal perforation	1 (0.2%)	0 (0%)
Haematemesis	0 (0%)	1 (0.2%)
Peptic ulcer haemorrhage	0 (0%)	1 (0.2%)
Small intestinal obstruction	0 (0%)	1 (0.2%)

Metabolism and nutrition disorders (SOC)	4 (0.8%)	2 (0.4%)
Dehydration	1 (0.2%)	0 (0%)
Hypernatraemia	1 (0.2%)	0 (0%)
Hyponatraemia	1 (0.2%)	0 (0%)
Acidosis	1 (0.2%)	1 (0.2%)
Decreased appetite	0 (0%)	1 (0.2%)
Investigations (SOC)	7 (1.3%)	5 (1.0%)
Glomerular filtration rate decreased	5 (0.9%)	2 (0.4%)
Blood creatinine increased	1 (0.2%)	0 (0%)
Lymphocyte count decreased	1 (0.2%)	0 (0%)
Oxygen saturation decreased	1 (0.2%)	1 (0.2%)
Haemoglobin decreased	1 (0.2%)	2 (0.4%)
Cardiac disorders (SOC)	24 (4.5%)	22 (4.3%)
Atrial fibrillation	5 (0.9%)	1 (0.2%)
Cardiac arrest	10 (1.9%)	7 (1.4%)
Ventricular tachycardia	2 (0.4%)	0 (0%)
Acute coronary syndrome	1 (0.2%)	0 (0%)
Arrhythmia	1 (0.2%)	0 (0%)
Palpitations	1 (0.2%)	0 (0%)
Pulseless electrical activity	1 (0.2%)	0 (0%)
Ventricular fibrillation	1 (0.2%)	0 (0%)
Acute myocardial infarction	1 (0.2%)	1 (0.2%)
Cardiac failure	1 (0.2%)	1 (0.2%)
Cardiac tamponade	0 (0%)	1 (0.2%)
Cardio-respiratory arrest	1 (0.2%)	3 (0.6%)
Cardiogenic shock	0 (0%)	2 (0.4%)
Supraventricular tachycardia	0 (0%)	3 (0.6%)
Myocardial infarction	0 (0%)	4 (0.8%)
Blood and lymphatic system disorders (SOC)	2 (0.4%)	1 (0.2%)
Coagulopathy	1 (0.2%)	0 (0%)
Febrile neutropenia	1 (0.2%)	0 (0%)
Anaemia	0 (0%)	1 (0.2%)
Injury, poisoning and procedural complications (SOC)	2 (0.4%)	1 (0.2%)
Hip fracture	1 (0.2%)	0 (0%)
Infusion related reaction	1 (0.2%)	0 (0%)
Procedural pneumothorax	0 (0%)	1 (0.2%)
Skin and subcutaneous tissue disorders (SOC)	1 (0.2%)	0 (0%)
Subcutaneous emphysema	1 (0.2%)	0 (0%)
Vascular disorders (SOC)	13 (2.4%)	12 (2.3%)
Embolism venous	1 (0.2%)	0 (0%)
Peripheral artery occlusion	1 (0.2%)	0 (0%)
Shock haemorrhagic	1 (0.2%)	0 (0%)
Shock	5 (0.9%)	4 (0.8%)
Deep vein thrombosis	1 (0.2%)	1 (0.2%)
Hypotension	4 (0.8)	7 (1.4%)

Nervous system disorders (SOC)	8 (1.5%)	7 (1.4%)
Cerebrovascular accident	3 (0.6%)	1 (0.2%)
Seizure	2 (0.4%)	1 (0.2%)
Cerebellar infarction	1 (0.2%)	0 (0%)
Cerebral haemorrhage	1 (0.2%)	0 (0%)
Encephalopathy	1 (0.2%)	0 (0%)
Subarachnoid haemorrhage	1 (0.2%)	0 (0%)
Depressed level of consciousness	0 (0%)	1 (0.2%)
Haemorrhagic transformation stroke	0 (0%)	1 (0.2%)
Hemiparesis	0 (0%)	1 (0.2%)
Intensive care unit acquired weakness	0 (0%)	1 (0.2%)
Ischaemic stroke	0 (0%)	1 (0.2%)
General disorders and administration site conditions (SOC)	7 (1.3%)	6 (1.2%)
Multiple organ dysfunction syndrome	5 (0.9%)	3 (0.6%)
Chest pain	1 (0.2%)	0 (0%)
Pyrexia	1 (0.2%)	2 (0.4%)
Death	0 (0%)	1 (0.2%)
Psychiatric disorders (SOC)	1 (0.2%)	1 (0.2%)
Mental status changes	1 (0.2%)	0 (0%)
Psychotic disorder	0 (0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.2%)	2 (0.4%)
Pain in extremity	1 (0.2%)	0 (0%)
Myalgia	0 (0%)	1 (0.2%)
Myopathy	0 (0%)	1 (0.2%)
Immune system disorders (SOC)	0 (0%)	1 (0.2%)
Drug hypersensitivity	0 (0%)	1 (0.2%)
Hepatobiliary disorders (SOC)	0 (0%)	2 (0.4%)
Hepatitis	0 (0%)	1 (0.2%)
Ischaemic hepatitis	0 (0%)	1 (0.2%)
Surgical and medical procedures (SOC)	7 (1.3%)	12 (2.3%)
Mechanical ventilation	1 (0.2%)	3 (0.6%)
Endotracheal intubation	6 (1.1%)	9 (1.7%)
Renal and urinary disorders (SOC)	10 (1.9%)	19 (3.7%)
Renal impairment	1 (0.2%)	3 (0.6%)
Renal failure	2 (0.4%)	5 (1.0%)
Acute kidney injury	7 (1.3%)	12 (2.3%)
Infections and infestations (SOC)	18 (3.4%)	28 (5.4%)
Catheter bacteraemia	1 (0.2%)	0 (0%)
Gangrene	1 (0.2%)	0 (0%)
Infectious pleural effusion	1 (0.2%)	0 (0%)
Staphylococcal bacteraemia	1 (0.2%)	0 (0%)
Urinary tract infection	1 (0.2%)	0 (0%)
Bacteraemia	1 (0.2%)	2 (0.4%)
Covid-19 pneumonia	1 (0.2%)	2 (0.4%)
Sepsis	1 (0.2%)	2 (0.4%)

Bacterial sepsis	0 (0%)	1 (0.2%)
Endocarditis bacterial	0 (0%)	1 (0.2%)
Pneumonia	0 (0%)	2 (0.4%)
Covid-19	2 (0.4%)	5 (1.0%)
Septic shock	8 (1.5%)	15 (2.9%)
Respiratory, thoracic and mediastinal disorders (SOC)	73 (13.7%)	100 (19.4%)
Pneumonia aspiration	4 (0.8%)	2 (0.4%)
Dyspnoea	3 (0.6%)	1 (0.2%)
Acute respiratory distress syndrome	7 (1.3%)	5 (1.0%)
Chronic respiratory failure	1 (0.2%)	0 (0%)
Haemoptysis	1 (0.2%)	0 (0%)
Pulmonary haemorrhage	1 (0.2%)	0 (0%)
Pulmonary embolism	5 (0.9%)	4 (0.8%)
Hypoxia	4 (0.8%)	4 (0.8%)
Pneumothorax	5 (0.9%)	5 (1.0%)
Respiratory disorder	0 (0%)	2 (0.4%)
Respiratory distress	6 (1.1%)	11 (2.1%)
Acute respiratory failure	8 (1.5%)	14 (2.7%)
Respiratory failure	35 (6.6%)	58 (11.2%)
TOTAL SUBJECTS	131 (24.6%)	163 (31.6%)

Source: ADAE dataset, ACTT-1

Reviewer Comment: Higher rates of SAEs occurred in the PBO group compared to the RDV group. The clinical narratives were reviewed and I agree with the investigators' assessments that most of these SAEs are unlikely to be related to study medication.

Related SAEs were reported in in 2 (0.4%) subjects in the RDV group. These narratives are briefly summarized below:

- Subject ID# (b) (6): 69-year-old male who received the first dose of RDV on (b) (6). On (b) (6), subject had a generalized tonic-clonic seizure shortly after receiving study drug. Physical examination revealed delirium and psychomotor agitation which persisted for 36 hours before resolving. Computerized tomography (CT) scan of the head revealed no acute intracranial abnormality. Study drug was permanently withdrawn following this event. Subject had no neurological history and was not receiving any medications known to cause seizure or lower seizure threshold.
- Subject ID# (b) (6): 73-year-old female on 4-6 L of oxygen with medical history of hypertension and hyperlipidemia experienced infusion related reaction described as rigors, fever, HR 144 bpm, BP 148/67 and increased oxygen requirements (O2 saturation 80% on 4 L nasal cannula, requiring use of a non-rebreather mask) 30 minutes after her first dose of RDV. No rash or stridor. Study drug was discontinued. Event resolved.

Reviewer Comment: The clinical narratives were reviewed and I agree with the investigators' assessments that these SAEs are related to study medication.

GS-US-540-5773

SAEs occurred in 22% of subjects in the RDV 5-day group and 35% of subjects in the RDV 10-day group. The majority of these SAEs were assessed by investigators as not related to study drug. Table 28 provides a summary of SAEs by system organ class (SOC) and Preferred Term (PT).

Table 28. Treatment-emergent SAEs by System Organ Class (SOC) and Preferred Term (PT), GS-US-540-5773

SOC PT	RDV 5 Days N=200	RDV 10 Days N=197
Gastrointestinal disorders (SOC)	1 (0.5%)	1 (0.5%)
Dysphagia	1 (0.5%)	0 (0%)
Gastrointestinal haemorrhage	0 (0%)	1 (0.5%)
Hepatobiliary disorders (SOC)	1 (0.5%)	1 (0.5%)
Hepatic failure	1 (0.5%)	0 (0%)
Hypertransaminasaemia	0 (0%)	1 (0.5%)
Investigations (SOC)	4 (2.0%)	5 (2.5%)
Transaminases increased	3 (1.5%)	2 (1.0%)
Oxygen saturation decreased	1 (0.5%)	0 (0%)
Glomerular filtration rate decreased	0 (0%)	1 (0.5%)
Hepatic enzyme increased	0 (0%)	1 (0.5%)
Liver function test increased	0 (0%)	1 (0.5%)
Cardiac disorders (SOC)	3 (1.5%)	4 (2.0%)
Arrhythmia	1 (0.5%)	0 (0%)
Bradycardia	1 (0.5%)	0 (0%)
Supraventricular tachycardia	1 (0.5%)	0 (0%)
Ventricular tachycardia	1 (0.5%)	0 (0%)
Acute myocardial infarction	0 (0%)	1 (0.5%)
Cardiac failure acute	0 (0%)	1 (0.5%)
Cardiac arrest	0 (0%)	2 (1.0%)
Renal and urinary disorders (SOC)	3 (1.5%)	4 (2.0%)
Renal failure	1 (0.5%)	1 (0.5%)
Acute kidney injury	2 (1.0%)	3 (1.5%)
Blood and lymphatic system disorders (SOC)	1 (0.5%)	2 (1.0)
Thrombocytopenia	1 (0.5%)	0 (0%)
Anaemia	0 (0%)	1 (0.5%)
Neutropenia	0 (0%)	1 (0.5%)
Nervous system disorders (SOC)	0 (0%)	1 (0.5%)
Cerebral microhaemorrhage	0 (0%)	1 (0.5%)
General disorders and administration site conditions (SOC)	3 (1.5%)	6 (3.0%)
Death	1 (0.5%)	0 (0%)
Asthenia	0 (0%)	1 (0.5%)
Pyrexia	0 (0%)	1 (0.5%)
Multiple organ dysfunction syndrome	2 (1.0%)	4 (2.0%)
Infections and infestations (SOC)	15 (7.5%)	18 (9.1%)
Pneumonia	2 (1.0%)	0 (0%)
Pneumonia viral	3 (1.5%)	2 (1.0%)

Sepsis	2 (1.0%)	1 (0.5%)
Superinfection bacterial	0 (0%)	1 (0.5%)
Corona virus infection	8 (4.0%)	10 (5.1%)
Septic shock	2 (1.0%)	5 (2.5%)
Vascular disorders (SOC)	1 (0.5%)	6 (3.0%)
Haemodynamic instability	0 (0%)	1 (0.5%)
Shock haemorrhagic	0 (0%)	1 (0.5%)
Thrombosis	0 (0%)	1 (0.5%)
Hypotension	1 (0.5%)	3 (1.5%)
Respiratory, thoracic and mediastinal disorders (SOC)	28 (14.0%)	46 (23.4%)
Dyspnoea	4 (2.0%)	1 (0.5%)
Pulmonary thrombosis	1 (0.5%)	0 (0%)
Respiratory arrest	1 (0.5%)	0 (0%)
Respiratory disorder	1 (0.5%)	1 (0.5%)
Haemoptysis	0 (0%)	1 (0.5%)
Respiratory distress	3 (1.5%)	5 (2.5%)
Hypoxia	2 (1.0%)	4 (2.0%)
Pneumothorax	2 (1.0%)	4 (2.0%)
Acute respiratory distress syndrome	1 (0.5%)	4 (2.0%)
Pulmonary embolism	1 (0.5%)	4 (2.0%)
Respiratory failure	6 (3.0%)	10 (5.1%)
Acute respiratory failure	10 (5.0%)	18 (9.1%)
TOTAL SUBJECTS	43 (21.5%)	68 (34.5%)

Source: ADAE dataset, Study 5773

Reviewer Comment: Higher rates of SAEs occurred in the RDV 10-day group compared to the RDV 5-day group. The clinical narratives were reviewed and I agree with the investigators' assessments that most of these SAEs are unlikely to be related to study medication.

Related SAEs were reported in 3 (2%) subjects in the RDV 5-day group. These narratives are briefly summarized below:

- Subject ID# (b) (6) (59-year-old male): On Day 3, subject experienced serious transaminases increased of Grade 4. RDV was discontinued. Duration of treatment was 3 days. The event was unresolved at the date of death on Day 24 due to respiratory failure.
- Subject ID# (b) (6) (30-year-old male): On Day 5, subject experienced serious transaminases increased of Grade 3. RDV was discontinued. Duration of treatment was 4 days. The event was resolved on Day 10.
- Subject ID# (b) (6) (43-year-old male): On Day 3, subject experienced serious transaminases increased of Grade 4. RDV was discontinued. Duration of treatment was 2 days. The event was unresolved as of the data cut-off date.

Related SAEs were reported in 4 (2%) subjects in the RDV 10-day group. These narratives are briefly summarized below:

- Subject ID# (b) (6) (69-year-old female): On Day 3, subject experienced serious transaminases increased of Grade 4. RDV was discontinued. Duration of treatment was 3 days. The event was resolved on Day 34.
- Subject ID: (b) (6) (71-year-old male): On Day 4, subject experienced serious transaminases increased of Grade 3. Duration of treatment was 3 days. The event was resolved on Day 34. (Of note, RDV had been discontinued on Day 3 after subject experienced non-serious acute kidney injury of Grade 3; although this renal event was considered not related to RDV, RDV was stopped because creatinine clearance decreased below the 50 mL/min threshold that was prespecified in the protocol. The renal Grade 3 event was resolved on Day 5.)
- Subject ID# (b) (6) (60-year-old male): On Day 4, subject experienced serious hepatic enzyme increased of Grade 4. RDV was discontinued. Duration of treatment was 5 days. The event was resolved on Day 9.
- Subject ID# (b) (6) (39-year-old male): On Day 5, subject experienced serious hypertransaminasaemia of Grade 3. RDV was discontinued. Duration of treatment was 4 days. The event was unresolved as of the data cut-off date.

Reviewer Comment: The clinical narratives were reviewed and I agree with the investigators' assessments that these SAEs may be related to study medication.

GS-US-540-5774

SAEs occurred in 4% of subjects in the RDV 5-day group, 4% of subjects in the RDV 10-day group, and 9% of subjects in the standard of care group. The majority of these SAEs were assessed by investigators as not related to study drug. Table 29 provides a summary of SAEs by system organ class (SOC) and Preferred Term (PT).

Table 29. Treatment-emergent SAEs by System Organ Class (SOC) and Preferred Term (PT), GS-US-540-5774

SOC PT	RDV 5 Days N=191	RDV 10 Days N=193	Standard of care N=200
Respiratory, thoracic and mediastinal disorders (SOC)	4 (2.1%)	2 (1.0%)	10 (5.0%)
Acute respiratory distress syndrome	1 (0.5%)	0 (0%)	0 (0%)
Pulmonary embolism	1 (0.5%)	0 (0%)	0 (0%)
Respiratory failure	1 (0.5%)	0 (0%)	2 (1.0%)
Dyspnoea	1 (0.5%)	1 (0.5%)	0 (0%)
Acute respiratory failure	0 (0%)	0 (0%)	5 (2.5%)
Lung opacity	0 (0%)	0 (0%)	1 (0.5%)
Pneumonia aspiration	0 (0%)	1 (0.5%)	0 (0%)
Respiratory distress	0 (0%)	1 (0.5%)	2 (1.0%)
Investigations (SOC)	1 (0.5%)	1 (0.5%)	0 (0%)
Heart rate decreased	1 (0.5%)	0 (0%)	0 (0%)
Alanine aminotransferase increased	0 (0%)	1 (0.5%)	0 (0%)
Nervous system disorders (SOC)	1 (0.5%)	1 (0.5%)	0 (0%)
Cerebrovascular accident	1 (0.5%)	0 (0%)	0 (0%)
Depressed level of consciousness	0 (0%)	1 (0.5%)	0 (0%)

Vascular disorders (SOC)	1 (0.5%)	1 (0.5%)	0 (0%)
Deep vein thrombosis	1 (0.5%)	0 (0%)	0 (0%)
Haemodynamic instability	0 (0%)	1 (0.5%)	0 (0%)
Blood and lymphatic system disorders (SOC)	1 (0.5%)	0 (0%)	1 (0.5%)
Febrile neutropenia	1 (0.5%)	0 (0%)	0 (0%)
Anaemia	0 (0%)	0 (0%)	1 (0.5%)
General disorders and administration site conditions (SOC)	1 (0.5%)	0 (0%)	1 (0.5%)
Impaired healing	1 (0.5%)	0 (0%)	0 (0%)
Chest pain	0 (0%)	0 (0%)	1 (0.5%)
Renal and urinary disorders (SOC)	1 (0.5%)	0 (0%)	1 (0.5%)
Renal colic	1 (0.5%)	0 (0%)	0 (0%)
Acute kidney injury	0 (0%)	0 (0%)	1 (0.5%)
Cardiac disorders (SOC)	0 (0%)	1 (0.5%)	3 (1.5%)
Cardiac arrest	0 (0%)	0 (0%)	2 (1.0%)
Myocardial infarction	0 (0%)	0 (0%)	1 (0.5%)
Atrioventricular block complete	0 (0%)	1 (0.5%)	0 (0%)
Infections and infestations (SOC)	0 (0%)	1 (0.5%)	3 (1.5%)
Bacteraemia	0 (0%)	0 (0%)	1 (0.5%)
Corona virus infection	0 (0%)	0 (0%)	1 (0.5%)
Pneumonia	0 (0%)	0 (0%)	1 (0.5%)
Arthritis infective	0 (0%)	1 (0.5%)	0 (0%)
Gastrointestinal disorders (SOC)	0 (0%)	1 (0.5%)	1 (0.5%)
Intestinal ischaemia	0 (0%)	0 (0%)	1 (0.5%)
Vomiting	0 (0%)	1 (0.5%)	0 (0%)
Metabolism and nutrition disorders (SOC)	0 (0%)	0 (0%)	1 (0.5%)
Fluid overload	0 (0%)	0 (0%)	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0 (0%)	0 (0%)	1 (0.5%)
Cancer pain	0 (0%)	0 (0%)	1 (0.5%)
TOTAL SUBJECTS	8 (4.2%)	7 (3.6%)	18 (9.0%)

Source: ADAE dataset, Study 5774

Reviewer Comment: Higher rates of SAEs occurred in the standard of care group compared to both RDV groups.

Related SAEs were reported in in 1 (0.5%) subject in the 5-day group. That subject (ID# (b) (6) (b) (6)) had heart rate decreased as the SAE.

- Subject ID# (b) (6) (26-year-old male): On Day 3, subject experienced Grade 4 heart rate decreased. Subject was asymptomatic. RDV was discontinued. Duration of treatment was 3 days. The event was resolved on Day 3.

Reviewer Comment: The clinical narrative was reviewed and I agree with the investigators' assessment that this SAE may be related to study medication.

Overall Assessment: No specific drug-related safety concern has been identified from the broad range of SAEs reported in ACTT-1, GS-US-540-5773 and GS-US-540-5774. All narratives were reviewed and did not uncover new concerns. The reviewer assessments and conclusions are similar to the Applicant's.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs were overall consistent with a hospitalized patient population.

ACTT-1

Discontinuations due to AEs occurred in 11% of subjects in the RDV group and 15% of subjects in the PBO group (Table 30). The majority of these events were assessed by investigators as not related to study drug.

Table 30. Adverse Events Leading to Study Drug Discontinuation by System Organ Class (SOC) and Preferred Term (PT), ACTT-1

SOC PT	RDV 10 Days N=532	PBO 10 Days N=516
Blood and lymphatic system disorders (SOC)	1 (0.2%)	0 (0%)
Anaemia	1 (0.2%)	0 (0%)
Hepatobiliary disorders (SOC)	1 (0.2%)	0 (0%)
Hepatic failure	1 (0.2%)	0 (0%)
Injury, poisoning and procedural complications (SOC)	1 (0.2%)	0 (0%)
Infusion related reaction	1 (0.2%)	0 (0%)
Nervous system disorders (SOC)	1 (0.2%)	0 (0%)
Seizure	1 (0.2%)	0 (0%)
General disorders and administration site conditions (SOC)	1 (0.2%)	1 (0.2%)
Multiple organ dysfunction syndrome	1 (0.2%)	1 (0.2%)
Infections and infestations (SOC)	3 (0.6%)	4 (0.8%)
COVID-19 pneumonia	1 (0.2%)	1 (0.2%)
Septic shock	1 (0.2%)	1 (0.2%)
COVIID-19	1 (0.2%)	2 (0.4%)
Vascular disorders (SOC)	1 (0.2%)	2 (0.4%)
Hypotension	1 (0.2%)	0 (0%)
Shock	0 (0%)	2 (0.4%)
Immune system disorders (SOC)	0 (0%)	1 (0.2%)
Drug hypersensitivity	0 (0%)	1 (0.2%)
Psychiatric disorders (SOC)	0 (0%)	1 (0.2%)
Psychotic disorder	0 (0%)	1 (0.2%)
Skin and subcutaneous tissue disorders (SOC)	0 (0%)	1 (0.2%)
Rash	0 (0%)	1 (0.2%)
Surgical and medical procedures (SOC)	0 (0%)	1 (0.2%)
Continuous haemodiafiltration	0 (0%)	1 (0.2%)

Respiratory, thoracic and mediastinal disorders (SOC)	12 (2.3%)	15 (2.9%)
Acute respiratory distress syndrome	3 (0.6%)	1 (0.2%%)
Respiratory failure	8 (1.5%)	7 (1.4%)
Acute respiratory failure	1 (0.2%)	2 (0.4%)
Respiratory distress	0 (0%)	1 (0.2%)
Hypoxia	0 (0%)	2 (0.4%)
Pulmonary embolism	0 (0%)	2 (0.4%)
Investigations (SOC)	24 (4.5%)	27 (5.2)
Creatinine renal clearance decreased	2 (0.4%)	0 (0%)
Electrocardiogram qt prolonged	1 (0.2%)	0 (0%)
Transaminases increased	5 (0.9%)	4 (0.8%)
Alanine aminotransferase increased	2 (0.4%)	2 (0.4%)
Oxygen saturation decreased	0 (0%)	1 (0.2%)
Glomerular filtration rate decreased	10 (1.9%)	13 (2.5%)
Aspartate aminotransferase increased	3 (0.6%)	6 (1.2%)
Blood creatinine increased	3 (0.6%)	6 (1.2%)
Cardiac disorders (SOC)	1 (0.2%)	7 (1.4%)
Cardiac arrest	1 (0.2%)	1 (0.2%)
Arrhythmia	0 (0%)	1 (0.2%)
Cardio-respiratory arrest	0 (0%)	1 (0.2%)
Cardiogenic shock	0 (0%)	2 (0.4%)
Myocardial infarction	0 (0%)	3 (0.6%)
Renal and urinary disorders (SOC)	15 (2.8)	22 (4.3%)
Renal failure	1 (0.2%)	2 (0.4%)
Renal impairment	0 (0%)	3 (0.6%)
Acute kidney injury	14 (2.6%)	17 (3.3%)
TOTAL SUBJECTS	57 (10.7%)	77 (14.9%)

Source: ADAE dataset, ACTT-1

Reviewer Comment: Higher rates of AEs leading to discontinuation occurred in the PBO group compared to the RDV group.

There were 11 discontinuations due to AEs that were assessed by investigators as related to RDV. These adverse reactions were seizure (n=1), infusion-related reaction (n=1), transaminases increased (n=4), glomerular filtration rate decreased (n=2), acute kidney injury (n=3). Two of these narratives (seizure, infusion-related reaction) were classified as SAEs and are described in Section 8.4.2. The other narratives are briefly summarized below:

- Subject ID# (b) (6) (52-year-old male): On Day 5, subject experienced non-serious transaminases increased of Grade 3. Study drug was discontinued. Duration of treatment was 4 days. The event was resolved on Day 14. Of note, baseline AST/ALT 2-3x ULN. Study drug was discontinued when AST/ALT reached 4x ULN. AE did not resolve prior to discharge but improved at Day 15 follow-up.
- Subject ID# (b) (6) (43-year-old female): On Day 5, subject experienced non-serious transaminases increased of Grade 4. Study drug was discontinued. Duration of treatment

was 3 days. The event was unresolved as of the end of study.

- Subject ID# (b) (6) (48-year-old male): On Day 5, subject experienced non-serious transaminases increased of Grade 4. Study drug was discontinued. Duration of treatment was 4 days. The event was unresolved as of the end of study.
- Subject ID# (b) (6) (49-year-old female): On Day 5, subject experienced non-serious ALT increased of Grade 3. Study drug was discontinued. Duration of treatment was 4 days. On Day 6, subject experienced non-serious AST increased of Grade 3. Both events were unresolved as of the end of study.
- Subject ID# (b) (6) (54-year-old male): On Day 5, subject experienced non-serious glomerular filtration rate decreased of Grade 4. Study drug was discontinued. Duration of treatment was 5 days. The event was unresolved as of the end of study.
- Subject ID# (b) (6) (67-year-old male): On Day 5, subject experienced non-serious glomerular filtration rate decreased of Grade 3. Study drug was discontinued. Duration of treatment was 4 days. The event was resolved on Day 7.
- Subject ID# (b) (6) (62-year-old male): On Day 9, subject experienced non-serious acute kidney injury of Grade 3. Study drug was discontinued. Duration of treatment was 8 days. The event was resolved on Day 16.
- Subject ID# (b) (6) (67-year-old male): On Day 9, subject experienced non-serious acute kidney injury of Grade 3. Study drug was discontinued. Duration of treatment was 9 days. The event was resolved on Day 20.
- Subject ID# (b) (6) (71-year-old male): On Day 5, subject experienced non-serious acute kidney injury of Grade 3. Study drug was discontinued. Duration of treatment was 4 days. The event was unresolved as of the end of study.

Reviewer Comment: The narratives were reviewed and I agree with the investigators' assessments.

GS-US-540-5773

Discontinuations due to AEs occurred in 5% of subjects in the RDV 5-day group and 11% of subjects in the RDV 10-day group (Table 31). The majority of these events were assessed by investigators as not related to study drug.

Table 31. Adverse Events Leading to Study Drug Discontinuation by System Organ Class (SOC) and Preferred Term (PT), GS-US-540-5573

SOC PT	RDV 5 Days N=200	RDV 10 Days N=197
Blood and lymphatic system disorders (SOC)	1 (0.5%)	1 (0.5%)
Thrombocytopenia	1 (0.5%)	0 (0%)
Anaemia	0 (0%)	1 (0.5%)
Infections and infestations (SOC)	1 (0.5%)	1 (0.5%)
Pneumonia	1 (0.5%)	0 (0%)
Septic shock	0 (0%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.5%)	2 (1.0%)

Respiratory failure	1 (0.5%)	0 (0%)
Acute respiratory failure	0 (0%)	1 (0.5%)
Respiratory disorder	0 (0%)	1 (0.5%)
General disorders and administration site conditions (SOC)	0 (0%)	1 (0.5%)
Injection site erythema	0 (0%)	1 (0.5%)
Skin and subcutaneous tissue disorders (SOC)	0 (0%)	1 (0.5%)
Rash	0 (0%)	1 (0.5%)
Hepatobiliary disorders (SOC)	0 (0%)	2 (1.0%)
Hypertransaminasaemia	0 (0%)	2 (1.0%)
Investigations (SOC)	6 (3.0%)	8 (4.1%)
Transaminases increased	3 (1.5%)	1 (0.5%)
Blood creatinine increased	1 (0.5%)	0 (0%)
Hepatic enzyme increased	1 (0.5%)	1 (0.5%)
Liver function test increased	1 (0.5%)	2 (1.0%)
Glomerular filtration rate decreased	0 (0%)	1 (0.5%)
Aspartate aminotransferase increased	0 (0%)	2 (1.0%)
Alanine aminotransferase increased	0 (0%)	3 (1.5%)
Renal and urinary disorders (SOC)	0 (0%)	6 (3.0%)
Renal failure	0 (0%)	1 (0.5%)
Acute kidney injury	0 (0%)	5 (2.5%)
TOTAL SUBJECTS	9 (4.5%)	22 (11.2%)

Source: ADAE dataset, Study 5773

Reviewer Comment: Higher rates of AEs leading to discontinuation occurred in the RDV 10-day group compared to the RDV 5-day group.

In the RDV 5-day group, 5 subjects (3%) had discontinuations due to AEs that were assessed by investigators as related to RDV. Three of these narratives (transaminases increased [n=3]) were classified as SAEs and are described in Section 8.4.2. The other narratives are briefly summarized below:

- Subject ID# (b) (6) (54-year-old male): On Day 3, subject experienced non-serious hepatic enzyme increased of Grade 3. Study drug was discontinued. Duration of treatment was 3 days. The event was unresolved as of the data cut-off date.
- Subject ID# (b) (6) (72-year-old male): On Day 4, subject experienced non-serious liver function test increased of grade 3. Study drug was discontinued. Duration of treatment was 4 days. The event was unresolved as of the data cut-off date.

In the RDV 10-day group, 9 subjects (5%) had discontinuations due to that were assessed by investigators as related to RDV. Three of these narratives (transaminases increased [n=1], hepatic enzyme increased [n=1], hypertransaminasaemia [n=1]) were classified as SAEs and are described in Section 8.4.2. The other narratives are briefly summarized below:

- Subject ID# (b) (6) (62-year-old female): On Day 1, subject experienced non-serious injection site erythema of Grade 1 severity. RDV was discontinued. Duration of treatment was 1 day. The event was resolved on Day 1.

- Subject ID# (b) (6) (56-year-old male): On Day 7, subject experienced non-serious rash of Grade 1 severity. RDV was discontinued. Duration of treatment was 6 days. The event was resolved on Day 29.
- Subject ID# (b) (6) (66-year-old male): On Day 3, subject experienced non-serious ALT increased of Grade 3 severity. RDV was discontinued. Duration of treatment was 2 days. The event was resolved on Day 10.
- Subject ID# (b) (6) (49-year-old male): On Day 9, subject experienced non-serious ALT increased of Grade 3 severity and non-serious AST increased of Grade 3 severity. RDV was discontinued. Duration of treatment was 9 days. The event of ALT increased was resolved on Day 11. The event of AST increased was resolved on Day 9.
- Subject ID# (b) (6) (49-year-old male): On Day 2, subject experienced non-serious ALT increased of Grade 3 severity and non-serious AST increased of Grade 3 severity. RDV was discontinued. Duration of treatment was 2 days. The events were unresolved as of the data cut-off date.
- Subject ID# (b) (6) (36-year-old male): On Day 9, subject experienced non-serious liver function test increased of Grade 1 severity. RDV was discontinued. Duration of treatment was 9 days. The event was resolved on Day 9.

Reviewer Comment: The narratives were reviewed, and I agree with the investigators' assessments that these events may be related to study medication.

GS-US-540-5774

Discontinuations due to AEs occurred in 2% of subjects in the RDV 5-day group and 4% of subjects in the RDV 10-day group (Table 32). The majority of these events were assessed by investigators as not related to study drug.

Table 32. Adverse Events Leading to Study Drug Discontinuation by System Organ Class (SOC) and Preferred Term (PT), RDV treatment groups, GS-US-540-5574

SOC PT	RDV 5 Days N=191	RDV 10 Days N=193
Investigations (SOC)	2 (1.0%)	5 (2.6%)
Heart rate decreased	1 (0.5%)	0 (0%)
Blood alkaline phosphatase increased	0 (0%)	1 (0.5%)
Blood bilirubin increased	0 (0%)	1 (0.5%)
Transaminases increased	0 (0%)	1 (0.5%)
Aspartate aminotransferase increased	0 (0%)	2 (1.0%)
Alanine aminotransferase increased	1 (0.5%)	3 (1.6)
Skin and subcutaneous tissue disorders (SOC)	2 (1.0%)	0 (0%)
Rash	2 (1.0%)	0 (0%)
Hepatobiliary disorders (SOC)	0 (0%)	1 (0.5%)
Hypertransaminasaemia	0 (0%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders (SOC)	0 (0%)	1 (0.5%)
Acute respiratory failure	0 (0%)	1 (0.5%)

TOTAL SUBJECTS	4 (2.1%)	7 (3.6%)

Source: ADAE dataset, Study 5774

Reviewer Comment: Higher rates of AEs leading to discontinuation occurred in the RDV 10-day group compared to the RDV 5-day group. Of note, these events were not collected for the standard of care group.

In the RDV 5-day group, 4 subjects (2%) had discontinuations due to AEs that were assessed by investigators as related to RDV. One of these narratives (heart rate decreased) was classified as a SAE and is described in Section 8.4.2. The other narratives are briefly summarized below:

- Subject ID# (b) (6) (48-year-old male): On Day 1, subject experienced Grade 2 rash. RDV was discontinued. Duration of treatment was 1 day. The event was resolved on Day 9.
- Subject ID# (b) (6) (49-year-old female): On Day 4, subject experienced Grade 1 rash. RDV was discontinued. Duration of treatment was 4 days. The outcome of this event was not available because the subject was lost to follow-up.
- Subject ID# (b) (6) (26-year-old male): On Day 3, subject experienced non-serious ALT increased of Grade 3 severity. RDV was discontinued. Duration of treatment was 3 days. The event was resolved on Day 15.

In the RDV 10-day group, 4 subjects (2%) had discontinuations due to that were assessed by investigators as related to RDV. These narratives are briefly summarized below:

- Subject (b) (6) (42-year-old male): On Day 5, subject experienced ALT increased of Grade 2 severity. RDV was discontinued. Duration of treatment was 9 days. The event was unresolved as of the data cut-off date.
- Subject (b) (6) (26-year-old male): On Day 4, subject experienced hypertransaminasaemia of Grade 3 severity. RDV was discontinued. Duration of treatment was 3 days. The event was resolved on Day 23.
- Subject (b) (6) (63-year-old male): On Day 5, subject experienced ALT increased of Grade 3 severity. On Day 7, subject experienced AST increased of Grade 2 severity. RDV was discontinued. Duration of treatment was 7 days. Both events were resolved on Day 14.
- Subject (b) (6) (23-year-old female): On Day 1, subject experienced blood alkaline phosphatase increased of Grade 3 severity. RDV was discontinued. Duration of treatment was 8 days. The event was resolved on Day 11.

Comment: The narratives were reviewed, and I agree with the investigators' assessments that these events may be related to study medication.

Overall Assessment: No clear safety signal emerges from the review of AEs leading to study drug discontinuation. Generalized seizure and rash will be included under Less Common Adverse Reactions in product labeling. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.4.4. Significant Adverse Events

This section describes Grade 3 and 4 events that occurred in the treatment emergent period. Adverse events (AEs) are treatment emergent and all cause. Adverse drug reactions (ADRs) are treatment emergent and at least possibly related by investigator. Some of these events were also considered SAEs; hence, there is some overlap between events reported in this section and 8.4.2.

In ACTT-1, GS-US-540-5773 and GS-US-540-5774, Grade 3 and 4 AEs were overall consistent with those observed in a hospitalized patient population.

ACTT-1
Grade 3/4 AEs occurred in 51% of subjects in the RDV group and 57% of subjects in the PBO group. The majority of these AEs were assessed by investigators as not related to study drug. The most common Grade 3/4 AEs in each group were:

- RDV: pyrexia (7%), dyspnea (6%), hypertension (5%), arrythmia (5%)
- Placebo: pyrexia (7%), dyspnea (7%), hypertension (5%), arrythmia (4%)

Grade 3/4 AEs considered related to study drug by the study investigators (i.e. ADRs) occurred in 8% of subjects in the RDV group and 9% of subjects in the PBO group (Table 34).

Reviewer Comment: No clear safety signal emerges from the review of Grade 3 and 4 events.

GS-US-540-5773
Grade 3/4 AEs occurred in 27% of subjects in the RDV 5-day group and 36% of subjects in the RDV 10-day group. The majority of ≥Grade 3 AEs were assessed by investigators as not related to study drug. The most common ≥Grade 3 AEs in each group were:

- RDV 5-day group: acute respiratory failure (6%), respiratory failure (4%), coronavirus infection (4%)
- RDV 10-day group: acute respiratory failure (10%), respiratory failure (8%), coronavirus infection, (5%), acute kidney injury (5%)

Grade 3/4 AEs considered related to study drug by the study investigators (i.e. ADRs) occurred in 4% of subjects in the RDV 5-day group and 5% of subjects in the RDV 10-day group:

- RDV 5-day group (n=8): transaminases increased (n=3), hepatic enzyme increased (n=2), liver function tests increased (n=2), hypertriglyceridemia (n=1)
- RDV 10-day group (n=10 [*note: subjects could have more than one event*]): transaminases increased (n=3), ALT increased (n=5), AST increased (n=3), hepatic enzyme increased (n=1), hypertransaminasemia (n=1)

Reviewer Comment: No clear safety signal emerges from the review of Grade 3 and 4 events.

GS-US-540-5774
Grade 3/4 AEs occurred in 11% of subjects in the RDV 5-day group, 10% of subjects in the RDV 10-day group, and 10% of subjects in the standard of care group. The majority of ≥Grade 3 AEs

were assessed by investigators as not related to study drug. The most common Grade 3/4 AEs in each group were:

- RDV 5-day group: hypotension (1%), ALT increased (1%), AST increased (1%)
- RDV 10-day group: hypotension (2%), ALT increased (1%), transaminases increased (1%), dyspnea (1%), respiratory distress (1%)
- Standard of care group: acute respiratory failure (3%), anemia (2%), respiratory distress (1%), respiratory failure (1%), ALT increased (1%), acute kidney injury (1%)

≥Grade 3 AEs considered related to study drug by the study investigators (i.e. ADRs) occurred in 3% of subjects in the RDV 5-day group and 3% of subjects in the RDV 10-day group:

- RDV 5-day group (n=6 [*note: subjects could have more than one event*]): ALT increased (n=2), AST increased (n=2), fatigue (n=1), heart rate decreased (n=1), nausea (n=1)
- RDV 10-day group (n=5): ALT increased (n=1), alkaline phosphatase increased (n=1), hypertransaminasemia (n=1), transaminases increased (n=1), fatigue (n=1)

Reviewer Comment: No clear safety signal emerges from the review of Grade 3 and 4 events.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In ACTT-1, GS-US-540-5773 and GS-US-540-5774, AEs were overall consistent with those observed in a hospitalized patient population. Across all 3 trials, the majority of these AEs were assessed by investigators as not related to study drug. Consequently, this section focuses on ADRs that occurred in these trials.

ACTT-1
Treatment-emergent AEs occurred in 57% of subjects in the RDV group and 63% of subjects in the PBO group. Table 33 summarizes TEAEs occurring with ≥5% frequency in either group.

Table 33. Treatment-emergent AEs by System Organ Class (SOC) and Preferred Term (PT), All Causality, occurring in **≥5%** in either treatment group, ACTT-1

SOC PT	RDV 10 Days N=532	PBO 10 Days N=516
Blood and lymphatic system disorders (SOC)		
Anaemia	42 (7.9%)	53 (10.3%)
Lymphopenia	13 (2.4%)	30 (5.8%)
General disorders and administration site conditions (SOC)		
Pyrexia	38 (7.1%)	34 (6.6%)
Investigations (SOC)		
Glomerular filtration rate decreased	60 (11.3%)	76 (14.7%)
Haemoglobin decreased	49 (9.2%)	62 (12.0%)
Lymphocyte count decreased	45 (8.5%)	54 (10.5%)
Blood glucose increased	39 (7.3%)	27 (5.2%)
Blood creatinine increased	32 (6.0%)	36 (7.0%)

Aspartate aminotransferase increased	18 (3.4%)	33 (6.4%)
Metabolism and nutrition disorders		
Hyperglycaemia	34 (6.4%)	34 (6.6%)
Renal and urinary disorders (SOC)		
Acute kidney injury	28 (5.3%)	33 (6.4%)
Respiratory, thoracic and mediastinal disorders (SOC)		
Respiratory failure	37 (7.0%)	60 (11.6%)
Respiratory distress	18 (3.4%)	27 (5.2%)

Source: ADAE dataset, ACTT-1

Table 34 summarizes related adverse events (hereafter referred to adverse drug reactions [ADR]) for any Grade 2 or higher suspected drug-related hypersensitivity ADR and all Grade 3 or higher ADRS. The investigator's determination of causality is the basis for classification. The limitations of this approach to causality assessment are acknowledged.

Table 34. Treatment-emergent ADRs*, ACTT-1

Preferred Term	RDV 10 Days N=532	PBO 10 Days N=516
Prothrombin time prolonged	9 (1.7%)	3 (0.6%)
Acute kidney injury	4 (0.8%)	3 (0.6%)
Anaemia	2 (0.4%)	1 (0.2%)
Liver function test increased	2 (0.4%)	1 (0.2%)
Chills	1 (0.2%)	0 (0%)
Haemoglobin decreased	1 (0.2%)	0 (0%)
Infusion related reaction	1 (0.2%)	0 (0%)
International normalised ratio increased	1 (0.2%)	0 (0%)
Jaundice	1 (0.2%)	0 (0%)
Liver injury	1 (0.2%)	0 (0%)
Seizure	1 (0.2%)	0 (0%)
Thrombocytopenia	1 (0.2%)	0 (0%)
Transaminases increased	5 (0.9%)	4 (0.8%)
Blood creatinine increased	3 (0.6%)	3 (0.6%)
Hyperbilirubinaemia	1 (0.2%)	1 (0.2%)
Pyrexia	1 (0.2%)	1 (0.2%)
Blood glucose increased	1 (0.2%)	2 (0.4%)
Drug hypersensitivity	0 (0%)	1 (0.2%)
Hepatitis	0 (0%)	1 (0.2%)
Lymphocyte count decreased	0 (0%)	1 (0.2%)
Lymphopenia	0 (0%)	1 (0.2%)
Glomerular filtration rate decreased	4 (0.8%)	6 (1.2%)
Rash	0 (0%)	2 (0.4%)
Blood bilirubin increased	1 (0.2%)	5 (1.0%)
Aspartate aminotransferase increased	7 (1.3%)	12 (2.3%)

Alanine aminotransferase increased	4 (0.8%)	11 (2.1%)
TOTAL SUBJECTS	41 (7.7%)	47 (9.1%)

*Any Grade 2 or higher suspected drug-related hypersensitivity reactions and all Grade 3 or higher adverse reactions.
Source: ADAE dataset, ACTT-1

Reviewer Comment: ADRs occurred in 8% of subjects in the RDV group and 9% of subjects in the placebo group. Most ADRs were laboratory-related events.

In ACTT-1, only Grade 3/4 AEs, SAEs, AEs leading to study drug discontinuation, and Grade 2 or higher hypersensitivity reactions were recorded; this limitation will be described in product labeling. Although data on all grades of adverse reactions was not collected, the above data represent the most clinically relevant safety outcomes for this hospitalized patient population.

GS-US-540-5773
Table 35 summarizes ADRs, irrespective of severity.

Table 35. Treatment-emergent ADRs, All Grade, GS-US-540-5773

Preferred Term	RDV 5 Days N=200	RDV 10 Days N=197
Nausea	9 (4.5%)	5 (2.5%)
Vomiting	4 (2.0%)	0 (0%)
Hypertriglyceridaemia	2 (1.0%)	0 (0%)
Transaminases increased	5 (2.5%)	4 (2.0%)
Hepatic enzyme increased	3 (1.5%)	2 (1.0%)
Insomnia	2 (1.0%)	1 (0.5%)
Liver function test increased	2 (1.0%)	1 (0.5%)
Atrial fibrillation	1 (0.5%)	0 (0%)
Diarrhoea	1 (0.5%)	0 (0%)
Dyspepsia	1 (0.5%)	0 (0%)
Infusion site pain	1 (0.5%)	0 (0%)
Infusion site phlebitis	1 (0.5%)	0 (0%)
Leukopenia	1 (0.5%)	0 (0%)
Pneumonia streptococcal	1 (0.5%)	0 (0%)
Constipation	3 (1.5%)	3 (1.5%)
Headache	1 (0.5%)	1 (0.5%)
Blood potassium decreased	0 (0%)	1 (0.5%)
Dizziness	0 (0%)	1 (0.5%)
Flushing	0 (0%)	1 (0.5%)
Heart rate irregular	0 (0%)	1 (0.5%)
Hepatitis	0 (0%)	1 (0.5%)
Injection site erythema	0 (0%)	1 (0.5%)
Oropharyngeal pain	0 (0%)	1 (0.5%)
Paraesthesia	0 (0%)	1 (0.5%)

Pruritus	0 (0%)	1 (0.5%)
Rash*	0 (0%)	3 (1.5%)
Hypertransaminasaemia	0 (0%)	2 (1.0%)
Aspartate aminotransferase increased	5 (2.5%)	11 (5.6%)
Alanine aminotransferase increased	4 (2.0%)	14 (7.1%)
TOTAL SUBJECTS	33 (16.5%)	40 (20.3%)

*Includes rash, rash macular
Source: ADAE dataset, Study 5773

For non-laboratory events, the most commonly reported ADRs in each group were:

- RDV 5-day group: nausea (5%), vomiting (2%), constipation (2%)
- RDV 10-day group: nausea (3%), constipation (2%), rash (2%)

Reviewer Comment: Higher rates of ADRs occurred in the RDV 10-day group compared to the RDV 5-day group (20% vs. 17%). Nausea was the only clinical ADR that occurred in ≥5% of either RDV group.

GS-US-540-5774
Table 36 summarizes ADRs, irrespective of severity, for the RDV groups.

Table 36. Treatment-emergent ADRs, All Grade, GS-US-540-5774

Preferred Term	RDV 5 Days N=191	RDV 10 Days N=193
Nausea	13 (6.8%)	7 (3.6%)
Alanine aminotransferase increased	7 (3.7%)	3 (1.6%)
Aspartate aminotransferase increased	5 (2.6%)	3 (1.6%)
Rash*	5 (2.6%)	2 (1.0%)
Headache	4 (2.1%)	3 (1.6%)
Diarrhoea	3 (1.6%)	3 (1.6%)
Hypertransaminasaemia	2 (1.0%)	4 (2.1%)
Phlebitis	2 (1.0%)	0 (0%)
Vomiting	1 (0.5%)	3 (1.6%)
Fatigue	1 (0.5%)	1 (0.5%)
Infusion site erythema	1 (0.5%)	1 (0.5%)
Infusion site pain	1 (0.5%)	1 (0.5%)
Abdominal pain	1 (0.5%)	0 (0%)
Back pain	1 (0.5%)	0 (0%)
Blood bilirubin increased	1 (0.5%)	0 (0%)
Conjunctival haemorrhage	1 (0.5%)	0 (0%)
Constipation	1 (0.5%)	0 (0%)
Dizziness	1 (0.5%)	0 (0%)
Dry eye	1 (0.5%)	0 (0%)
Dysgeusia	1 (0.5%)	0 (0%)
Eye pruritus	1 (0.5%)	0 (0%)

Fall	1 (0.5%)	0 (0%)
Flatulence	1 (0.5%)	0 (0%)
Heart rate decreased	1 (0.5%)	0 (0%)
Hypercalcaemia	1 (0.5%)	0 (0%)
Infusion site pruritus	1 (0.5%)	0 (0%)
Insomnia	1 (0.5%)	0 (0%)
Lymphangitis	1 (0.5%)	0 (0%)
Musculoskeletal pain	1 (0.5%)	0 (0%)
Myalgia	1 (0.5%)	0 (0%)
Pruritus	1 (0.5%)	0 (0%)
Pyrexia	1 (0.5%)	0 (0%)
Urinary tract infection	1 (0.5%)	0 (0%)
Acute kidney injury	0 (0%)	1 (0.5%)
Blood alkaline phosphatase increased	0 (0%)	1 (0.5%)
Chest pain	0 (0%)	1 (0.5%)
Cholestasis	0 (0%)	1 (0.5%)
Gamma-glutamyltransferase increased	0 (0%)	1 (0.5%)
Infusion site swelling	0 (0%)	1 (0.5%)
Sleep disorder	0 (0%)	1 (0.5%)
Transaminases increased	0 (0%)	1 (0.5%)
TOTAL SUBJECTS	36 (18.8%)	24 (12.4%)

*Includes rash, rash papular
Source: ADAE dataset, Study 5774

For non-laboratory events, the most commonly reported ADRs in each group were:

- RDV 5-day group: nausea (7%), rash (3%), headache (2%), diarrhea (2%)
- RDV 10-day group: nausea (4%), headache (2%), diarrhea (2%), vomiting (2%)

Reviewer Comment: Higher rates of ADRs occurred in the RDV 5-day group compared to the RDV 10-day group (19% vs. 12%). Nausea was the only clinical ADR that occurred in ≥5% of either RDV group.

Overall Assessment: Nausea was the most commonly reported ADR in the Phase 3 clinical trials.

8.4.6. Laboratory Findings

The tables in this section display treatment-emergent graded laboratory abnormalities for chemistry and hematology parameters in ACTT-1, GS-US-540-5773 and GS-US-540-5774. These analyses represent the worst change from baseline per subject.

ACTT-1
Graded chemistry results are summarized in Table 37, and hematology results in Table 38.
Table 37: Liver Function Tests and Other Chemistry Lab Results, All Grade, ACTT-1

OTHER CHEMISTRY LABS		
Parameter and max Analysis Toxicity Grade	RDV 10 Days N=532	PBO 10 Days N=516
LIVER FUNCTION TESTS		
Increased Alanine Aminotransferase (U/L)		
Grade 1 (1.25 to <2.5 × ULN)	103 (20.0%)	108 (21.5%)
Grade 2 (2.5 to <5 × ULN)	48 (9.3%)	77 (15.3%)
Grade 3 (5 to <10 × ULN)	11 (2.1%)	22 (4.4%)
Grade 4 (≥10 × ULN)	5 (1.0%)	9 (1.8%)
Increased Aspartate Aminotransferase (U/L)		
Grade 1 (1.25 to <2.5 × ULN)	83 (16.5%)	102 (20.7%)
Grade 2 (2.5 to <5 × ULN)	55 (10.9%)	74 (15.0%)
Grade 3 (5 to <10 × ULN)	25 (5.0%)	30 (6.1%)
Grade 4 (≥10 × ULN)	5 (1.0%)	10 (2.0%)
Increased Total Bilirubin (mg/dL)		
Grade 1 (1.1 to <1.6 × ULN)	26 (5.1%)	22 (4.4%)
Grade 2 (1.6 to <2.6 × ULN)	15 (2.9%)	22 (4.4%)
Grade 3 (2.6 to <5 x ULN)	4 (0.8%)	16 (3.2%)
Grade 4 (≥5 x ULN)	8 (1.6%)	7 (1.4%)
Increased Creatinine (mg/dL)		
Grade 1 (1.1 to 1.3 × ULN)	8 (1.5%)	6 (1.2%)
Grade 2 (>1.3 to 1.8 × ULN)	43 (8.3%)	54 (10.7%)
Grade 3 (>1.8 to <3.5 x ULN)	33 (6.4%)	22 (4.4%)
Grade 4 (≥3.5 x ULN)	46 (8.9%)	61 (12.1%)
Decreased Creatinine Clearance (mL/min)		
Grade 1 (NA)	0 (0%)	0 (0%)
Grade 2 (<90 to 60 ml/min)	115 (23.6%)	106 (22.4%)
Grade 3 (<60 to 30 ml/min)	45 (9.2%)	41 (8.6%)
Grade 4 (<30 ml/min)	45 (9.2%)	53 (11.2%)
Decreased eGFR (mL/min/1.73 m^2)		
Grade 1 (NA)	0 (0%)	0 (0%)
Grade 2 (<90 to 60 ml/min/1.73 m^2)	95 (18.3%)	90 (17.8%)
Grade 3 (<60 to 30 ml/min/1.73 m^2)	46 (8.9%)	55 (10.9%)
Grade 4 (<30 ml/min/1.73 m^2)	49 (9.4%)	64 (12.7%)
Increased Glucose (mg/dL)		
Grade 1 (116 to 160 mg/dL)	95 (18.5%)	87 (17.5%)
Grade 2 (>160 to 250 mg/dL)	86 (16.7%)	90 (18.1%)
Grade 3 (>250 to 500 mg/dL)	60 (11.7%)	64 (12.9%)
Grade 4 (≥500 mg/dL)	2 (0.4%)	1 (0.2%)

Source: ADLB dataset, ACTT-1

Reviewer Comment: All Grade 3/4 chemistry laboratory abnormalities occurred at lower rates in in the RDV group compared to the PBO group.

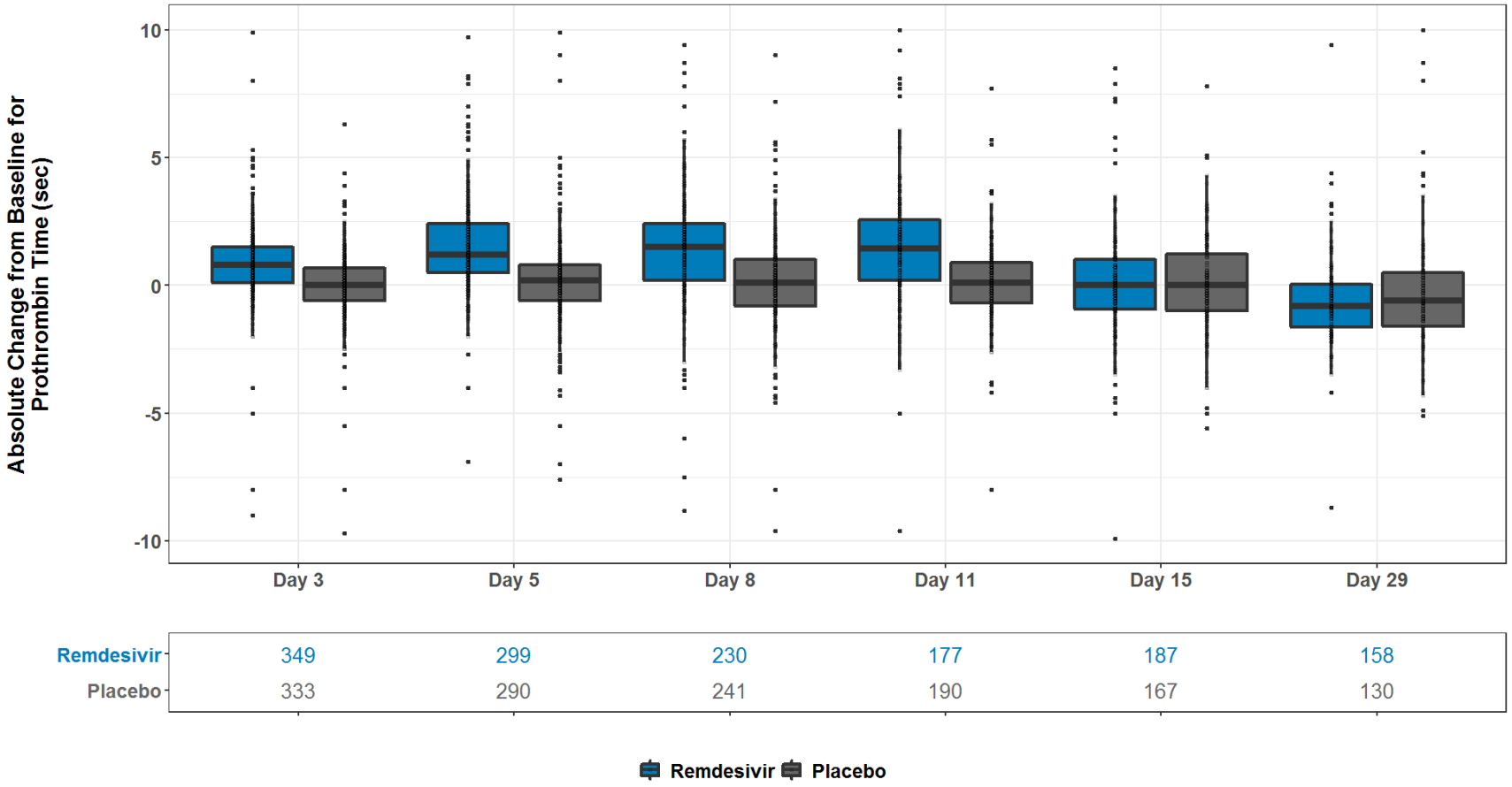
Table 38. Hematology Laboratory Results, All Grade, ACTT-1

Parameter/ max Analysis Toxicity Grade	RDV 10 Days N=532	PBO 10 Days N=516
Decreased Hemoglobin (g/dL)		
Grade 1 (10 to < 10.9 g/dL)	58 (11.2%)	62 (12.3%)
Grade 2 (9 to < 10 g/dL)	49 (9.4%)	62 (12.3%)
Grade 3 (7 to < 9 g/dL)	61 (11.8%)	96 (19.0%)
Grade 4 (< 7 g/dL)	14 (2.7%)	12 (2.4%)
Decreased Leukocytes (cells/mm^3)		
Grade 1 (2000 to 2499/mm^3)	6 (1.2%)	6 (1.2%)
Grade 2 (1500 to 1999/mm^3)	1 (0.2%)	1 (0.2%)
Grade 3 (1000 to 1499/mm^3)	2 (0.4%)	0 (0%)
Grade 4 (< 1000/mm^3)	0 (0%)	2 (0.4%)
Decreased Lymphocytes (cells/mm^3)		
Grade 1 (600 to 650/mm^3)	17 (3.3%)	23 (4.6%)
Grade 2 (500 to < 600/mm^3)	21 (4.1%)	25 (5.0%)
Grade 3 (350 to < 500/mm^3)	26 (5.0%)	41 (8.1%)
Grade 4 (< 350/mm^3)	32 (6.2%)	48 (9.5%)
Decreased Platelets (cells/mm^3)		
Grade 1 (100,000 to < 125,000/mm^3)	21 (4.1%)	19 (3.8%)
Grade 2 (50,000 to < 100,000/mm^3)	13 (2.5%)	14 (2.8%)
Grade 3 (25,000 to < 50,000/mm^3)	3 (0.6%)	2 (0.4%)
Grade 4 (< 25,000/mm^3)	3 (0.6%)	4 (0.8%)
Prothrombin Time Increased		
Grade 1 (1.1 to <1.25 × ULN)	106 (22.6%)	52 (11.6%)
Grade 2 (1.25 to <1.5 × ULN)	58 (12.4%)	44 (9.8%)
Grade 3 (1.5 to <3 x ULN)	37 (7.9%)	18 (4.0%)
Grade 4 (≥3 x ULN)	4 (0.9%)	1 (0.2%)

Source: ADLB dataset, ACTT-1

Reviewer Comment: Higher rates of Grade 3/4 prothrombin time (PT) elevations occurred in the RDV group compared to the PBO group. Figure 2 displays the absolute change from baseline in PT over time. These PT abnormalities tended to occur during Days 5-11. All other Grade 3/4 hematologic laboratory abnormalities occurred at similar or lower rates in subjects treated with RDV relative to PBO.

Figure 2. Absolute Change from Baseline in Prothrombin Time Over Time, Safety Population, ACTT-1



Source: ADLB dataset, ACTT-1
Note: Scheduled safety laboratory assessment visits were Day 3, 5, 8, 11 (all ± 1 day) if hospitalized and Day 15 and 29 (if able to return to clinic or still hospitalized). Outliers of absolute change from baseline for PT (>=10 sec and <=-10 sec) were excluded to increase the readability of mean change of PT over time.
1Boxes span the interquartile range (25th to 75th percentile); horizontal line = median; whiskers = 1.5 × the interquartile range; individual points are outliers beyond this range.
2If multiple values (scheduled and unscheduled) are associated with a patient for a visit, the worst value obtained (i.e., maximum increase in prothrombin time) are displayed at the prespecified scheduled visit.

Graded chemistry results are summarized in Table 39, and hematology results in Table 40.

Table 39: Liver Function Tests and Other Chemistry Lab Results, All Grade, GS-US-540-5773

OTHER CHEMISTRY LABS		
Parameter and max Analysis Toxicity Grade	RDV 5 Days N=200	RDV 10 Days N=197
LIVER FUNCTION TESTS		
Increased Alanine Aminotransferase (U/L)		
Grade 1 (1.25 to <2.5 × ULN)	41 (20.5%)	29 (14.7%)
Grade 2 (2.5 to <5 × ULN)	28 (14%)	37 (18.8%)
Grade 3 (5 to <10 × ULN)	8 (4%)	11 (5.6%)
Grade 4 (≥10 × ULN)	4 (2%)	5 (2.5%)
Increased Aspartate Aminotransferase (U/L)		
Grade 1 (1.25 to <2.5 × ULN)	31 (15.5%)	23 (11.7%)
Grade 2 (2.5 to <5 × ULN)	26 (13%)	45 (22.8%)
Grade 3 (5 to <10 × ULN)	10 (5%)	7 (3.6%)
Grade 4 (≥10 × ULN)	3 (1.5%)	4 (2%)
Increased Total Bilirubin (mg/dL)		
Grade 1 (1.1 to <1.6 × ULN)	10 (5%)	12 (6.1%)
Grade 2 (1.6 to <2.6 × ULN)	5 (2.5%)	10 (5.1%)
Grade 3 (2.6 to <5 x ULN)	1 (0.5%)	3 (1.5%)
Grade 4 (≥5 x ULN)	0 (0%)	1 (0.5%)
Increased Creatinine (mg/dL)		
Grade 1 (1.1 to 1.3 × ULN)	2 (1%)	1 (0.5%)
Grade 2 (>1.3 to 1.8 × ULN)	13 (6.5%)	7 (3.6%)
Grade 3 (>1.8 to <3.5 x ULN)	5 (2.5%)	7 (3.6%)
Grade 4 (≥3.5 x ULN)	5 (2.5%)	22 (11.2%)
Decreased Creatinine Clearance (mL/min)		
Grade 1 (NA)	0 (0%)	0 (0%)
Grade 2 (<90 to 60 ml/min)	37 (18.5%)	39 (19.8%)
Grade 3 (<60 to 30 ml/min)	13 (6.5%)	13 (6.6%)
Grade 4 (<30 ml/min)	6 (3%)	23 (11.7%)
Increased Glucose (mg/dL)		
Grade 1 (116 to 160 mg/dL)	27 (13.5%)	33 (16.8%)
Grade 2 (>160 to 250 mg/dL)	19 (9.5%)	20 (10.2%)
Grade 3 (>250 to 500 mg/dL)	20 (10%)	12 (6.1)
Grade 4 (≥500 mg/dL)	0 (0%)	1 (0.5%)

Source: ADLB dataset, Study 5773

Reviewer Comment: Higher rates of Grade 3/4 ALT elevations, Grade 3/4 bilirubin elevations, and Grade 3/4 renal laboratory abnormalities occurred in the RDV 10-day group compared to the RDV 5-day group. Higher rates of Grade 3/4 AST elevations and Grade 3/4 glucose elevations occurred in the RDV 5-day group compared to the RDV 10-day group.

Table 40. Hematology Laboratory Results, All Grade, GS-US-540-5773

Parameter/ max Analysis Toxicity Grade	RDV 5 Days N=200	RDV 10 Days N=197
Decreased Hemoglobin (g/dL)		
Grade 1 (10 to < 10.9 g/dL)	17 (8.5%)	25 (12.7%)
Grade 2 (9 to < 10 g/dL)	8 (4%)	15 (7.6%)
Grade 3 (7 to < 9 g/dL)	11 (5.5%)	13 (6.6%)
Grade 4 (< 7 g/dL)	0 (0%)	2 (1%)
Decreased Leukocytes (cells/mm^3)		
Grade 1 (2000 to 2499/mm^3)	2 (1%)	4 (2%)
Grade 2 (1500 to 1999/mm^3)	2 (1%)	0 (0%)
Grade 3 (1000 to 1499/mm^3)	0 (0%)	0 (0%)
Grade 4 (< 1000/mm^3)	0 (0%)	0 (0%)
Decreased Platelets (cells/mm^3)		
Grade 1 (100,000 to < 125,000/mm^3)	6 (3%)	5 (2.5%)
Grade 2 (50,000 to < 100,000/mm^3)	1 (0.5%)	5 (2.5%)
Grade 3 (25,000 to < 50,000/mm^3)	1 (0.5%)	1 (0.5%)
Grade 4 (< 25,000/mm^3)	1 (0.5%)	0 (0%)

Source: ADLB dataset, Study 5773

Reviewer Comment: Higher rates of Grade 3/4 decreased hemoglobin occurred in the RDV 10-day group compared to the RDV 5-day group. Rates of Grade 3/4 decreased platelets were generally similar across both RDV groups. No Grade 3/4 decreased leukocytes occurred in either group.

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Graded chemistry results are summarized in Table 41, and hematology results in Table 42.

Table 41: Liver Function Tests and Other Chemistry Lab Results, All Grade, GS-US-540-5774

Parameter and max Analysis Toxicity Grade	RDV 5 Days N=191	RDV 10 Days N=193	Standard of care N=200
LIVER FUNCTION TESTS			
Increased Alanine Aminotransferase (U/L)			
Grade 1 (1.25 to <2.5 × ULN)	42 (22%)	34 (17.6%)	28 (14%)
Grade 2 (2.5 to <5 × ULN)	17 (8.9%)	17 (8.8%)	30 (15%)
Grade 3 (5 to <10 × ULN)	4 (2.1%)	6 (3.1%)	10 (5%)
Grade 4 (≥10 × ULN)	0 (0%)	0 (0%)	3 (1.5%)
Increased Aspartate Aminotransferase (U/L)			
Grade 1 (1.25 to <2.5 × ULN)	35 (18.3%)	34 (17.6%)	30 (15%)
Grade 2 (2.5 to <5 × ULN)	15 (7.9%)	20 (10.4%)	14 (7%)
Grade 3 (5 to <10 × ULN)	3 (1.6%)	2 (1%)	6 (3%)

Grade 4 (≥10 × ULN)	1 (0.5%)	0 (0%)	5 (2.5%)
Increased Total Bilirubin (mg/dL)			
Grade 1 (1.1 to <1.6 × ULN)	2 (1%)	3 (1.6%)	8 (4%)
Grade 2 (1.6 to <2.6 × ULN)	3 (1.6%)	0	3 (1.5%)
Grade 3 (2.6 to <5 x ULN)	1 (0.5%)	3 (1.6%)	1 (0.5%)
Grade 4 (≥5 x ULN)	0 (0%)	1 (0.5%)	1 (0.5%)
OTHER CHEMISTRY LABS			
Increased Creatinine (mg/dL)			
Grade 1 (1.1 to 1.3 × ULN)	2 (1%)	0 (0%)	1 (0.5%)
Grade 2 (>1.3 to 1.8 × ULN)	8 (4.2%)	10 (5.2%)	7 (3.5%)
Grade 3 (>1.8 to <3.5 x ULN)	1 (0.5%)	3 (1.6%)	4 (2%)
Grade 4 (≥3.5 x ULN)	0 (0%)	1 (0.5%)	5 (2.5%)
Decreased Creatinine Clearance (mL/min)			
Grade 1 (NA)	0 (0%)	0 (0%)	0 (0%)
Grade 2 (<90 to 60 ml/min)	24 (12.6%)	39 (20.2%)	42 (21%)
Grade 3 (<60 to 30 ml/min)	4 (2.1%)	8 (4.1%)	10 (5%)
Grade 4 (<30 ml/min)	0 (0%)	2 (1%)	4 (2%)
Increased Glucose (mg/dL)			
Grade 1 (116 to 160 mg/dL)	35 (18.3%)	35 (18.1%)	43 (21.5%)
Grade 2 (>160 to 250 mg/dL)	7 (3.7%)	11 (5.7%)	12 (6%)
Grade 3 (>250 to 500 mg/dL)	8 (4.2%)	5 (2.6%)	4 (2%)
Grade 4 (≥500 mg/dL)	0 (0%)	0 (0%)	0 (0%)

Source: ADLB dataset, Study 5774

Reviewer Comment: Grade 3/4 transaminase elevations and Grade 3/4 renal laboratory abnormalities occurred at higher rates in the standard of care group compared to both RDV groups. Grade 3/4 glucose elevations occurred at slightly higher rates in the RDV 5-day group compared to the RDV 10-day group and standard of care group, respectively. Grade 3/4 bilirubin elevations occurred at generally similar rates across treatment groups.

Comparing the RDV groups, Grade 3/4 renal laboratory abnormalities occurred at higher rates in the RDV 10-day group relative to the RDV 5-day group. Grade 3/4 ALT elevations and Grade 3/4 bilirubin elevations occurred at slightly higher rates in the RDV 10-day group relative to the RDV 5-day group. Grade 3/4 AST elevations occurred at slightly higher rates in the RDV 5-day group relative to the RDV 10-day group.

Table 42. Hematology Laboratory Results, All Grade, GS-US-540-5774

Parameter and max Analysis Toxicity Grade	RDV 5 Days N=191	RDV 10 Days N=193	Standard of care N=200
Decreased Hemoglobin (g/dL)			
Grade 1 (10 to < 10.9 g/dL)	11 (5.8%)	8 (4.1%)	11 (5.5%)
Grade 2 (9 to < 10 g/dL)	5 (2.6%)	5 (2.6%)	4 (2%)
Grade 3 (7 to < 9 g/dL)	3 (1.6%)	2 (1%)	7 (3.5%)

Grade 4 (< 7 g/dL)	2 (1%)	0 (0%)	2 (1%)
Decreased Leukocytes (cells/mm^3)			
Grade 1 (2000 to 2499/mm^3)	7 (3.7%)	4 (2.1%)	6 (3%)
Grade 2 (1500 to 1999/mm^3)	1 (0.5%)	4 (2.1%)	1 (0.5%)
Grade 3 (1000 to 1499/mm^3)	1 (0.5%)	3 (1.6%)	2 (1%)
Grade 4 (< 1000/mm^3)	1 (0.5%)	1 (0.5%)	0 (0%)
Decreased Platelets (cells/mm^3)			
Grade 1 (100,000 to < 125,000/mm^3)	7 (3.7%)	6 (3.1%)	1 (0.5%)
Grade 2 (50,000 to < 100,000/mm^3)	1 (0.5%)	3 (1.6%)	6 (3%)
Grade 3 (25,000 to < 50,000/mm^3)	0 (0%)	1 (0.5%)	0 (0%)
Grade 4 (< 25,000/mm^3)	3 (1.6%)	0 (0%)	0 (0%)

Source: ADLB dataset, Study 5774

Reviewer Comment: Grade 3/4 decreased hemoglobin occurred at higher rates in the standard of care group compared to RDV 5-day group and RDV 10-day group, respectively. Grade 3/4 decreased leukocytes occurred at slightly higher rates in the RDV 10-day group compared to the RDV 5-day group and standard of care group, respectively. Grade 3/4 decreased platelets occurred at slightly higher rates in the RDV 5-day group compared to the RDV 10-day group and standard of care group, respectively.

Overall Assessment: In ACTT-1, Grade 3/4 PT elevations occurred in 9% of subjects in the RDV group compared to 4% of subjects in the PBO group. Given that these Grade 3/4 elevations may impact management of patients receiving anticoagulants, this information is clinically relevant and will be described in labeling, outlining that monitoring is recommended while receiving RDV. Although all other Grade 3/4 laboratory abnormalities occurred at similar or lower rates in subjects treated with RDV relative to PBO, these data will be displayed in product labeling to provide the most complete picture of the findings that have been observed to date with RDV.

For GS-US-540-5773, the Grade 3/4 laboratory abnormalities will be displayed in product labeling to show the trends towards higher rates in the RDV 10-day group compared to the RDV 5-day group.

For GS-US-540-5774, describing the Grade 3/4 laboratory abnormalities in product labeling provides important additional context. Similar to GS-US-540-5773, these findings also illustrate the trends towards higher rates in transaminase elevations and renal laboratory abnormalities the RDV 10-day group compared to the RDV 5-day group. It is also noteworthy that these Grade 3/4 transaminase elevations and Grade 3/4 renal laboratory abnormalities occurred at lower rates in both RDV groups compared to standard of care. Additionally, despite the caveats of cross-study comparisons, these data also suggest the potential contribution of COVID-19 to hepatotoxicity, given the lower overall rates of transaminase elevations in patients with moderate COVID-19 compared to severe disease. Transaminase elevations will be discussed as

part of the Warnings and Precautions labeling for hepatotoxicity. Please see Section 8.5.1 for a summary of hepatic safety.

These data also suggest the potential contribution of COVID-19 to renal injury, given the lower overall rates of renal laboratory abnormalities in patients with moderate COVID-19 compared to severe disease. Please see Section 8.5.10 for a summary of renal safety.

8.4.7. Vital Signs

In the Phase 3 trials, vital signs were measured daily until discharge, and at the follow-up visits if these were conducted in-person. No clinically meaningful changes in vital signs were observed in association with RDV use.

8.4.8. Electrocardiograms (ECGs)

ECGs were not assessed in the Phase 3 trials unless clinically indicated. The Applicant reports that one subject developed a treatment-emergent abnormal ECG but was clinically asymptomatic and was assessed as not related to study drug; her narrative is briefly summarized:

Subject ID# (b) (6) (ACTT-1): 67-year-old Caucasian female experienced Grade 3 QT prolongation on study Day 9. According to the investigator, there were no associated symptoms. Concurrent medications included olanzapine and escitalopram, and investigator noted that these medications can cause QT prolongation. The event was considered not related to study drug by the investigator and resolved on study Day 12. Investigator describes that "study drug was stopped out of abundance of precaution."

Reviewer Comment: I agree with the investigator that the subject described above was asymptomatic at the time of abnormal ECG, had concurrent medications that confounded assessment, and the abnormal ECG was not clinically significant.

8.4.9. QT

A thorough QT (TQT) study was not conducted at the time of this review. Data from the Phase 1, multi-dose study (Study GS-US-399-1954) in 24 healthy adults (RDV [n=16]; PBO [n=8]) was submitted to evaluate the potential of RDV to prolong the QT interval. Study GS-US-399-1954 was a Phase 1, partial-blinded, randomized, placebo-controlled, multiple-dose study evaluating the safety, tolerability, and pharmacokinetics of IV RDV (150 mg/day x 7 days; 150 mg/day x 14 days). The results were reviewed by the Interdisciplinary Review Team (IRT) for Cardiac Safety Studies, who concluded the following:

- The Study GS-US-399-1954 data are not adequate as a substitute for a TQT study as per ICH E14 Q&A (R3) 5.1.
- Although a large mean increase in QTc was not observed in the concentration-QTc assessment, the absence of small mean increases in the QTc interval could not be excluded for the following reasons:

I. There was no positive control or large exposure margin. The highest dose tested in this QT assessment covers approximately 75% of the parent drug and approximately 150% of the major metabolites at the highest recommended therapeutic dose (i.e., 200 mg on Day 1 and 100 mg once daily for up to 9 days, as a 30-min intravenous infusion).
II. RDV and metabolites have the potential to directly block the hERG current at therapeutic exposures.
III. There were unexplained mean increases in QTc of around 10 msec on day 14, which included only 8 subjects.

IRT recommended that a thorough QT study be conducted to obtain a better estimate of the QTc prolongation effect. This study will be conducted as a post-marketing requirement (PMR). Please refer to the QT-IRT review by Nan Zheng for additional details (IND 125566; letter date: May 8, 2020).

8.4.10. Immunogenicity

Because RDV is a small molecule and not a peptide, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials.

8.5. Analysis of Submission-Specific Safety Issues

This section includes analyses conducted to address safety concerns such as hepatotoxicity, as well as issues which can be associated with antiviral nucleoside/nucleotide inhibitors, such as cardiac events, rash, and elevations of creatine kinase and lipase.

8.5.1. Hepatotoxicity

A hepatic safety signal, manifested as transaminase elevations, is the dose-limiting toxicity for RDV and has been observed across the RDV development program. A hepatotoxicity safety signal was clearly demonstrated in trials in healthy subjects, and transaminase elevations have been reported in patients with COVID-19 in clinical trials[11, 13-15], in the EUA population, and in published literature.[4-7, 25-28] Additionally, PK data in the setting of renal or hepatic impairment are not available, and drug exposures could be elevated in these settings, increasing the potential risk of adverse reactions, including hepatotoxicity. However, the interpretation of cases in the setting of COVID-19 is challenging because SARS-CoV-2 is hepatotropic and hepatotoxicity has been observed in COVID-19 disease.[4-7]

Detailed analyses of hepatic events were performed. Based on review of the available data, we believe that a Warnings and Precautions labeling for hepatotoxicity is supported. This conclusion incorporates the following considerations:

- In a Phase 1, randomized, blinded, placebo-controlled trial (Study GS-US-399-5505) of RDV in healthy volunteers, subjects received one 200 mg dose of RDV followed by 100 mg for either 4 days or 9 days. Transient mild (Grade 1) or moderate (Grade 2) elevations in ALT were observed in 9 of 20 subjects receiving 10 days of RDV. No subjects who received 5 days of RDV (0 of 9 subjects) or placebo (0 of 7 subjects) had graded increases in ALT.

- In the Phase 3 trials, the majority of hepatic AEs were laboratory events. Consequently, the laboratory data provide the most objective assessment of hepatotoxicity in the trials.

ACTT-1

- Hepatic AEs (all causality) occurred in 13% (71 of 532 subjects) in the RDV group and 16% (80 of 516 subjects) in the PBO group. Hepatic events that occurred in at least 2% of either group are summarized below:
    - RDV: PT prolonged (5%), AST increased (3%), ALT increased (2%), blood bilirubin increased (2%)
    - PBO: AST increased (6%), ALT increased (5%), blood bilirubin increased (3%), PT prolonged (2%), transaminases increased (2%)
- Grade 3/4 hepatic ADRs occurred in 6% (31 of 532 subjects) in the RDV group and 6% (31 of 516 subjects) in the PBO group.
- No hepatic SAEs were assessed as related to RDV.
    - There was one case of hepatic failure in ACTT-1 (Subject ID# (b) (6)): 60-year-old male, medical history notable for COPD, CAD, HTN, type 2 DM. Subject had progressively worsening respiratory failure and multi-organ failure. He developed hepatic failure on Day 7, six days after onset of RDV. Hepatic failure was considered not related to RDV. Multi-organ failure and acidosis also worsened, and subject died on Day 7 due to cardiac arrest.
    - The only hepatic SAE was one subject in the PBO group who had a Grade 4 SAE of hepatitis with Day 3 onset and was ongoing at the end of the study.
- Hepatic AEs that led to discontinuation occurred in 2% (11 of 532 subjects) in the RDV group and 2% (12 of 516 subjects) in the PBO group:
    - RDV: transaminases increased (n=5), AST increased (n=3), ALT increased (n=2), and hepatic failure (n=1)
    - PBO: AST increased (n=6), transaminase increased (n=4), ALT increased (n=2).
- Hepatic ADRs that led to discontinuation were transaminases increased (n=3), ALT increased (n=1). (see Section 8.4.3).
- Rates of Grade 3/4 ALT elevations were 3% in the RDV group compared to 6% in the PBO group. Rates of Grade 3/4 AST elevations were 6% in the RDV group compared to 8% in the PBO group (see Section 8.4.6).

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- Hepatic AEs (all causality) occurred in 13.5% (27 of 200 subjects) in the RDV 5-day group and 18.8% (37 of 197 subjects) in the RDV 10-day group.
- Hepatic ADRs occurred in 8% (16 of 200 subjects) in the RDV 5-day group and 13.2% (26 of 197 subjects) in the RDV 10-day group.
- Grade 3/4 hepatic AEs occurred in 5% (10 of 200 subjects) in the RDV 5-day group and 7.6% (15 of 197 subjects) in the RDV 10-day group.
- Grade 3/4 hepatic ADRs occurred in 3.5% (7 of 200 subjects) in the RDV 5-day group and 5.1% (10 of 197 subjects) in the RDV 10-day group.
- Hepatic SAEs occurred in 2% (4 of 200 subjects) in the RDV 5-day group and 2.5% (5 of 197

subjects) in the RDV 10-day group.

- One SAE of Grade 4 hepatic failure was reported in 1 subject (ID# (b) (6)) in the RDV 5-day group on Day 20, 15 days after RDV completion. Subject (67-year-old Caucasian male; medical history included obesity, BMI 34 kg/m^2) had SAEs of acute respiratory failure and acute kidney failure at the time of the event and died as a result of pulmonary thromboembolism on Day 26. Hepatic failure was considered not related to RDV.
- Hepatic serious adverse reactions were reported in 1.5% (3 of 200 subjects) in the RDV 5-day group and 2.1% (4 of 197 subjects) in the 10-day group:
    - 5-day group: transaminases increased (n=3)
    - 10-day group: transaminases increased (n=2), hepatic enzyme increased (n=1), hypertransaminasaemia (n=1)
- Hepatic AEs that led to discontinuation occurred in 2.5% (5 of 200 subjects) in the RDV 5-day group and 4.6% (9 of 197 subjects) in the RDV 10-day group:
    - 5-day group: transaminases increased (n=3), hepatic enzyme increased (n=1), liver function test increased (n=1)
    - 10-day group: transaminases increased (n=1), hepatic enzyme increased (n=1), hypertransaminasaemia (n=2), ALT and AST increased (n=2), ALT increased (n=1), liver function test increased (n=2)
- Hepatic ADRs that led to discontinuation occurred in 2.5% (5 of 200 subjects) in the RDV 5-day group and 3.6% (7 of 197 subjects) in the RDV 10-day group:
    - 5-day group: transaminases increased (n=3), hepatic enzyme increased (n=1), liver function test increased (n=1)
    - 10-day group: transaminases increased (n=1), hepatic enzyme increased (n=1), hypertransaminasaemia (n=1), ALT and AST increased (n=2), ALT increased (n=1), liver function test increased (n=1)
- Rates of Grade 3/4 ALT elevations were 6% in the RDV 5-day group and 8% in the RDV 10-day group. Rates of Grade 3/4 AST elevations were 7% in the RDV 5-day group and 6% in the RDV 10-day group (see Section 8.4.6). The higher rates of ALT elevations in the RDV 10-day group compared to the RDV 5-day group are similar to the trends observed in the healthy volunteer studies.

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- Hepatic AEs (all causality) occurred in 7.9% (15 of 191 subjects) in the RDV 5-day group, 10.4% (20 of 193 subjects) in the RDV 10-day group, and 5.5% (11 of 200 subjects) in the standard of care group.
- Hepatic ADRs occurred in 4.7% (9 of 191 subjects) in the RDV 5-day group and 6.2% (12 of 193 subjects) in the RDV 10-day group.
- Grade 3/4 hepatic AEs occurred in 2.1% (4 of 191 subjects) in the RDV 5-day group, 3.6% (7 of 193 subjects) in the RDV 10-day group, and 1% (2 of 200 subjects) in the standard of care group.
- Grade 3/4 hepatic ADRs occurred in 1.6% (3 of 191 subjects) in the RDV 5-day group and 2.1% (4 of 193 subjects) in the RDV 10-day group.

- One hepatic SAE occurred in the RDV 10-day group and was assessed as unrelated to RDV.
- Hepatic AEs that led to discontinuation occurred in 0.5% (1 of 191 subjects) in the RDV 5-day group and 3.1% (6 of 193 subjects) in the RDV 10-day group:
    - 5-day group: ALT increased (n=1)
    - 10-day group: ALT increased (n=2), AST increased (n=1), hypertransaminasaemia (n=1), ALT increased and AST increased (n=1), blood alkaline phosphatase (n=1)
- Hepatic ADRs that led to discontinuation occurred in 0.5% (1 of 191 subjects) in the RDV 5-day group and 2.1% (4 of 193 subjects) in the RDV 10-day group:
    - 5-day group: ALT increased (n=1)
    - 10-day group: ALT increased (n=1), hypertransaminasaemia (n=1), ALT increased and AST increased (n=1), blood alkaline phosphatase (n=1)
- Rates of Grade 3/4 ALT elevations were 2% in the RDV 5-day group, 3% in the RDV 10-day group, and 8% in the standard of care group. Rates of Grade 3/4 AST elevations were 2% in the RDV 5-day group, 1% in the RDV 10-day group, and 6% in the standard of care group (see Section 8.4.6).
    - The rates of transaminase elevations were higher in the standard of care group compared to the RDV groups.
    - Although less prominent than in GS-US-540-5773, higher rates of ALT elevations occurred in the RDV 10-day group compared to the RDV 5-day group, similar to the findings in the healthy volunteer studies.

EUA (summary of reviews performed by the Office of Surveillance and Epidemiology [OSE])

- On July 9, 2020, OSE completed a pharmacovigilance memorandum that summarized the available safety data in FAERS and the medical literature related to the use of RDV under the EUA through June 3, 2020. Of the 402 cases identified, 114 (28%) reported transaminase elevations/increased liver function tests. Of those 114 cases, 55 (48%) reported an increase in ALT or AST > 5x ULN, with 21 (19%) that reported an ALT or AST increase of > 10x ULN. The majority of cases (57%) had both ALT and AST elevations. Twenty-seven cases (24%) reported resolution of increased transaminases/liver function tests after discontinuation of RDV. No cases reported signs and symptoms of liver inflammation or liver injury such as jaundice, ascites, weakness, nausea, and vomiting. A fatal outcome was reported in 9 cases: 5 deaths were assessed as likely due to worsening COVID-19 (e.g., septic shock, multi-organ failure, respiratory failure); 3 cases did not report the cause of death; one case was due to cardiac arrest. Of note, in one of the fatal cases, ALT levels were over 3300 (units unspecified) on the day the patient expired. Overall, the review assessed that, due to confounders such as underlying comorbidities, concomitant medications, and liver injury that can occur in patients with COVID-19, especially in those with severe disease, determining the contribution of RDV to these events is challenging. Please refer to the OSE review by Kate McCartan (entered into DARRTs by Kate McCartan on July 9, 2020), Kimberley Swank, Miriam Chehab, Paolo Fanti, Rachna Kapoor and Ida-Lina Diak for details.

- On August 28, 2020, OSE completed a pharmacovigilance memorandum that summarized the available safety data in FAERS related to the use of RDV under the EUA over the period from June 4, 2020 to August 16, 2020. A total of 600 cases reporting signs of hepatotoxicity (e.g., increased transaminases, increased liver function tests, hepatic failure) were identified. Of those 600 cases, 19 cases met the following case definition:
    - Any increase of AST or ALT above the ULN and at least one of the following:
        - A reported laboratory parameter suggestive of hepatic failure (e.g., decreased platelets, increased PT/INR, or increased total bilirubin levels).
        - Clinical signs/symptoms of hepatic failure (e.g., jaundice, ascites).
    - An increase in AST or ALT of at least 10x ULN with or without reported laboratory parameters (e.g., decreased platelets, increased PT/INR, or increased total bilirubin levels) or clinical signs/symptoms (e.g., jaundice, ascites) suggestive of hepatic failure.
- All 19 cases had increased transaminases of at least 10x ULN and no other reported laboratory parameters suggestive of hepatic failure (e.g., decreased platelets, increased PT/INR, or increased total bilirubin levels) or clinical signs/symptoms of hepatic failure (e.g., jaundice, ascites).
- Eight cases reported either AST, ALT or both AST and ALT values greater than 20x ULN, including two cases that reported either AST or ALT values greater than 50x ULN. Two cases also reported alkaline phosphatase levels at least 3x ULN.
- Median time to onset of increased transaminases (n=18) was 3 days after initiating RDV.
- A positive dechallenge was reported in four of the cases, all of which required early discontinuation of RDV. The majority of the cases did not report follow-up AST/ALT values after discontinuation of RDV. None of the 19 cases reported a negative dechallenge.
- The review did not identify any non-confounded cases of hepatic failure with sufficient information to assess as related to RDV. Please refer to the OSE review by Kate McCartan (entered into DARRTs by Kate McCartan on August 28, 2020), Kimberley Swank, Rachna Kapoor, Neha Gada and Ida-Lina Diak for details.

Overall Assessment: Hepatotoxicity was noted in early Phase 1 clinical development and led to dosing restrictions due to drug-related toxicity. The healthy volunteer trial GS-US-399-5505 (that evaluated the dosing regimens currently being used in the Applicant's COVID-19 development program) showed that the observed risk of hepatotoxicity associated with RDV is related to duration of drug exposure. Additionally, GS-US-540-5773 also demonstrated higher rates grade 3/4 adverse events, SAEs, and discontinuations due to AEs in the 10-day group compared to the 5-day group. These findings have implications for assessing safety risks with potential exposure-response relationships.

Because transaminase elevations have been reported as a clinical feature of COVID-19, discerning the contribution of RDV to transaminase elevations in patients with COVID-19 can be challenging.

In ACTT-1, the rates of hepatic AEs and Grade 3/4 laboratory abnormalities were lower in the RDV group compared to PBO.

In GS-US-540-5773, the rates of hepatic AEs and Grade 3/4 laboratory abnormalities were higher in the 10-day group compared to the 5-day group.

In GS-US-540-5774, the rates of hepatic AEs and Grade 3/4 laboratory abnormalities were higher in the 10-day group compared to the 5-day group, although the potential exposure-response relationship was less evident than that observed in GS-US-540-5773.

Overall, the rates of hepatic AEs and Grade 3/4 laboratory abnormalities were lower in GS-US-540-5774 in subjects with moderate COVID-19 compared to GS-US-540-5773 in subjects with severe COVID-19. Despite the caveats associated with cross-study comparisons, these observations highlight the contribution of disease severity to adverse outcomes.

Review of EUA data did not identify any non-confounded cases of hepatic failure with sufficient information to assess as related to RDV.

The Applicant plans to conduct a pharmacokinetic and safety study in adults with moderate and severe hepatic impairment to better define potential safety risks and inform dosage recommendations for this subpopulation.

Based on all available information, the Warnings and Precautions section will provide wording that clearly describes the hepatotoxicity safety signal that has been observed for RDV and outline risk mitigation strategies for health care providers to consider. Product labeling will also display hepatic laboratory data in Section 6. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.2. Hypersensitivity Reactions

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of RDV. Clinical manifestations have included hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering.

A search of the Applicant's global safety database cumulative to May 31, 2020, identified 10 cases that had temporal association to RDV administration and no confounders: 4 cases from clinical studies (ACTT-1 [n=1]; GS-US-540-5773 [n=2]; INSERM [n=1]), 3 cases from the EUA, and 3 cases from the expanded access program (GS-US-540-5821).

After the May 31, 2020 cut-off used in the Applicant's search, the Applicant received 8 additional cases with temporal association to RDV administration and no confounders:

• The Agency provided 7 EUA cases that were identified in the OSE review of EUA safety data through June 3, 2020.
• NIAID provided one case from ACTT-2.

Overall, the Applicant's June 18, 2020 summary report described a total of 13 cases of infusion-related reactions and 5 cases of hypersensitivity reactions with temporal association to RDV administration and no confounders. These narratives are briefly summarized below.

Infusion-related reactions (n=13)
• Case 2020-(b) (6) (EUA): 71-year-old woman with history of stage 2 chronic kidney disease, pacemaker, and 3 drug allergies experienced hypotension, shivering, and nausea during the first RDV infusion. The infusion was stopped, and 250 cc normal saline bolus infusion was initiated. The patient's vitals stabilized. There was no treatment reported for nausea. RDV infusion was restarted at "a slower rate," and the patient reportedly still had a reaction. RDV was discontinued. The patient's blood pressure was 126/101 prior to RDV infusion and 79/59 during the infusion. Subsequent blood pressure readings were 90/67 and 93/51. Blood pressure reportedly was 125/77 about 2 hours after RDV was permanently discontinued. Hypotension resolved, and outcome for nausea and chills were not reported.

• Case 2020-(b) (6) (FDA Case ID 17849369, EUA): 70-year-old man with history of heart failure and atherosclerotic heart diseased experienced hypotension and ventricular tachycardia ("VT broke spontaneously") during the first RDV infusion. During his second dose, he experienced hypotension and atrial bigeminy. The event abated after RDV was stopped and re-appeared after RDV was re-introduced. The final outcome of the events was not reported.

• Case 2020-(b) (6) (CO-US-540-5804; INSERM): 61-year-old man on 1 L of oxygen experienced hypotension after his eighth dose of RDV, which resolved after 8 hours. Although the time to onset was not reported, the investigator considered the hypotension possibly related to RDV. The subject did not have evidence of tachycardia or signs of shock. No other causes of hypotension were investigated. There was no corrective treatment reported. RDV was discontinued.

• Case 2020-(b) (6) (EUA): 55-year-old man experienced "infusion related hypotension" (88/36) 30 minutes after completion of his 3rd 1-hour infusion. 30 minutes later, BP 108/51, no intervention required. Three additional doses were administered daily over 2 hours without recurrence of hypotension. Event resolved.

• Case 2020-(b) (6) (EAP, GS-US-540-5821): mechanically ventilated 64-year-old man requiring vasopressor support with a history of diabetes experienced tachycardia (110s), tremors, and hypertension (SBPs 150s-170s) after the first RDV infusion, which resolved on the same day. Prior to the second RDV infusion, the patient was requiring norepinephrine. Ten minutes into the second 30-minute RDV infusion, the patient experienced hypertension (SBP > 220 with MAP > 130) and bradycardia (50s). Norepinephrine was discontinued, and RDV was permanently discontinued; propofol was increased; the patient's MAP was 70 within several minutes.

• Case 2020-(b) (6) (EUA): 34-year-old woman started feeling anxious, nauseous, diaphoretic, "face turned beet red" while respiratory rate, heart rate, and blood pressure increased 30 minutes into her 1st dose of RDV. She was afebrile and given diphenhydramine and methylprednisolone (unknown if

these medications were continued with additional RDV dosing). RDV was re-started at a slower rate without recurrence.

• Case 2020-(b) (6) (blinded, ACTT-I): 73-year-old woman on 4-6 L of oxygen with medical history of hypertension and hyperlipidemia experienced infusion related reaction described as rigors, fever, HR 144 bpm, BP 148/67 and increased oxygen requirements (O2 saturation 80% on 4 L nasal cannula, requiring use of a non-rebreather mask) that occurred 30 minutes after her first dose of RDV. No rash or stridor. Study drug was discontinued. Event resolved.

• Case 2020-(b) (6) (EAP, GS-US-540-5821): mechanically ventilated 79-year-old man requiring vasopressor support with a history of hypertension experienced hypertension (240/120), tachycardia, and atrial flutter 1.5 hours after completion of the second dose of RDV. Vasopressors were stopped, and he had sustained blood pressure of 180/120. He was treated with metoprolol as needed. Dosing was resumed the next day at a slower rate, and the events did not recur. Methylprednisolone was started the next day though the indication was not provided. The events resolved.

• Case 2020-(b) (6) (FDA case ID 17845081, EUA): (age-not provided) woman experienced "allergic reaction symptoms of laryngeal swelling, swelling of hands and feet and periorbital swelling" on day 3 of RDV. No excess fluids were given, and the case was described as "temporally related to administration" of RDV. As of the report date (a day after the onset of symptoms), the events had not abated after RDV was stopped.

• Case 2020-(b) (6) (FDA case ID 17812599, EUA): 39-year-old woman experienced throat itching and difficulty swallowing 1 hour into her first 2-hour infusion of RDV. Given diphenhydramine. Events abated after RDV stopped.

• Case 2020-(b) (6) (FDA case ID 17801815, EUA): (age-not provided) woman experienced throat itching, swelling, and difficulty swallowing 1.5 hours after starting first dose of RDV, which had already completed at the time of event onset. Given methylprednisolone. IV diphenhydramine ordered as needed. Events abated after RDV stopped.

• Case 2020-(b) (6) (FDA case ID 17844983, EUA): 47-year-old man with hypotension a few hours prior to RDV initiation (though BP had normalized prior to RDV) experienced diaphoresis and oxygen saturation of 85% requiring intubation 30 minutes into his first RDV dose. The reporter noted this could be progression of disease. RDV continued without report of increasing oxygen requirements or changes in ventilator settings. Event outcome was not reported.

• Case 2020-(b) (6) (FDA case ID 17838972, EUA): 34-year-old man with atrial fibrillation while receiving tocilizumab 8 days prior to event onset experienced sustained ventricular tachycardia (HR 174) 30 minutes into his fifth and last 60-minute infusion of RDV. Given metoprolol. HR returned to 108. Event abated after RDV stopped.

Hypersensitivity reactions (n=5)

• Case 2020-(b) (6) (GS-US-540-5773): 52-year-old man on room air with no known drug allergies experienced "possible allergic reaction to RDV" (peri-oral swelling and itching) 4.5 hours after completion of his second RDV dose, which was discontinued. He had completed a cefepime infusion 5.5

hours before event onset (last dose was on the day of event onset). He was given diphenhydramine. Three days later, peri-oral/throat swelling and bilateral thigh urticaria resolved.

• Case 2020-(b) (6) (GS-US-540-5773): 40-year-old man on 3 L of oxygen at baseline (who reported improvement in shortness of breath but persistent cough prior to RDV infusion) experienced intolerable burning at the IV site during the first dose of RDV. The infusion was stopped, diluted, slowed, and re-initiated. During the resumed infusion, the patient experienced “acute allergic reaction,” reporting that his "throat was itchy and it was hard to breathe." The infusion was stopped, and diphenhydramine was administered. At that time, the patient’s respirations were 36 and oxygen saturation was 93% on 3L NC. An hour later, the patient reported difficulty breathing. He was at 89% on 3L, so his oxygen was turned up to 4L nasal cannula. The patient refused to move to a prone position and reported that he was "breathing too fast to lay on his stomach." The patient began saturating around 87% and required 6L via oxymask to return to 90%. The patient was reporting increased difficulty in breathing with a respiratory rate of 44 and use of accessory muscles. The patient was able to be weaned back down to 3L oxymask with the physician at the bedside. The patient reported that coughing was the source of shortness of breath to the physician. Six hours after the onset of symptoms, the patient was back on 3L NC. Oxygen saturations were stable, but respirations were in the high 30s with continued accessory muscle use. Acute allergic reaction resolved on the same day as event onset. RDV was discontinued.

• Case 2020-(b) (6) (NIAID Case Number 20-0006-04531, CO-US-540-5776, ACTT-II [RDV not blinded]): mechanically ventilated 73-year-old man with labile blood pressures (60s-200s, on vasopressin and 0.06 of norepinephrine, BP 151/56, prior to RDV initiation), particularly with prone to supine position changes, baseline grade 3 total bilirubin, and no significant past medical history experienced “acute allergic reaction” with SBP to the 50s, requiring an increase in norepinephrine to 0.3 to maintain his BP, 15 minutes into his third RDV dose. RDV was immediately discontinued. The patient did not have rash, change in oxygen requirements, or procedures done during the time of the infusion. Norepinephrine was continued with titration to MAP of > 65, and within 45 minutes, his blood pressure was 172/67. Two day later, hypotension resolved with no sequelae. It appears the patient only received 1 dose of baricitinib vs. placebo 2 days prior to the event as dosing was interrupted for an absolute lymphocyte count < 200.

• Case 2020-(b) (6) (EAP, GS-US-540-5821): mechanically ventilated man in his 50s requiring vasopressor support with increase in pulmonary infiltrates and changes in ventilator settings prior to event onset experienced ventilator dyssynchrony requiring paralysis 12 hours after his first (and only) dose of RDV. Several hours later, he developed diffuse rash maculo-papular on the back and chest, more severe fever, increase in pulmonary infiltrates and difficult gas exchange progressing to ARDS and severe vasodistributive shock, requiring 3 vasopressors. Given methylprednisolone, H1 blocker, and empiric vancomycin and meropenem. Blood and urine cultures were negative. The rash did not progress to an exfoliative dermatitis or Stevens-Johnson syndrome. The rash gradually resolved, and the patient eventually became hemodynamically stable. When this case was retrospectively reviewed by the site, it was discovered that the patient was administered a RDV 400 mg (rather than 200 mg) loading dose.

• Case 2020-(b) (6) (FDA case ID 17823181, EUA): a woman on 3 L of NC and history of acute-on-chronic heart failure experienced worsening respiratory distress with diffuse end expiratory wheezing and poor air movement, increasing oxygen requirements (to 6 L NC) and pruritic rash on the chest and face during the end of her fourth RDV dose. Given diphenhydramine, methylprednisolone and albuterol with improvement. Event abated after RDV stopped.

Subsequent review of the EUA data cumulative to August 16, 2020 identified two additional cases of anaphylaxis:

• CaseID# (b) (6) (56-year-old female): Patient received RDV for three days. On each of these days, patient experienced sharp substernal chest discomfort with wheezing a few hours after each RDV dose. On the third day, the patient also experienced epigastric pain and throat/tongue swelling. RDV was stopped after the third dose likely due to the recurring sharp substernal chest discomfort. The next day, the patient was transferred to step down unit, reported breathing more comfortably. Later that night, the patient experienced shortness of breath, became hypoxic and was intubated. Within 1.5 hours, the patient coded and expired.

• CaseID# (b) (6) (78-year-old female): Patient started on RDV and after the third dose she developed anaphylactic shock (unknown time) requiring epinephrine. Patient received convalescent plasma that day within 3 hours of receiving RDV. Patient was placed on vasopressors and intubated. The patient had multi-organ failure and placed on CRRT. Family decided to stop all aggressive treatments and patient was compassionately extubated and died three days later. Concomitant medications: amiodarone, aspirin, dexamethasone, enoxaparin, famotidine, furosemide, meropenem, montelukast, spironolactone, vancomycin. Patient had allergies to corticosteroids, penicillin, and stadol. Narrative notes that patient also received concomitant convalescent plasma and dexamethasone (reported allergy to corticosteroids) on the day that anaphylactic shock developed; therefore, it is unclear if RDV caused the anaphylactic shock. The patient started receiving dexamethasone one day prior to starting RDV and continued until the day the patient expired.

Overall Assessment: Based on these findings, the primary review team recommends safety labeling in the Warning and Precautions that clearly describes the hypersensitivity reactions, including infusion-related and anaphylactic reactions, that have been observed for RDV.

8.5.3. Cardiac Disorders

Please see Section 8.4.8 and Section 8.4.9 of this review for details.

Overall Assessment: The primary review team concludes that the available reported cardiac data do not require specific safety labeling. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.4. Seizure

Seizure events were infrequent in ACTT-1, occurring in 3 subjects (0.6%) in the RDV group and 2 subjects (0.4%) in the PBO group. In one subject, the event was assessed as related to RDV and resulted in RDV discontinuation (see Section 8.4.3).

One seizure event occurred in GS-US-540-5773 and was assessed as unrelated to RDV.

No seizure events were reported in GS-US-540-5774.

Overall Assessment: Although there is no clear indication for an increased risk of seizure events with RDV, seizure will be included under Less Common Adverse Reactions in product labeling due to the drug-related seizure event that led to RDV discontinuation in ACTT-1. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.5. Rash

Rash events were infrequent in ACTT-1, occurring in no subjects in the RDV group and 4 subjects (0.8%) in the PBO group.

In GS-US-540-5773, rash occurred in subjects 5 (2.5%) in the RDV 5-day group and 9 subjects (4.6%) in the RDV 10-day group.

- Rash events that were considered related occurred in 3 subjects (1.5%) in the RDV 10-day group; one of these subjects discontinued RDV due to rash (see Section 8.4.3).

In GS-US-540-5774, rash occurred in 7 subjects (3.7%) in the RDV 5-day group, 4 subjects (2.1%) in the RDV 10-day group, and 6 subjects (3%) in the standard of care group.

- Rash events that were considered related occurred in 5 subjects (2.6%) in the RDV 5-day group and 2 subjects (1.0%) in the RDV 5-day group.
- In the RDV 5-day group, 2 subjects discontinued RDV due to rash (see Section 8.4.3).

Overall, the majority of events was Grade 1 in severity. No Grade 3/4 events, and no events of Stevens Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme were observed in ACTT-1, GS-US-540-5773 and GS-US-540-5774.

Overall Assessment: The frequency and severity of rash events occurring in RDV was low. Although no specific safety signal was detected for rash events, rash will be included under Less Common Adverse Reactions in product labeling because some drug-related rash events led to RDV discontinuation. Any potential signals of serious rash events associated with RDV use will be closely monitored in the postmarketing setting.

8.5.6. Rhabdomyolysis

There were no cases of rhabdomyolysis in ACTT-1, GS-US-540-5773 and GS-US-540-5774.

Overall Assessment: Rhabdomyolysis was not an adverse event of specific concern during the RDV development program. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.7. Pancreatitis

There was one case of pancreatitis in ACTT-1 and I concur with the investigator assessment that it was unrelated to RDV. No clinical cases of pancreatitis were reported in GS-US-540-5773 and GS-US-540-5774. Of note, amylase and lipase were not measured in these trials.

Overall Assessment: Pancreatitis was not an adverse event of specific concern during the RDV development program. Routine pharmacovigilance will be in place to detect postmarketing signals.

8.5.8. Pancytopenia

There were no cases of pancytopenia in ACTT-1, GS-US-540-5773 and GS-US-540-5774.

Overall Assessment: The primary review team concludes that the available reported data do not require specific safety labeling for pancytopenia. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.9. Hemorrhagic events

In GS-US-399-5505, mild PT/INR elevations were observed in the majority of healthy volunteers, regardless of whether they received RDV or matching PBO. These laboratory abnormalities were transient and resolved while on or shortly after study drug administration. Similar findings were previously observed in Studies GS-US-399-1812 and GS-US-399-1954 and the mild PT/INR elevations in these healthy volunteer studies also resolved on or shortly after study drug discontinuation.

In ACTT-1, Grade 3-4 PT/INR elevations occurred in 9% of subjects in the RDV group compared to 4% of subjects in the PBO group (see Section 8.4.6).

In ACTT-1, there was one SAE of cerebral hemorrhage and one SAE of subarachnoid hemorrhage in the RDV group. These narratives are briefly summarized below:

- Subject ID# COV(b) (6) (57-year-old female): On Day 7, subject experienced cerebral hemorrhage. No action taken was with study drug. Event was considered not related to study drug. Event was assessed as related to anticoagulation from ECMO. The event was considered not recovered/not resolved.
- Subject ID# COV(b) (6) (66-year-old female): On Day 14, subject experienced subarachnoid hemorrhage. Event occurred after completion of RDV course. Event was considered not related to study drug. Event was assessed as related to anticoagulation. The event was considered not recovered/not resolved.

In GS-US-540-5773, there was one SAE of cerebral microhemorrhage in the RDV 10-day group:

- Subject ID#(b) (6) (71-year-old male): On Day 12, subject experienced cerebral microhemorrhage of Grade 4. No action taken was with study drug. Event was considered not related to study drug. The event was unresolved as of the data cut-off date.

Comment: The narratives were reviewed, and I agree with the investigators' assessments.

Overall Assessment: The primary review team concludes that the available reported data do not require specific safety labeling for hemorrhagic events. Routine pharmacovigilance will be in

place to detect post-marketing signals. Labeling will document the disproportionate incidence of elevated PT in ACTT-1 and will recommend monitoring PT as appropriate.

8.5.10. Renal

In nonclinical safety studies, the kidney was identified as the target organ of toxicity, mainly driven by the excipient SBECD (see Section 4.4). However, a renal safety signal was not observed in the healthy volunteer studies with RDV.

SARS-CoV-2 has multi-organ tropism, including the lungs, pharynx, heart, liver, brain, and kidney.[6] Renal tropism is a potential explanation of commonly reported clinical signs of kidney injury in patients with COVID-19.[4-7, 29-31] As renal injury and abnormal renal laboratory parameters have been reported in patients with COVID-19, including in patients receiving placebo in clinical trials of RDV, as well as in the EUA cases, and in published literature, discerning the contribution of RDV to renal events in this hospitalized patient population is challenging.[4-7, 11, 13-15, 29-31]

In the Phase 3 trials, the majority of renal AEs were laboratory events. Consequently, the laboratory data provide the most objective assessment of nephrotoxicity in the trials.

ACTT-1

- Renal AEs (all causality) occurred in 18% (94 of 532 subjects) in the RDV group and 23% (118 of 516 subjects) in the PBO group. Renal events that occurred in at least 2% of either group are summarized below:
    - RDV: glomerular filtration rate decreased (11%), blood creatinine increased (6%), acute kidney injury (5%)
    - PBO: glomerular filtration rate decreased (15%), blood creatinine increased (7%), acute kidney injury (6%)
- Grade 3/4 renal ADRs occurred in 2% (9 of 532 subjects) in the RDV group and 2% (9 of 516 subjects) in the PBO group.
- Renal SAEs occurred in 3% (15 of 532 subjects) in the RDV group and 4% (20 of 516 subjects) in the PBO group. The most frequently reported renal SAE was acute kidney injury (RDV 1.3%, 7 subjects; PBO: 2%, 12 subjects). No renal SAEs were assessed as related to RDV.
- Renal AEs that led to discontinuation occurred in 4% (22 of 532 subjects) in the RDV group and 5% (28 of 516 subjects) in the PBO group:
    - RDV: acute kidney injury (n=10), glomerular filtration rate decreased (n=8), blood creatinine increased (n=2), and creatinine renal clearance decreased (n=2).
    - PBO: AST increased (n=6), transaminase increased (n=4), ALT increased (n=2).
- Renal ADRs that led to discontinuation were acute kidney injury (n=3 and glomerular filtration rate decreased (n=2). (see Section 8.4.3).
- All Grade 3/4 renal laboratory abnormalities occurred at lower rates in in the RDV group compared to the PBO group (see Section 8.4.6).

GS-US-540-5773

- Renal AEs (all causality) occurred in 4% (8 of 200 subjects) in the RDV 5-day group and 9.6% (19 of 197 subjects) in the RDV 10-day group.
- Acute kidney injury was the predominant renal AE, occurring in 2% (4 of 200 subjects) in the RDV 5-day group and 8.1% (16 of 197 subjects) in the RDV 10-day group.
- Renal SAEs occurred in 1.5% (3 of 200 subjects) in the RDV 5-day group and 2% (4of 197 subjects) in the RDV 10-day group. No renal SAEs were assessed as related to RDV.
- Renal AEs that led to discontinuation occurred in 0.5% (1 of 200 subjects) in the RDV 5-day group and 4% (7 of 197 subjects) in the RDV 10-day group:
    - RDV 5-day group: blood creatinine increased (n=1)
    - RDV 10-day group: acute kidney injury (n=5), renal failure (n=1), glomerular filtration rate decreased (n=1)
- All Grade 3/4 renal laboratory abnormalities occurred at higher rates in in the RDV 10-day group compared to the RDV 5-day group (see Section 8.4.6).

GS-US-540-5774

- Renal AEs (all causality) occurred in 1.6% (3 of 191 subjects) in the RDV 5-day group, 2.1% (4 of 193 subjects) in the RDV 10-day group, and 2% (4 of 200 subjects) in the standard of care group.
- There were no renal SAEs in the RDV 5-day or 10-day groups. One renal SAE (acute kidney injury) occurred in in the standard of care group.
- There were no renal AEs that led to discontinuation in any of the treatment group.
- All Grade 3/4 renal laboratory abnormalities occurred at higher rates in the standard of care group compared to both RDV groups (see Section 8.4.6).
- Comparing the RDV groups, all Grade 3/4 renal laboratory abnormalities occurred at higher rates in in the RDV 10-day group compared to the RDV 5-day group (see Section 8.4.6).

EUA (summary of OSE review)
On July 9, 2020, OSE completed a pharmacovigilance memorandum that summarized the available safety data in FAERS and the medical literature related to the use of RDV under the EUA through June 3, 2020. A total of 137 cases of acute kidney injury/renal failure were identified. The review noted that the complexity of the cases and the limited clinical information, which in no case included renal histology or urine sediment, hindered the adjudication of causality to RDV. The review also assessed that, due to confounders such as underlying comorbidities, concomitant medications, and renal injury that can occur in patients with COVID-19, especially in those with severe disease, determining the contribution of RDV to these events is challenging.

Overall Assessment: A renal safety signal was identified in nonclinical studies but was not observed in healthy volunteer studies.

In ACTT-1, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were lower in the RDV group compared to PBO.

In GS-US-540-5773, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were higher in the 10-day group compared to the 5-day group.

In GS-US-540-5774, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were higher in the 10-day group compared to the 5-day group; however, rates of Grade 3/4 renal laboratory abnormalities were higher in the SOC group than in either RDV group.

Overall, the rates of renal AEs and Grade 3/4 renal laboratory abnormalities were lower in GS-US-540-5774 in subjects with moderate COVID-19 compared to GS-US-540-5773 in subjects with severe COVID-19. Despite the caveats associated with cross-study comparisons, these observations highlight the contribution of disease severity to adverse renal outcomes.

Review of EUA data did not identify any non-confounded cases of renal injury with sufficient information to assess as related to RDV.

Based on all available information, no specific product labeling is warranted aside from highlighting the preclinical renal findings in Section 13 and displaying renal laboratory data in Section 6. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.11. Safety Profile by Baseline Renal Function

The safety profile of RDV could be adversely impacted by increasing degrees of renal impairment. PK data in the setting of renal impairment are not available, and drug exposures could be elevated in these settings, increasing the potential risk of adverse reactions.

Safety analyses were performed to identify unique RDV safety signals in subjects by baseline renal function (Tables 43-45). The findings are overall similar across all treatment groups in ACTT-1, GS-US-540-5773 and GS-US-540-5774 (including the PBO group in ACTT-1 and standard of care group in GS-US-540-5774):

- The majority of subjects (>60%) had normal baseline renal function.
- Higher rates of AEs were observed with increasing degrees of renal impairment.
- The proportion of subjects with moderate renal impairment at baseline was small (~10%) and precludes definitive analyses.
- The proportion of subjects with severe renal impairment at baseline was minimal (<1% in ACTT-1; zero in GS-US-540-5773; zero in GS-US-540-5774) and precludes definitive analyses.

Table 43. Treatment-emergent AEs by Baseline Renal Function - CLCr, ACTT-1

	RDV 10 Days N=532					PBO 10 Days N=516				
Renal Function (CLCr)	Normal N=352 n (%)	Mild N=105 n (%)	Moderate N=40 n (%)	Severe N=1 n (%)	Missing N=34 n (%)	Normal N=310 n (%)	Mild N=114 n (%)	Moderate N=54 n (%)	Severe N=3 n (%)	Missing N=34 n (%)
Any AE	192 (54.5)	65 (61.9)	28 (70)	1 (100)	19 (55.9)	178 (57.4)	74 (64.9)	43 (79.6)	3 (100)	24 (70.6)
Moderate (Grade 2)	0	0	0	0	0	1 (0.3)	0	0	0	0
Severe (Grade 3)	97 (27.6)	31 (29.5)	16 (40)	0	10 (29.4)	73 (23.5)	29 (25.4)	7 (13)	0	8 (23.5)
Life Threatening or Disabling (Grade 4)	69 (19.6)	15 (14.3)	4 (10)	0	3 (8.8)	78 (25.2)	22 (19.3)	17 (31.5)	2 (66.7)	8 (23.5)
Death (Grade 5)	26 (7.4)	19 (18.1)	8 (20)	1 (100)	6 (17.6)	26 (8.4)	23 (20.2)	19 (35.2)	1 (33.3)	8 (23.5)
Any SAE	74 (21)	32 (30.5)	13 (32.5)	1 (100)	11 (32.4)	77 (24.8)	38 (33.3)	31 (57.4)	1 (33.3)	15 (44.1)
SAE with fatal outcome	26 (7.4)	19 (18.1)	8 (20)	1 (100)	6 (17.6)	26 (8.4)	23 (20.2)	19 (35.2)	1 (33.3)	8 (23.5)
AE leading to discontinuation of study drug	29 (8.2)	19 (18.1)	4 (10)	1 (100)	4 (11.8)	34 (11)	18 (15.8)	14 (25.9)	0	10 (29.4)
AE leading to interruption of study drug	22 (6.2)	5 (4.8)	2 (5)	0	3 (8.8)	30 (9.7)	7 (6.1)	8 (14.8)	1 (33.3)	3 (8.8)

Source: ADLB, ADSL datasets; ACTT-1
CLCr was used to classify renal function based on FDA Guidance - Pharmacokinetics in Patients with Impaired Renal Function.
There were 68 missing values of CLCr due to missing values of baseline weight.
There was 1 subject (COV.01634) in the placebo group with baseline renal function as ESRD (end-stage renal disease) that was not included in the table.

Proportion of subjects with normal renal function: RDV 352/498 (71%), PBO 310/482 (64%)
Proportion of subjects with mild renal impairment: RDV 105/498 (21%), PBO 114/482 (24%)
Proportion of subjects with moderate renal impairment: RDV 40/498 (8%), PBO 54/482 (11%)
Proportion of subjects with severe renal impairment: RDV 1/498 (0.2%), PBO 3/482 (0.6%)

Table 44. Treatment-emergent AEs by Baseline Renal Function - CLCr, GS-US-540-5573

	RDV 5 Days N=200					RDV 10 Days N=197				
Renal Function (CLCr)	Normal N=127 n (%)	Mild N=53 n (%)	Moderate N=17 n (%)	Severe N=0 n (%)	Missing N=3 n (%)	Normal N=130 n (%)	Mild N=46 n (%)	Moderate N=14 n (%)	Severe N=0 n (%)	Missing N=7 n (%)
Any AE	92 (72.4)	38 (71.7)	13 (76.5)	0	0	89 (68.5)	41 (89.1)	12 (85.7)	0	6 (85.7)
Mild (Grade 1)	36 (28.3)	13 (24.5)	4 (23.5)	0	0	21 (16.2)	8 (17.4)	1 (7.1)	0	1 (14.3)
Moderate (Grade 2)	19 (15)	6 (11.3)	2 (11.8)	0	0	21 (16.2)	9 (19.6)	3 (21.4)	0	0
Severe (Grade 3)	13 (10.2)	8 (15.1)	2 (11.8)	0	0	12 (9.2)	3 (6.5)	3 (21.4)	0	1 (14.3)
Life Threatening or Disabling (Grade 4)	12 (9.4)	4 (7.5)	0	0	0	23 (17.7)	12 (26.1)	1 (7.1)	0	1 (14.3)
Death (Grade 5)	12 (9.4)	7 (13.2)	5 (29.4)	0	0	12 (9.2)	9 (19.6)	4 (28.6)	0	3 (42.9)
Any SAE	26 (20.5)	12 (22.6)	5 (29.4)	0	0	38 (29.2)	21 (45.7)	5 (35.7)	0	4 (57.1)
SAE with fatal outcome	12 (9.4)	7 (13.2)	5 (29.4)	0	0	12 (9.2)	9 (19.6)	4 (28.6)	0	3 (42.9)
AE leading to discontinuation of study drug	5 (3.9)	3 (5.7)	1 (5.9)	0	0	13 (10)	6 (13)	2 (14.3)	0	1 (14.3)
AE leading to interruption of study drug	0	0	0	0	0	2 (1.5)	1 (2.2)	1 (7.1)	0	0

Source: ADAE, ADSL datasets; Study 5773
CLCr was used to classify renal function based on FDA Guidance - Pharmacokinetics in Patients with Impaired Renal Function.
There were 10 subjects have missing values of CLCr. 8 of them were because of missing values of baseline weight and 2 of them were because of missing values of baseline creatinine.

Proportion of subjects with normal renal function: RDV 5-days, 127/197 (64%); RDV 10-days, 130/190 (68%)
Proportion of subjects with mild renal impairment: RDV 5-days, 53/197 (27%); RDV 10-days, 46/190 (24%)
Proportion of subjects with moderate renal impairment: RDV 5-days, 17/197 (9%); RDV 10-days, 14/190 (7%)

Table 45. Treatment-emergent AEs by Baseline Renal Function - CLCr, GS-US-540-5574

	RDV 5 Days N=191					RDV 10 Days N=193					Standard of care N=200				
Renal Function (CLCr)	Normal N=113	Mild N=55	Moderate N=18	Severe N=0	Missing N=5	Normal N=129	Mild N=44	Moderate N=14	Severe N=0	Missing N=6	Normal N=128	Mild N=50	Moderate N=19	Severe N=0	Missing N=3

	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	47 (41.6)	35 (63.6)	12 (66.7)	0	4 (80)	73 (56.6)	28 (63.6)	9 (64.3)	0	3 (50)	54 (42.2)	28 (56)	9 (47.4)	0	2 (66.7)
Mild (Grade 1)	23 (20.4)	21 (38.2)	5 (27.8)	0	2 (40)	30 (23.3)	16 (36.4)	0	0	2 (33.3)	24 (18.8)	9 (18)	3 (15.8)	0	1 (33.3)
Moderate (Grade 2)	16 (14.2)	6 (10.9)	3 (16.7)	0	2 (40)	29 (22.5)	8 (18.2)	3 (21.4)	0	1 (16.7)	19 (14.8)	11 (22)	2 (10.5)	0	0
Severe (Grade 3)	7 (6.2)	6 (10.9)	4 (22.2)	0	0	12 (9.3)	3 (6.8)	4 (28.6)	0	0	8 (6.2)	2 (4)	2 (10.5)	0	1 (33.3)
Life Threatening or Disabling (Grade 4)	1 (0.9)	0	0	0	0	2 (1.6)	0	0	0	0	2 (1.6)	4 (8)	1 (5.3)	0	0
Death (Grade 5)	0	2 (3.6)	0	0	0	0	1 (2.3)	2 (14.3)	0	0	1 (0.8)	2 (4)	1 (5.3)	0	0
Any SAE	4 (3.5)	4 (7.3)	1 (5.6)	0	0	5 (3.9)	2 (4.5)	3 (21.4)	0	0	8 (6.2)	7 (14)	3 (15.8)	0	0
SAE with fatal outcome	0	2 (3.6)	0	0	0	0	1 (2.3)	2 (14.3)	0	0	0	2 (4)	1 (5.3)	0	0
AE leading to discontinuation of study drug	4 (3.5)	0	0	0	0	6 (4.7)	2 (4.5)	0	0	0	0	0	0	0	0
AE leading to interruption of study drug	3 (2.7)	1 (1.8)	0	0	0	0	0	0	0	0	0	0	0	0	0

Source: ADAE, ADSL datasets; Study 5774
CLCr was used to classify renal function based on FDA Guidance - Pharmacokinetics in Patients with Impaired Renal Function.
There were 14 subjects have missing values of CLCr due to missing values of baseline weight.

Proportion of subjects with normal renal function: RDV 5-days, 113/186 (61%); RDV 10-days, 129/187 (69%); Standard of care, 129/197 (65%)
Proportion of subjects with mild renal impairment: RDV 5-days, 55/186 (30%); RDV 10-days, 44/187 (24%); Standard of care, 50/197 (25%)
Proportion of subjects with moderate renal impairment: RDV 5-days, 18/186 (10%); RDV 10-days, 14/187 (7%); Standard of care, 19/197 (10%)

Overall Assessment: The limitations of the currently available Phase 3 data preclude a comprehensive assessment of safety in patients with eGFR ≥ 30 - <90 mL/min, and there remains uncertainty about aspects of the safety profile of RDV in the setting of renal impairment. Furthermore, the subdivision of acutely ill subjects based on study entry eGFR is problematic as these subjects may already have an unstable serum creatinine at the time of enrollment. However, patients with eGFR > 30 were permitted to enroll in ACTT-1, and the review team concludes that the potential benefit of RDV in this population outweighs the potential risk.

The Applicant plans to conduct a pharmacokinetic and safety study to further assess potential safety risks in adults with varying degrees of chronic renal impairment (i.e., mild, moderate, and severe) and to inform dosage recommendations for this subpopulation.

We will continue to monitor closely in the postmarketing setting for any potential serious safety signals associated with RDV use in the subpopulations with renal impairment.

8.6. Safety Analyses by Demographic Subgroups

Consistent with our approach for the overall safety review, the impact of weight, age, sex, and race on the frequencies of adverse events were assessed for ACTT-1, GS-US-540-5773 and GS-US-540-5774. While subjects aged ≥65 years had higher rates of serious or severe AEs compared to younger subjects, these findings were also observed in the placebo group from ACTT-1 and the standard of care group from GS-US-540-5774, and reflect the epidemiology of COVID-19 and the disproportionately higher rates of COVID-19 infection, hospitalization, and death among older subjects. Otherwise, we did not find any demographic subgroups at substantially higher risk for serious or severe AEs. This section contains a brief summary of our findings, organized by demographic variable. The discussion is limited to ACTT-1, GS-US-540-5773 and GS-US-540-5774 subjects treated with RDV.

Weight

The Phase 3 clinical trials included 30 adult subjects weighing 40-50kg who received RDV (ACTT-1 [n=10]; GS-US-540-5773 [n=9]; GS-US-540-5774 [n=11]). The safety in this weight group was similar to adult subjects weighing >50kg.

Reviewer Comment: The demonstration of an acceptable safety profile among adults with lower body weights (e.g. 40-50 kg) provided additional support for the adolescent indication.

Age

ACTT-1: Subjects <65 years of age (n=349) were compared to subjects ≥65 years old (n=183). The older cohort comprised 34% of the RDV group. All-cause AEs of any severity occurred in 53% and 66% respectively; SAEs occurred in 20% and 34% respectively; graded laboratory abnormalities occurred in 97% and 100% respectively.

GS-US-540-5773
• 5-day group: Subjects <65 years of age (n=116) were compared to subjects ≥65 years old (n=84). The older cohort comprised 42% of the RDV 5-day group. All-cause AEs of any severity occurred in 69% and 75% respectively; SAEs occurred in 19% and 25% respectively; graded laboratory abnormalities occurred in 79% and 77% respectively.
• 10-day group: Subjects <65 years of age (n=113) were compared to subjects ≥65 years old (n=84). The older cohort comprised 43% of the RDV 10-day group. All-cause AEs of any severity occurred in 66% and 88% respectively; SAEs occurred in 21% and 52% respectively; graded laboratory abnormalities occurred in 77% and 85% respectively.

GS-US-540-5774
• 5-day group: Subjects <65 years of age (n=142) were compared to subjects ≥65 years old (n=49). The older cohort comprised 26% of the RDV 5-day group. All-cause AEs of any severity occurred in 49% and 59% respectively; SAEs occurred in 3% and 10% respectively; graded laboratory abnormalities occurred in 72% and 76% respectively.
• 10-day group: Subjects <65 years of age (n=141) were compared to subjects ≥65 years old (n=52). The older cohort comprised 27% of the RDV 10-day group. All-cause AEs of any severity occurred in 57% and 64% respectively; SAEs occurred in 4 and 10% respectively; graded laboratory abnormalities occurred in 68% and 80% respectively.

Reviewer Comment: Subjects aged ≥65 years had higher rates of death, SAEs, Grade 3/4 AEs, and overall AEs compared to younger subjects. Similar findings were also observed in the placebo group in ACTT-1 and the standard of care group in GS-US-540-5774. These findings reflect the epidemiology of COVID-19 where elderly subjects are at higher risk for severe disease and adverse outcomes.[1-7]

Gender
ACTT-1: Women comprised 35% of the RDV group (185/352). All-cause AEs of any severity occurred in 57% of women and 58% of men; SAEs occurred in 24% of women and 25% of men; graded laboratory abnormalities occurred in 99% of women and 97% of men.

GS-US-540-5773
• 5-day group: Women comprised 35% of the RDV group (80/200). All-cause AEs of any severity occurred in 71% of women and 72% of men; SAEs occurred in 10% of women and 29% of men; graded laboratory abnormalities occurred in 68% of women and 85% of men.
• 10-day group: Women comprised 32% of the RDV group (64/197). All-cause AEs of any severity occurred in 70% of women and 77% of men; SAEs occurred in 25% of women and 39% of men; graded laboratory abnormalities occurred in 84% of women and 84% of men.

GS-US-540-5774
• 5-day group: Women comprised 40% of the RDV group (77/191). All-cause AEs of any severity occurred in 60% of women and 46% of men; SAEs occurred in 3% of women and 6% of men; graded laboratory abnormalities occurred in 71% of women and 74% of men.

• 10-day group: Women comprised 39% of the RDV group (75/193). All-cause AEs of any severity occurred in 60% of women and 58% of men; SAEs occurred in 4% of women and 6% of men; graded laboratory abnormalities occurred in 68% of women and 74% of men.

Reviewer Comment: No overall safety differences were observed between male and female subjects.

Race
Differences between racial groups were more difficult to assess due to the predominance of white subjects in the Phase 3 clinical trials.

ACTT-1 comprised 51% white subjects, 20% black subjects, 15% Asian subjects, and 14% other race. All-cause AEs of any severity occurred in 55% of white subjects, 67% of black subjects, 57% of Asian subjects, and 52% of other race. SAEs occurred in 23% of white subjects, 32% of black subjects, 24% of Asian subjects, and 19% of other race. Graded laboratory abnormalities occurred in 97% of white subjects, 100% of black subjects, 100% of Asian subjects, and 97% of other race.

GS-US-540-5773
• 5-day group comprised 71% white subjects, 10.5% black subjects, 10% Asian subjects, and 8.5% other race. All-cause AEs of any severity occurred in 72% of white subjects, 66% of black subjects, 75% of Asian subjects, and 71% of other race. SAEs occurred in 20% of white subjects, 10% of black subjects, 40% of Asian subjects, and 24% of other race. Graded laboratory abnormalities occurred in 76% of white subjects, 80% of black subjects, 90% of Asian subjects, and 77% of other race.
• 10-day group comprised 68% white subjects, 12% black subjects, 13% Asian subjects, and 8% other race. All-cause AEs of any severity occurred in 76% of white subjects, 61% of black subjects, 84% of Asian subjects, and 73% of other race. SAEs occurred in 39% of white subjects, 13% of black subjects, 24% of Asian subjects, and 47% of other race. Graded laboratory abnormalities occurred in 85% of white subjects, 74% of black subjects, 84% of Asian subjects, and 86% of other race.

GS-US-540-5774
• 5-day group comprised 57% white subjects, 18% black subjects, 18% Asian subjects, and 7% other race. All-cause AEs of any severity occurred in 55% of white subjects, 40% of black subjects, 56% of Asian subjects, and 39% of other race. SAEs occurred in 5% of white subjects, 9% of black subjects, 3% of Asian subjects, and no subjects of other race. Graded laboratory abnormalities occurred in 75% of white subjects, 77% of black subjects, 58% of Asian subjects, and 82% of other race.
• 10-day group comprised 55% white subjects, 19% black subjects, 16% Asian subjects, and 9% other race. All-cause AEs of any severity occurred in 62% of white subjects, 51% of black subjects, 58% of Asian subjects, and 56% of other race. SAEs occurred in 4% of white subjects, 10% of black subjects, no Asian subjects, and 11% subjects of other race. Graded laboratory

abnormalities occurred in 74% of white subjects, 61% of black subjects, 71% of Asian subjects, and 77% of other race.

Reviewer Comment: No clear safety differences were apparent based on race, but the lower enrollment percentages of some racial subgroups preclude definitive conclusions.

Overall Demographic Safety Analysis Conclusion: Adverse events occurred more frequently in subjects aged ≥65 years (regardless of RDV, PBO, or standard of care) and are consistent with the epidemiology of COVID-19 where elderly subjects are at higher risk for severe disease and adverse outcomes.[1-7] Safety analyses by weight, sex, and race showed that adverse events occurred with similar frequency and severity in these demographic subgroups.

8.7. Specific Safety Studies/Clinical Trials

No additional trials have been conducted to evaluate specific safety concerns.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The relatively short duration of RDV treatment (up to 10 days) and follow-up (generally 29 days) in clinical trials limits the assessment for oncologic events. There were no treatment-emergent oncologic events in any of the RDV arms in the Phase 3 trials.

Reviewer Comment: Based on the available data from the Phase 3 trials, there is no clinical evidence of carcinogenicity for RDV.

8.8.2. Human Reproduction and Pregnancy

Pregnant and lactating women were excluded from participation for all Phase 3 trials in the RDV COVID-19 development program by the trials' sponsor.

A search of the Applicant's global safety database identified a total of 156 pregnancy cases involving RDV exposure cumulative to August 18, 2020. The majority of the pregnancy cases were reported from the expanded access program.

Of the 156 pregnancy cases, 33 reported live birth and 13 reported adverse pregnancy outcomes (abortion induced [n=2]; abortion spontaneous [n=7]; still birth [n=4]). The birth outcomes of the remaining 110 cases are unknown. Of the 13 pregnancies with adverse pregnancy outcomes:

- Nine cases were reported in women who received RDV for the treatment of acute Ebola virus (EVD) and 4 cases were reported in women who received RDV for the treatment of COVID-19.
- Four cases were reported from prospective pregnancies and 9 cases were reported retrospectively.
- Four women with COVID-19 who had spontaneous abortions (n = 2) or still births (n=2) were on baseline invasive mechanical ventilation (IMV) or required it within 1 day of RDV initiation, suggesting that their underlying conditions significantly impacted their pregnancy outcome.

There were 5 cases of congenital anomalies (4 from live births and 1 from a still birth) which were identified in patients who received RDV for COVID-19. In 4 cases, RDV exposure was not in the first trimester. In the fifth case, the precise timing of earliest RDV exposure was unknown since the date of the last menstrual period (LMP) was not provided but could be deduced to be after the first trimester based on the gestational age at birth and RDV administration dates. These 5 cases are summarized below:

- Two prospective cases (2020-(b) (6), 2020-(b) (6)) included congenital cardiac anomalies, which develop in the first 8 weeks of gestation, and RDV administration late in pregnancy (third trimester RDV exposure in 1 case and missing LMP in the other case).
- One retrospective case (2020(b) (6)) of tuberous sclerosis complex, a genetic condition that was noted in the mother (second trimester RDV exposure).
- One retrospective case (2020-(b) (6)) of microcephaly and small for gestational age attributed to intrauterine growth restriction, which was likely multi-factorial (third trimester RDV exposure).
- One retrospective case (2020-(b) (6)) of still birth with a reported congenital anomaly but no additional clinical information or specific congenital anomaly was provided (second trimester RDV exposure).

The Applicant also submitted data on 67 pregnant individuals and 19 post-partum individuals who received at least 1 dose of RDV for treatment of COVID-19 under EA between March 21, 2020 and April 22, 2020. The available clinical data from these patients are limited.

A search of the Applicant's global safety database identified no reports of infants who were exposed to RDV through breastfeeding cumulative to August 18, 2020.

Overall Assessment: The reported events occurred in patients who are at risk for adverse pregnancy outcomes due to the sequelae of acute EVD and COVID-19. There is insufficient evidence to suggest a causal relationship between RDV and adverse pregnancy or infant outcomes based on the limited data currently available.

The Applicant is collaborating with the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) to initiate the IMPAACT 2032 study (Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States).[32] This study will enroll approximately 20 pregnant individuals who are hospitalized with COVID-19 and treated with RDV. The clinical and safety outcomes of the subjects will be monitored through four weeks post-last infusion and during delivery. The IMPAACT 2032 study is scheduled to start in 4Q 2020.

Additionally, as part of their pharmacovigilance plan, the Applicant intends to collect data on pregnancy exposures and outcomes as reported to their global safety database.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant included an initial indication for RDV for the treatment of COVID-19 in adolescents ≥ 12 years of age and weighing ≥ 40 kg through extrapolation of efficacy from adults receiving the same dose of RDV as proposed for adolescent patients. The Agency agreed with this proposal because adult and pediatric populations with moderate to severe COVID-19 generally display similar symptoms, and virologic response to an antiviral drug such as RDV is expected to be similar in adults and pediatric patients.[26, 33-37] Furthermore, the Agency concluded that it was appropriate to include adolescents (≥ 12 years old and ≥ 40 kg) based on the historical concordance of adult and adolescent dosing regimens observed for other drugs.[37] Additionally, the physiologically based pharmacokinetic (PBPK) model and the population pharmacokinetic (popPK) model supported use of the adult dose above this weight cutoff. The Agency assessed that, using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of RDV and metabolites in adolescents ≥ 12 years old and ≥ 40 kg as observed in healthy adults. Additional supportive data was provided from the RDV Phase 3 clinical trials in which the safety in adult subjects weighing 40-50kg (i.e. encompassing weight ranges that are observed in adolescents) was similar to adult subjects weighing >50kg. There was also supportive data from 39 pediatric patients ≥ 12 years of age and ≥ 40 kg who received RDV via expanded access; however, the available clinical data from these patients was limited. Confirmatory data will be requested in this age and weight range (i.e. 12 years of age and older and weighing at least 40 kg) in the PREA PMR.[38]

The Agency determined that the current PBPK model and popPK model were not reliable for selecting dosing for < 40 kg weight bands. Furthermore, the Agency concluded that refinement of the PBPK model would require actual PK data, which are not currently available. In a future submission, the results from a dedicated pediatric trial will be provided (b) (4) (b) (4) Pediatric study GS-US-540-5823 (ClinicalTrials.gov Identifier: NCT04431453) was initiated in July 2020, and its regulatory history and design are summarized below.

In conformance with current regulatory requirements, the Applicant submitted an initial Pediatric Study Plan (iPSP) for RDV on April 9, 2020. The document was reviewed and found to be generally satisfactory by both the review division as well as the Pediatric Review Committee (PeRC). The Applicant incorporated the Agency's recommendations and the revised PSP was approved by the Division and the PeRC. The Division issued a notice of Agreed PSP on July 9, 2020. The Agreed iPSP included the Applicant's agreement to ensure adolescents weighing ≥ 40kg are included in the dedicated pediatric trial irrespective of whether adolescents are included in the initial indication. The Applicant agreed with the Agency's assessment that PK data generated in adolescents: (1) will help confirm that use of the adult dose in the adolescent population is appropriate and; (2) will help inform dosing for the younger/lower weight populations. The proposed pediatric study reflects the PREA PMR that will be issued.

In brief, the proposed pediatric development plan includes the following study to evaluate the safety and efficacy of RDV in children ages 0 to < 18 years of age:

- Study GS-US-540-5823 is an open-label, single-arm study to investigate the safety, tolerability, efficacy, and PK of RDV in pediatric subjects birth to < 18 years of age who are hospitalized with laboratory proven SARS-CoV-2 infection. The study will allow for enrollment of adolescents <18 years of age. (b) (4)

Table 46. Study GS-US-540-5823

Cohort	N	Description	Dosing
1	12	≥ 12 years to < 18 years and weight ≥ 40 kg	200 mg IV on Day 1 followed by 100 mg IV QD for up to 10 days
2	12	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg	5 mg/kg IV on Day 1 followed by 2.5 mg/kg IV QD for up to 10 days
3	12	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg	
4	12	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg	
5	4	≥ 14 days to < 28 days of age, gestational age > 37 weeks and weight at Screening ≥ 2.5 kg	
6	*	0 days to < 14 days of age, gestational age > 37 weeks and birth weight ≥ 2.5 kg	Dose-TBD; duration is for up to 10 days
7	*	0 days to < 56 days of age, gestational age ≤ 37 weeks and birth weight ≥ 1.5 kg	Dose-TBD; duration is for up to 10 days

*No minimum number; TBD, to be determined

Cohorts 1-5 will be enrolled in parallel. Subjects in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined. The Division agreed with the Applicant's proposal that there is no minimum number of subjects to be enrolled in Cohorts 6 and 7 due to the rarity of this subpopulation with COVID-19.

The Applicant intends to use (b) (4)

The Applicant has requested a deferral of required pediatric assessments in pediatric patients birth to < (b) (4) years of age, until data from Study GS-US-540-5823 (including the preliminary PK data) are available and have been reviewed by the Agency. The Division is in agreement with this proposal. The deferral request was presented to the PeRC, and the PeRC agreed with the Applicant's proposal and the Division's recommendations.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The potential for drug abuse, withdrawal, or rebound with RDV was not evaluated but is not anticipated.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Emergency Use Authorization (EUA)

The EUA outlines mandatory reporting of all medication errors and adverse events (death, serious adverse events) considered to be potentially related to RDV. The relevant aspects of the EUA safety data have been incorporated into the relevant sections of this review.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 3 trial populations. The eligibility criteria for the three Phase 3 trials may mitigate potential safety concerns that may be observed with wider usage in the postmarket setting. Emergence of new events can be managed by routine pharmacovigilance activities.

8.10. Additional Safety Issues From Other Disciplines

All additional safety issues from other disciplines are included in this review.

8.11. Integrated Assessment of Safety

Hypersensitivity reactions and hepatotoxicity were the major safety issues identified in this review.

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of RDV. Clinical manifestations have included hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. These reactions have been reported in patients with COVID-19 in clinical trials and in the EUA population. The Warnings and Precautions section will provide wording that clearly describes the hypersensitivity reactions that have been observed for RDV.

A hepatotoxicity safety signal was clearly demonstrated in trials in healthy subjects, and transaminase elevations have been reported in patients with COVID-19 in clinical trials, in the EUA population, and in published literature; however, the interpretation of cases in the setting of COVID-19 is challenging. Additionally, PK data in the setting of renal or hepatic impairment are not available, and drug exposures could be elevated in these settings, increasing the potential risk of adverse reactions, including hepatotoxicity. The Warnings and Precautions section will provide wording that clearly describes the hepatotoxicity safety signal that has been observed for RDV.

In ACTT-1, Grade 3/4 ADRs were infrequent and occurred at similar or lower rates compared to placebo. In GS-US-540-5773 and GS-US-540-5774, nausea was the only clinical ADR that occurred with ≥5% greater frequency.

In GS-US-540-5773, higher rates of AEs, grade 3/4 adverse events, SAEs, discontinuations due to AEs, and Grade 3/4 laboratory abnormalities occurred in the 10-day group compared to the 5-day group. These findings were also generally observed in GS-US-540-5774, however the differences between the groups was less prominent.

Overall, the rates of AEs, grade 3/4 adverse events, SAEs, discontinuations due to AEs, and Grade 3/4 laboratory abnormalities were lower in GS-US-540-5774 in subjects with moderate COVID-19 compared to GS-US-540-5773 in subjects with severe COVID-19. These trends were also consistent for each of the treatment durations. Despite the caveats associated with cross-study comparisons, these observations highlight the contribution of COVID-19 disease severity to adverse outcomes.

The notable laboratory abnormality was the higher rate of prothrombin time elevation in the RDV group compared to PBO group in ACTT-1. Given that these elevations may impact management of patients receiving anticoagulants, this information is clinically relevant and will be described in labeling, outlining that monitoring is recommended while receiving RDV.

EUA safety analyses identified a greater number of cases of hypersensitivity reactions, including infusion-related and anaphylactic reactions, compared to the Phase 3 clinical trials. Otherwise, no notable differences appeared.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting will not be convened for this application.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed labeling. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted.

1 INDICATIONS AND USAGE

The Applicant proposed an indication for RDV (b) (4) The review team recommends that the indication be limited to the hospitalized patient population because the Phase 3 trials (ACTT-1, Study 5773, and Study 5774) were all conducted in hospitalized patients.

2 DOSAGE AND ADMINISTRATION

- The review team recommends the following dosages for hospitalized adult and pediatric patients ≥ 12 years of age and weighing ≥ 40 kg: single loading dose of RDV 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of RDV 100 mg from Day 2 via intravenous infusion.
    - The recommended treatment duration for patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
    - The recommended total treatment duration for patients requiring invasive mechanical ventilation and/or ECMO is 10 days.
- Given the disproportionately higher rates of prothrombin time elevations with RDV compared to placebo in ACTT-1, the review team recommends that prothrombin time should be determined in all patients prior to starting RDV and monitored while receiving RDV as clinically appropriate.

4 CONTRAINDICATIONS

- The review team recommends that RDV be contraindicated in patients with a history of clinically significant hypersensitivity reactions to RDV or any components of the product. *(See Section 8.5.2)*

5 WARNINGS AND PRECAUTIONS

- The Warnings/Precautions section will provide wording that clearly describes the hepatotoxicity safety signal and hypersensitivity reactions (including infusion-related and anaphylactic reactions) that have been observed for RDV. *(See Sections 8.5.1 and 8.5.2)*
- The Warnings and Precautions section will provide wording that clearly describes that concomitant use of RDV with CQ/HCQ is not recommended due to the risk of reduced antiviral activity to RDV. *(See Section 4.2)*

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience

- ACTT-1, Study 5773, and Study 5774 will be displayed separately.
- For ACTT-1, data from the placebo group will also be described. For Study 5774, data from the standard of care group will also be described. Adverse reactions from both of these comparator groups comprise the best available data to help inform the safety profile of RDV. *(See Section 8.4.5)*
- The review team added a section entitled “Less Common Adverse Reactions.” The purpose of this section is to include information about ADRs observed in clinical trials evaluating RDV, even if events occurred rarely in the RDV trials. This section will likely include hypersensitivity reactions, generalized seizure, and rash. *(See Sections 8.5.2, 8.5.4 and 8.5.5)*

- The review team added a section entitled "Emergency Use Authorization Experience in Patients with COVID-19." The purpose of this section is to include information about ADRs observed in the EUA. This section will likely include hypersensitivity reactions, administration site extravasation, rash, anaphylaxis, angioedema, and transaminase elevations. *(See Section 8.9.1)*
- Laboratory data from the Phase 3 trials will be displayed separately in the Laboratory Abnormalities so that the placebo group from ACTT-1 and the standard of care group from Study 5774 are described. *(See Section 8.4.6)*

7 DRUG INTERACTIONS

Established and Potentially Significant Drug Interactions

The following changes are proposed:

- Describes drug interaction information that, due to antagonism observed in cell culture, concomitant use of RDV with CQ or HCQ is not recommended.
- Drug-drug interaction trials of RDV and other concomitant medications have not been conducted in humans. The review team proposed additional wording to clarify that:
    - RDV and its metabolites are in vitro substrates and/or inhibitors of certain drug metabolizing enzymes and transporters. The clinical relevance of these in vitro assessments has not been established.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

- Revise to describe that supportive data was provided from: (1) the Phase 3 clinical trials in which the safety in adult subjects weighing 40-50kg (i.e. encompassing weight ranges that are observed in adolescents) was similar to adult subjects weighing >50kg; (2) 39 pediatric patients ≥ 12 years of age and ≥ 40 kg who received RDV via expanded access. *(See Section 8.8.3)*

8.6 Renal Impairment

- Revise to state that the pharmacokinetics of RDV have not been evaluated in patients with renal impairment. *(See Section 4.5.3)*

8.7 Hepatic Impairment

- Revise to state that the pharmacokinetics of RDV have not been evaluated in patients with hepatic impairment. *(See Section 4.5.3)*

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

- The review team recommends describing that exposure-response relationships and the time course of the pharmacodynamic response are unknown for RDV and its metabolites.

14 CLINICAL STUDIES

- Removed the Applicant's proposed [redacted] (b) (4) (*See Section 6.1.2)*
- The numbers of ACTT-1 subjects with baseline mild/moderate disease and baseline severe disease were revised using the actual [redacted] (b) (4) final datasets. (*See Section 6.1.2)*
- Added the ordinal scale definition used in the primary endpoint in GS-US-540-5773 and GS-US-540-57734, respectively. (*See Sections 6.2.1 and 6.3.1)*
- For each trial, clarified that RDV was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the Package Insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

11 Risk Evaluation and Mitigation Strategies (REMS)

No issues were identified to necessitate REMS.

12 Postmarketing Requirements and Commitments

Post-marketing requirements and commitments were still under discussion at the time this review was completed. This section includes PMRs and PMCs that will be proposed by the clinical review team.

- A PMR will be issued for pediatric trials to assess safety, pharmacokinetics, and efficacy of RDV in pediatric subjects ages 0 to < 18 years of age with COVID-19, as required under the Pediatric Research Equity Act (PREA).
- A PMR will be issued to evaluate the pharmacokinetics and safety of RDV in subjects with moderate and severe hepatic impairment to inform appropriate dosage recommendations in patients with COVID-19 with impaired hepatic function.
- A PMR will be issued to evaluate the pharmacokinetics and safety of RDV in subjects with mild, moderate, and severe renal impairment to inform appropriate dosage recommendations in patients with COVID-19 with impaired renal function.
- A PMR will be issued to conduct a study to select for RDV resistant SARS-CoV-2 variants in cell culture and characterize several independent isolates phenotypically and genotypically.
- A PMR will be issued to submit all SARS-CoV-2 viral shedding and viral load data from ACTT-1, GS-540-5773, and GS-US-5774 assessing RDV including quantitation of viral

shedding and viral load for any subject samples that have not been completed to date.

- A PMR will be issued to conduct a thorough QT study to evaluate the effect of RDV on the QTc interval.
- A PMR will be issued to conduct a drug interaction trial to evaluate the pharmacokinetics of RDV when coadministered with rifampin.
- A PMC will be issued to submit all sequencing data from ACTT-1, GS-540-5773, and GS-US-5774 assessing RDV including sequencing of any subject samples that have not been completed to date.
- A PMC will be issued to submit a comprehensive resistance study reports from ACTT-1, GS-US-540-5773, and GS-54-5774 describing all resistance assessments performed for RDV.
- A PMC will be issued to submit a complete study report for the assessment of the antagonistic effect of chloroquine/hydroxychloroquine on the antiviral activity of RDV against SARS-CoV-2 in human lung cells.
- A PMC will be issued to conduct a study to evaluate the pharmacokinetics and safety of RDV in pregnant individuals with COVID-19.

Additional postmarketing requirements or commitments may be proposed at a later time based on ongoing labeling and review discussions.

13 Appendices

13.1. References

1. CDC Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
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13.2. Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The financial disclosures described below do not affect approvability of RDV.

Covered Clinical Study (Name and/or Number): ACTT-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 453 Overall: 60 Principal Investigators, 393 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 *Dr. Patricia Jackson is a Principal Investigator (PI) on ACTT-1; Dr. Christoph Stephan is a sub-investigator on ACTT-1.* Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1 *Dr. Nikhil Huprikar is a PI on ACTT-1.*		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): GS-US-540-5773

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 457 Overall: 45 Principal Investigators, 412 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0		

Significant equity interest held by investigator in Sponsor of covered study: 2 (b) (6) *are sub-investigators on Study 5773.*		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): GS-US-540-5774

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 926 Overall: 97 Principal Investigators, 829 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 (b) (6) *are sub-investigators on Study 5774.* Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 2 (b) (6) *are sub-investigators on Study 5774.*		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant adequately examined financial disclosure information from all clinical investigators

for the covered clinical trials, as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Those investigators who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3) are noted in the above template. The Form FDA 3455 for each investigator was provided.

Overall, the number of investigators with a financial interest is low. Due to the multicenter nature of these trials, the potential bias by any one investigator is minimized.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

13.3. Other Supporting Information

On April 29, 2020, the results for a smaller RCT (CO-US-540-5758) conducted in China in patients hospitalized with severe COVID-19 (clinicaltrials.gov identifier NCT04257656) were published.[14] This investigator-sponsored, double-blind trial randomized patients in a 2:1 ratio to receive RDV or PBO for 10 days. RDV was administered intravenously at a dose of 200 mg on Day 1 followed by 100 mg on Days 2-10 in single daily infusions.

Inclusion criteria specified that patients were to be males and non-pregnant female patients aged ≥18 years who were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had a SpO2 ≤94% on room air or a PaO2/FiO2 ratio ≤300mgHg, and were within 12 days of illness onset. Exclusion criteria disallowed pregnancy or breast-feeding; hepatic cirrhosis or ALT/AST > 5x ULN; known severe renal impairment (estimated eGFR< 30 mL/min/1.73m^2), or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis; or possibility of transfer to a non-study hospital within 72 hours.

Between February 6, 2020 and March 12, 2020, a total of 237 patients out of the planned 453 patients were enrolled. The authors stated that no patients were enrolled after March 12, 2020 because public health interventions resulted in marked reductions in new cases and restrictions on hospital bed availability resulted in most patients being enrolled later in the course of disease. On March 29, 2020, the DSMB recommended study termination due to operational futility. This resulted in the study being underpowered, such that the statistical power was reduced from 80% to 58%. Consequently, this study could not adequately assess whether RDV treatment might have provided clinical benefit.

Among 255 patients who were screened, 237 patients were eligible, consented and were randomized, of whom 1 withdrew. 158 patients were assigned to receive RDV and 78 patients were assigned to PBO. In the RDV group, 155 (98%) received RDV as assigned and PBO was given to all patients in the PBO group. The median age was 65 years (interquartile range [IQR], 56 to 71 years) and 140 (59%) were males. The most common comorbidities were hypertension (43%), diabetes (24%) and coronary heart disease (7%). Lopinavir-ritonavir was co-administered in 42 (18%) patients at Day 1. Most patients (82% in the RDV group and 83% in the PBO group) were hospitalized for oxygen therapy at baseline but did not require high flow or noninvasive ventilation at baseline. Median days from illness onset to randomization was 10 days (IQR 9 to 12 days), and more patients (60%) in the PBO group than the RDV group (44%) had been symptomatic for 10 days or less at the time of randomization.

The efficacy analyses were conducted in an intention-to-treat population of all randomized patients. The primary endpoint was the time to clinical improvement. This was defined as a decline in 2 points (on a 6-point ordinal scale) or discharge. The 6-point scale included death: 6; hospitalized for ECMO and/or mechanical ventilation: 5; hospitalized for noninvasive ventilation and/or high flow oxygen therapy: 4; hospitalized for oxygen therapy (but not requiring high flow or noninvasive ventilation): 3; hospitalization but not requiring oxygen therapy: 2; discharged or having reached discharge criteria (defined as clinical recovery, i.e., normalization of pyrexia, respiratory rate [<24/minute], and SpO2 [>94% on room air], and relief of cough, all maintained for at least 72 hours): 1.

In the primary efficacy analysis, the median time to clinical improvement was 21 days for RDV versus 23 days for PBO. The hazard ratio (on a scale with values greater than 1.00 favoring RDV) was 1.23, with a 95% confidence interval from 0.87 to 1.75, and a two-sided p-value of 0.24 from a log-rank test. At Day 28, the proportion of patients with at least a 2-point improvement on the ordinal scale was 103/158 (65.2%) for RDV versus 45/78 (57.7%) for PBO, with a 7.5% difference in rates, and a 95% confidence interval for the difference from -5.7% to 20.7%. These primary efficacy results represented a numerical trend in favor of RDV that did not reach conventional levels of statistical significance.

Day 28 all-cause mortality rates were similar in the two treatment groups. Mortality rates were 22/158 (13.9%) for the RDV group versus 10/78 (12.8%) for the PBO group, with a difference in mortality rates of 1.1% and a 95% confidence interval for the difference from -8.1% to 10.3%.

The table below displays results for the ordinal scale at Day 28. The odds ratio estimated from a proportional odds model (on a scale with values greater than 1.00 favoring RDV) was 1.15, with a 95% confidence interval from 0.67 to 1.96.

Table 47. C0-US-540-5758 Results for the 6-point ordinal scale at Day 28

Ordinal scale categories	RDV (n = 158) n (%)	PBO (n = 78) n (%)
1 = Discharge (alive)	92 (58.2%)	45 (57.7%)
2 = Hospitalization, not requiring supplemental oxygen	14 (8.9%)	4 (5.1%)

3 = Hospitalization requiring supplemental oxygen	18 (11.4%)	13 (16.7%)
4 = Hospitalization requiring HFNC and/or non-IMV	2 (1.3%)	2 (2.6)
5 = Hospitalization requiring ECMO and/or IMV	2 (1.3%)	3 (3.8%)
6 = Death	22 (13.9%)	10 (12.8%)
Missing	8 (5.1%)	1 (1.3%)

Source: Wang et al. (2020), Table 3.

Rates of viral clearance appeared similar between RDV and PBO, and viral load decreased similarly in both groups through Day 28.

Adverse events (AEs) occurred in 66% of the RDV group and 64% of the PBO group. Rates of study drug discontinuation due to AEs or SAEs occurred in 12% of the RDV group and 5% of the PBO group.

Overall, this investigator-sponsored trial was much smaller than ACTT-1. Consequently, there was a higher degree of uncertainty in estimating treatment effects. Nevertheless, favorable numerical trends for RDV in this trial were consistent with results from ACTT-1.

13.4. Expanded Access (EA)

The Applicant submitted data on 163 adult patients who received at least 1 dose of RDV for treatment of COVID-19 under expanded access (EA) between January 26, 2020 and March 14, 2020. The Applicant also submitted data on 39 pediatric patients ≥ 12 years of age and ≥ 40 kg who received at least 1 dose of RDV for treatment of COVID-19 under EA between March 21, 2020 and April 22, 2020. The available clinical data from these patients are limited. Due to these limitations, assessments of safety and efficacy should be based on the randomized controlled trials discussed in this review rather than the EA program.

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/s/

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