SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.1—SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

REMDESIVIR
(GS-5734™)

Gilead Sciences

[redacted] **2020**

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

%CV	percentage coefficient of variation
%RE	percentage relative error
ADME	absorption, distribution, metabolism, and excretion
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
C_{max}	maximum observed concentration of drug
CSR	clinical study report
EC_{50}	half-maximal effective concentration
FA	formic acid
FIH	first in human
GLSM	geometric least-squares mean
IV	intravenous
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LTSS	long-term storage stability
MAD	multiple ascending dose
PBMC	peripheral blood mononuclear cell
PK	pharmacokinetic(s)
RDV	Remdesivir (GS-5734™)
SARS	severe acute respiratory syndrome
SBECD	sulfobutylether β-cyclodextrin sodium
Tween 80	polysorbate 80
w/v	weight-to-volume ratio
WHO	World Health Organization

1. BACKGROUND AND OVERVIEW

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei province, China {Huang 2020}. Sequencing analyses from respiratory tract samples of patients identified a novel coronavirus (CoV), which was named severe acute respiratory syndrome (SARS)-CoV-2 {Zhou 2020}. Cases of the novel infectious disease caused by the SARS-CoV-2 virus, coronavirus disease 2019 (COVID-19), rapidly increased throughout the world. The situation is a major global health emergency, as evident by the International Health Regulations Emergency Committee of the World Health Organization declaration on 30 January 2020 that the SARS-CoV-2 outbreak constitutes a public health emergency of international concern {World Health Organization (WHO) 2020b}. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic {World Health Organization (WHO) 2020c}. As of 08 April 2020, more than 1,353,000 confirmed cases and 79,000 associated deaths were reported worldwide, including more than 720,000 cases and 57,000 deaths in the European Region {World Health Organization (WHO) 2020a}. There are currently no approved therapeutic agents available for the treatment of COVID-19, and the availability of an effective antiviral agent with a favorable benefit-risk profile would address a serious unmet medical need for the treatment of patients with COVID-19.

Remdesivir (RDV, GS-5734™) is a novel antiviral drug that has been evaluated for the treatment of COVID-19. Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad-spectrum activity against members of the CoVs (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (eg, Ebola virus, Marburg virus), and paramyxoviruses (eg, respiratory syncytial virus, Nipah virus, Hendra virus).

Remdesivir has demonstrated safety and efficacy for the treatment of COVID-19 through clinical evaluation at the proposed dosing regimen, as described in this dossier.

In addition, RDV exhibits potent in vitro and in vivo antiviral activity against SARS-CoV-2. Remdesivir showed potent in vitro activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells (half-maximal effective concentration [EC_{50}] = 0.0099 μM) and also potently inhibited a recombinant chimeric virus expressing the polymerase (nsp12) gene of SARS-CoV-2 in a backbone of SARS-CoV in Huh7 cells (EC_{50} = 0.0035 μM). In SARS-CoV-2-infected rhesus monkeys, administration of RDV (10 mg/kg for the first dose, followed by 5 mg/kg once daily thereafter) using intravenous (IV) bolus injection initiated 12 hours postinoculation of SARS-CoV-2 resulted in a significant reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals. Remdesivir may provide an effective treatment for patients with COVID-19.

This Summary of Biopharmaceutical Studies and Associated Analytical Methods is being submitted in support of the marketing application for RDV IV injection for the treatment of COVID-19.

This document provides a summary of the associated analytical methods that support Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505. Bioanalytical and method validation reports and long-term storage stability (LTSS) data are provided in Section 5.

1.1. Formulation Development

There are 2 designated commercial drug products of RDV: RDV injection, 5 mg/mL, and RDV for injection, 100 mg.

Remdesivir injection, 5 mg/mL, is a sterile, preservative-free, clear, colorless to yellow solution for dilution into IV infusion fluids. Each unit of RDV injection, 5 mg/mL, is supplied in a single-use, Type I clear glass vial sealed with an elastomeric closure and an aluminum overseal with a flip-off cap. Each vial contains sufficient volume to allow withdrawal of 20 mL sterile solution containing 100 mg of RDV.

Remdesivir for injection, is a preservative-free, white to off-white to yellow solid available as 100-mg strength. Remdesivir for injection, 100 mg, contains 100 mg RDV that is to be reconstituted with 19 mL of sterile water for injection and diluted into IV infusion fluids prior to IV administration. Following reconstitution, each vial contains a 5 mg/mL RDV solution with sufficient volume to allow withdrawal of 20 mL (100 mg RDV). It is supplied as a sterile product in a single use, Type I clear glass vial sealed with an elastomeric closure and an aluminum overseal with a flip-off cap.

In addition to the active ingredient, the solution and lyophilized formulations contain the following inactive ingredients: water for injection, sulfobutylether β-cyclodextrin sodium (SBECD), and hydrochloric acid and/or sodium hydroxide. Hydrochloric acid and/or sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0.

Remdesivir injection, 5 mg/mL, solution formulation was initially developed to support Phase 1 clinical studies. Due to [redacted], the solution formulation contained 30% w/v SBECD as [redacted], and the pH was adjusted to 3.5 ± 0.5 to provide [redacted]. Sterilization was performed [redacted] and approximately 30 mL was filled into Type I clear glass vials to provide 150 mg RDV per vial for clinical studies. For the commercial product, vials are filled with approximately 20 mL solution to provide 100 mg RDV per vial. The quantitative compositions of the clinical and commercial formulations are identical. The recommended storage condition for RDV injection is “Store at 2−8 °C”. Refrigerated storage is recommended to [redacted].

The RDV for injection lyophilized formulation was subsequently developed during Phase 1 and Phase 2 clinical trials to [redacted]. In this formulation approach, the bulk solution contains a reduced amount of the solubilizer SBECD compared to the RDV injection, 5 mg/mL, solution formulation. The bulk solution is adjusted to a pH of 3.5 ± 0.5 [redacted] sterilization [redacted] and removal of water by lyophilization. For clinical trials, the lyophilized formulation was supplied as vials containing 150 mg RDV; the powder was reconstituted by addition of 29 mL sterile water for injection to yield approximately 30 mL of 5 mg/mL RDV solution. The commercial product is a lyophilized powder supplied as vials containing 100 mg RDV; the powder is reconstituted by addition of 19 mL sterile water for injection to yield approximately 20 mL of 5 mg/mL RDV solution. The quantitative compositions of the clinical and commercial formulations are identical.

After completion of the Phase 1 single-ascending dose study GS-US-399-1812 with the RDV injection, 5 mg/mL, solution formulation, the study was extended to evaluate the RDV for injection lyophilized formulation at doses of 75 mg and 150 mg. Following administration of the lyophilized formulation at these doses, exposures were similar to those observed for equivalent doses of the 5 mg/mL solution formulation.

Detailed information on the formulation development of RDV, including the qualitative and quantitative composition, is provided in Section 3.2.P.2.2 of Module 3.

Table 1. Formulation Summary for Studies with RDV

Product	Formulation	Study	Summary of Results Location
RDV for Injection	Solution (150 mg)	GS-US-399-1812 Phase 1, FIH	m2.7.2, Section 2.2.1
		GS-US-399-1954 Phase 1, MAD	m2.7.2, Section 2.2.2
	Lyophilized Powder (150 mg)	GS-US-399-1812 Phase 1, FIH	m2.7.2, Section 2.2.1
		GS-US-399-5505 Phase 1, MAD	m2.7.2, Section 2.2.4
		GS-US-399-4231 Phase 1, ADME	m2.7.2, Section 2.2.3

ADME = absorption, distribution, metabolism, and excretion; FIH = first in human; MAD = multiple-ascending dose; RDV = remdesivir (GS-5734™)

1.2. Bioanalytical Methods

This section describes the bioanalytical methods for quantitation of RDV and RDV metabolites (GS-704277, GS-441524, and GS 443902) in human plasma, urine, semen, and peripheral blood mononuclear cells (PBMCs) as well as the corresponding validation data. The most current validation reports and sample analysis reports are listed and are cumulative of all previous versions. Validation reports and sample analysis reports cited in the corresponding clinical study reports (CSRs) were those in effect at the time of final approval of the CSR.

1.2.1. Determination of Remdesivir and its Metabolites in Human Plasma, Blood, and Urine

1.2.1.1. Determination of RDV and GS-441524 in Human Plasma

The bioanalytical method was validated for determination of RDV and its human metabolite, GS-441524, in human plasma. This method involved protein precipitation extraction of RDV and GS-441524, and internal standards (GS-465124 and GS-441285, respectively) from formic acid-treated human plasma followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). All samples were analyzed within the time frame supported by LTSS data. The assays for RDV and GS-441524 were all performed and validated by [redacted] ([redacted], USA). Bioanalytical method validation parameters are summarized in Table 2.

Table 2. Bioanalytical Method Validation Parameters for Determination of RDV and GS-441524 in Human Plasma

Parameter	RDV	GS-441524
Calibrated range (ng/mL)	4 to 4000	2 to 2000
Interday precision range (%CV)	2.2 to 5.4	1.8 to 4.2
Interday accuracy range (%RE)	−10.0 to −4.5	−7.5 to 2.0
Long-term storage stability frozen matrix (days)	85 at −70°C	85 at −70°C
Studies supported	GS-US-399-1812	

%CV = percentage coefficient of variation; RDV = remdesivir (GS-5734™); %RE = percentage relative error
Source: [redacted]60-1560 Amendment 1

1.2.1.2. Determination of RDV, GS-704277, and GS-441524 in Human Plasma

The bioanalytical method was validated for determination of RDV and its 2 major human metabolites, GS-704277 and GS-441524, in human plasma. This method involved protein precipitation extraction of RDV, GS-704277, and GS-441524 and internal standards ([$^{13}C_3$]-RDV [GS-829143], [$^{13}C_3$]-GS-704277 [GS-829466], and [$^{13}C_3$]-GS-441524 [GS-828840], respectively) from human plasma followed by LC-MS/MS. All samples were analyzed within the time frame supported by LTSS data. The assays for RDV, GS-704277, and GS-441524 were all performed and validated by [redacted] ([redacted], USA). Bioanalytical method validation parameters are summarized in Table 3.

Table 3. Bioanalytical Method Validation Parameters for Determination of RDV, GS-704277, and GS-441524 in Human Plasma

Parameter	RDV	GS-704277	GS-441524
Calibrated range (ng/mL)	4 to 4000	2 to 2000	2 to 2000
Interday precision range (%CV)	2.3 to 3.8	2.1 to 3.8	3.5 to 5.3
Interday accuracy range (%RE)	0.0 to 9.5	−9.8 to −3.5	−0.6 to 8.0
Long-term storage stability frozen matrix (days)	3 at −20°C 392 at−70°C	257 at −70°C	3 at −20°C 392 at −70°C
Studies supported	GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505		

%CV = percentage coefficient of variation; RDV = remdesivir (GS-5734™); %RE = percentage relative error
Source: [redacted]60 15117 Amendment 6

1.2.1.3. Determination of RDV and GS-441524 in Human Urine

The bioanalytical method was validated for determination of RDV and its major metabolite, GS-441524, in human urine. This method involved protein precipitation extraction of RDV and GS-441524, and internal standards (GS-465124 and GS-441285, respectively) from human urine followed by LC-MS/MS. All samples were analyzed within the time frame supported by LTSS data. The assays for RDV and GS-441524 were all performed and validated by [redacted] ([redacted], USA). Bioanalytical method validation parameters are summarized in Table 4.

Table 4 Bioanalytical Method Validation Parameters for Determination of RDV and GS-441524 in Human Urine

Parameter	RDV	GS-441524
Calibrated range (ng/mL)	10 to 5000	10 to 5000
Interday precision range (%CV)	2.1 to 4.4	1.7 to 3.1
Interday accuracy range (%RE)	−6.8 to 1.0	−3.3 to 1.0
Long-term storage stability frozen matrix (days)	103 at −70°C	43 at −20°C 103 at −70°C
Studies supported	GS-US-399-1812, GS-US-399-1954	

%CV = percentage coefficient of variation; RDV = remdesivir (GS-5734™); %RE = percentage relative error
Source: [redacted]60-1539 Amendment 1

1.2.1.4. Determination of RDV, GS-704277, and GS-441524 in Tween 80 (polysorbate 80) and Ammonium Formate Buffer-Treated Human Urine

The bioanalytical method was validated for determination of RDV, GS-704277, and GS-441524 in Tween 80 and ammonium formate buffer-treated human urine. This method involved protein precipitation extraction of RDV, GS-704277, and GS-441524 and internal standards ([$^{13}C_3$]-RDV [GS-829143], [$^{13}C_3$]-GS-704277 [GS-829466], and [$^{13}C_3$]-GS-441524 [GS-828840], respectively) from human urine followed by LC-MS/MS. All samples were analyzed within the time frame supported by LTSS data. The assays for RDV, GS-704277, and GS-441524 were all performed and validated by [redacted] ([redacted], USA). Bioanalytical method validation parameters are summarized in Table 5.

Table 5 Bioanalytical Method Validation Parameters for Determination of RDV, GS-704277, and GS-441524 in Human Urine

Parameter	RDV	GS-704277	GS-441524
Calibrated range (ng/mL)	10 to 5000	10 to 5000	10 to 5000
Interday precision range (%CV)	1.1 to 2.3	5.6 to 7.3	2.2 to 4.6
Interday accuracy range (%RE)	−1.5 to 2.8	0.0 to 4.7	3.0 to 6.2
Long-term storage stability frozen matrix (days)	30 at −20°C 62 at −70°C	16 at −20°C 62 at −70°C	62 at −20°C 133 at −70°C
Studies supported	GS-US-399-1812, GS-US-399-4231		

%CV = percentage coefficient of variation; RDV = remdesivir (GS-5734™); %RE = percentage relative error
Source: [redacted]60-15118 Amendment 2

1.2.1.5. Determination of RDV, GS 704277, and GS 441524 in Human Semen

The bioanalytical method was validated for determination of RDV and its 2 major human metabolites, GS-704277 and GS-441524, in human semen. This method involved protein precipitation extraction of RDV, GS-704277, and GS-441524 and internal standards ([$^{13}C_3$]-RDV [GS-829143], [$^{13}C_3$]-GS-704277 [GS-829466], and [$^{13}C_3$]-GS-441524 [GS-828840], respectively) from human semen followed by LC-MS/MS. All samples were analyzed within the time frame supported by LTSS data. The assays for RDV, GS-704277, and GS-441524 were all performed and validated by [redacted] ([redacted], USA). Bioanalytical method validation parameters are summarized in Table 6.

Table 6 Bioanalytical Method Validation Parameters for Determination of RDV, GS-704277, and GS-441524 in Human Semen

Parameter	RDV	GS-704277	GS-441524
Calibrated range (ng/mL)	2 to 200	2 to 200	2 to 200
Interday precision range (%CV)	2.7 to 5.2	4.0 to 7.0	3.8 to 6.5
Interday accuracy range (%RE)	−0.5 to 10.6	−2.8 to 6.3	−0.9 to 5.0
Long-term storage stability frozen matrix (days)	268 at −20°C 268 at -70°C	91 at −70°C	364 at −20°C 364 at −70°C
Studies supported	GS-US-399-1812, GS-US-399-1954		

%CV = percentage coefficient of variation; RDV = remdesivir (GS-5734™); %RE = percentage relative error
Source: [redacted]60-15119 Amendment 2

1.2.1.6. Determination of GS 441524 in Human Peripheral Blood Mononuclear Cells

Total concentrations of GS-441524, defined as the sum of the endogenous concentration of GS-441524 plus concentrations of GS-441524 resulting from enzymatic dephosphorylation of its phosphorylated conjugates, in human PBMCs were determined using a validated method at [redacted] ([redacted], USA). This method involved addition of internal standard (GS-441285) to a PBMC sample, cell lysis, extraction of soluble components, enzymatic dephosphorylation of any mono-, di-, and triphosphate (GS-443902) conjugates of GS-441524 that were present, and determination of total GS-441524 in the extracted, dephosphorylated sample by LC-MS/MS. The method was validated as fit-for-purpose for determination of total GS-441524. All samples were analyzed within the time frame supported by LTSS data. Bioanalytical method validation parameters are summarized in Table 7.

Table 7 Bioanalytical Method Validation Parameters for Determination of GS-441524 in PBMCs

Parameter	GS-441524
Calibrated range (nmol/L)	4 to 2000
Interassay precision range (%CV)	2.4 to 7.2
Interassay accuracy range (%RE)	−0.6 to 5.8
Long-term storage stability in frozen matrix with PBMC pellet (days)	127 at −70°C
Long-term storage stability in incurred PBMC (days)	32 at −70ºC
Studies supported	GS-US-399-1812, GS-US-399-1954

%CV = percentage coefficient of variation; PBMC = peripheral blood mononuclear cell; %RE = percentage relative error
Source: [redacted]60N-1576 Amendment 1

1.2.1.7. Determination of GS 443902 in Human Peripheral Blood Mononuclear Cells

Concentrations of GS-443902 in human PBMCs were determined using a validated LC-MS/MS method. This method involved cell lysis extraction of GS-443902 and its internal standard ([$^{13}C_3$]-GS-443902 [GS-829492]) from human PBMC lysate. The assays for GS-443902 were performed and validated by [redacted]. ([redacted], USA). All samples were analyzed within the time frame supported by LTSS data. Bioanalytical method validation parameters are summarized in Table 8.

Table 8 Bioanalytical Method Validation Parameters for Determination of GS-443902 in PBMCs

Parameter	GS-443902
Calibrated range (ng/mL)	5 to 2500
Interassay precision range (%CV)	1.8 to 4.5
Interassay accuracy range (%RE)	−10.0 to −0.9
Long-term storage stability in incurred PBMCs (days)	59 at −70°C (thawed at ambient temperature) 87 at −70°C (thawed on dry ice)
Studies supported	GS-US-399-1812, GS-US-399-5505

%CV = percentage coefficient of variation; PBMC = peripheral blood mononuclear cell; %RE = percentage relative error
Source: [redacted]60-1623 Amendment 4

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Summaries of clinical pharmacology studies of RDV included in this marketing application are presented in m2.7.2.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Bioavailability of Remdesivir

The pharmacokinetics (PK) of the lyophilized formulation and the solution formulation of RDV were evaluated in healthy volunteers in Study GS-US-399-1812. Single-dose PK of the lyophilized formulation of RDV 75 mg and 150 mg IV infused over 2 hours was evaluated in Cohorts 7 and 8, respectively. The same doses or infusion duration of the solution formulation have been previously evaluated in Cohorts 4 and 5, respectively, thereby enabling direct comparison of the PK of RDV, an intermediate metabolite GS-704277, and the predominant circulating metabolite GS-441524 between the 2 formulations.

Although not powered or designed for formal equivalence testing, a comparison of the solution and lyophilized formulations exhibited similar exposures of RDV, GS-441524, and GS-704277 at the same dose, supporting the use of both formulations in patients with COVID-19 (Table 9 and Table 10).

Table 9 Statistical Comparison of Plasma Pharmacokinetic Parameters Between Lyophilized and Solution Formulations at 75 mg Dose Infused Over 2 hours

Mean (%CV)[a]	Lyophilized Formulation (Test) 75 mg N = 10	Solution Formulation (Reference) 75 mg N = 8	% GLSM Ratio (90%CI) Test/Reference
RDV			
AUC_{inf} (h*ng/mL)	1839.9 (17.1)	1999.6 (27.1)	93.59 (77.71, 112.70)
AUC_{last} (h*ng/mL)	1832.5 (17.1)	1989.9 (27.3)	93.69 (77.73, 112.91)
C_{max} (ng/mL)	1722.0 (28.4)	1626.0 (38.6)	112.12 (77.10, 163.03)
GS-441524			
AUC_{inf} (h*ng/mL)	2200.1 (18.4)	2471.8 (22.7)	89.93 (74.57, 108.22)
AUC_{last} (h*ng/mL)	2091.1 (19.0)	2374.0 (23.2)	88.87 (73.47, 107.50)
C_{max} (ng/mL)	77.5 (21.0)	85.8 (23.9)	90.88 (74.92, 110.25)
GS-704277			
AUC_{inf} (h*ng/mL)	294.5 (27.9)	270.0 (49.0)	116.95 (81.95, 166.92)
AUC_{last} (h*ng/mL)	286.8 (28.3)	262.5 (49.9)	117.85 (81.54, 170.33)
C_{max} (ng/mL)	113.5 (25.7)	100.8 (57.9)	127.07 (83.78, 192.72)

CI = confidence interval; %CV = percentage coefficient of variation; RDV = remdesivir (GS-5734™); GLSM = geometric least-squares mean
a Unadjusted mean is presented
Source: GS-US-399-1812 CSR, Tables 18, 21, 24, and 25; Ad hoc req10562, Table 4

Table 10 Statistical Comparison of Plasma Pharmacokinetic Parameters Between Lyophilized and Solution Formulations at 150 mg Dose Infused Over 2 hours

Mean (%CV)[a]	Lyophilized Formulation (Test) 150-mg N = 10	Solution Formulation (Reference) 150 mg N = 8	% GLSM Ratio (90%CI) Test/Reference
RDV			
AUC_{inf} (h*ng/mL)	3261.1 (22.2)[b]	2976.1 (19.0)	108.83 (91.98, 128.76)
AUC_{last} (h*ng/mL)	3265.4 (21.3)	2965.4 (19.1)	109.46 (93.16, 128.60)
C_{max} (ng/mL)	2722.0 (35.0)	2280.0 (30.1)	117.85 (88.97, 156.09)
GS-441524			
AUC_{inf} (h*ng/mL)	4330.6 (22.2)[b]	4642.5 (16.2)	92.24 (78.62, 108.22)
AUC_{last} (h*ng/mL)	4194.6 (22.2)	4517.4 (16.4)	91.85 (78.19, 107.90)
C_{max} (ng/mL)	148.1 (26.5)	152.0 (23.6)	96.71 (77.97, 119.95)
GS-704277			
AUC_{inf} (h*ng/mL)	618.7 (24.6)	459.8 (19.7)	132.85 (109.68, 160.92)
AUC_{last} (h*ng/mL)	610.6 (24.9)	453.2 (20.0)	132.96 (109.57, 161.36)
C_{max} (ng/mL)	233.6 (28.8)	171.3 (22.3)	133.24 (105.72, 167.93)

CI = confidence interval; %CV = percentage coefficient of variation; RDV = remdesivir (GS-5734™); GLSM = geometric least-squares mean
a Unadjusted mean is presented
b n = 9 for this parameter
Source: GS-US-399-1812 CSR, Tables 18, 21, 24, and 25; Ad hoc req10562, Table 4

3.2. Effect of Food

Remdesivir is being developed for IV administration. The effect of food was not evaluated.

3.3. Discussion and Conclusions

Although the study was not powered or designed for formal equivalence testing of the lyophilized and solution formulations, the results of the statistical analysis comparing 75 mg and 150 mg doses of RDV infused over 2 hours show that RDV, GS-704277, and GS-441524 plasma exposures were similar with each formulation, supporting the use of both formulations in patients with COVID-19.

4. REFERENCES

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Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. Nature 2020;579:270-3.

5. APPENDICES

5.1. List of Appendices

Appendix Number	Appendix Title
5.2	Tabular Summary of Biopharmaceutic Studies
5.3	Biopharmaceutic Ad Hoc Analyses
5.4	Tabular Summary of Bioanalytical Methods for Individual Studies
5.5	Long-Term Storage Stability of RDV, GS-704277, and GS-441524

5.2. Tabular Summary of Biopharmaceutic Studies

Tabular summaries of biopharmaceutic studies included in this marketing application are provided in m2.7.2.

5.3. Biopharmaceutic Ad Hoc Analyses

Additional outputs with numbering beginning with "Ad Req" present data from analyses that were not prespecified in a Statistical Analysis Plan.

Ad Req 10562, Table 4: Statistical Comparisons of Plasma Pharmacokinetic Parameter Estimates Between Lyophilized and Solution Formulations, PK Analysis Set

5.4. Tabular Summary of Bioanalytical Methods for Individual Studies

A tabular summary of bioanalytical methods, method validation reports, and sample analysis reports for individual studies is provided below for studies conducted to support the RDV clinical development program. The most current versions of the validation reports and sample analysis reports are listed and are cumulative of all previous versions. Validation reports and sample analysis reports cited in the corresponding CSRs were those in effect at the time of sample analysis.

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range (ng/mL)	Sample Analysis Report
GS-US-399-5505	Human Plasma	RDV	[redacted] 60-15117 Amendment 6	LC-MS/MS	4 to 4000	[redacted] 60-1955A
		GS-704277			2 to 2000	
		GS-441524			2 to 2000	
	Human PBMC	GS-443902	[redacted] 60-1623 Amendment 4	LC-MS/MS	5 to 2500	[redacted] 60-1955B/C
GS-US-399-4231	Human Plasma	RDV	[redacted] 60-15117 Amendment 6	LC-MS/MS	4 to 4000	[redacted] 60-1850A
		GS-704277			2 to 2000	
		GS-441524			2 to 2000	
	Human Urine	RDV	[redacted] 60-15118 Amendment 2	LC-MS/MS	10 to 5000	[redacted] 60-1850B
		GS-704277			10 to 5000	
		GS-441524			10 to 5000	
GS-US-399-1954	Human Plasma	RDV	[redacted] 60-15117 Amendment 6	LC-MS/MS	4 to 4000	[redacted] 60-15124A
		GS-704277			2 to 2000	
		GS-441524			2 to 2000	
	Human Urine	RDV	[redacted] 60-1539 Amendment 1	LC-MS/MS	10 to 5000	[redacted] 60-15124C
		GS-441524			10 to 5000	
	Human Semen	RDV	[redacted] 60-15119 Amendment 2	LC-MS/MS	2 to 200	[redacted] 60-15124D
		GS-704277			2 to 200	
		GS-441524			2 to 200	
	Human PBMCs	GS-441524	[redacted] 60N-1576 Amendment 1	LC-MS/MS	4 to 2000[b]	[redacted] 60N-15124E

Study No.	Matrix	Analytes	Current Validation Report[a]	Bioanalytical Technique	Calibrated Range (ng/mL)	Sample Analysis Report
GS-US-399-1812	Human Plasma	RDV	[redacted] 60-1560 Amendment 1	LC-MS/MS	4 to 4000	[redacted] 60-1566A
		GS-441524			2 to 2000	
	Human Urine	RDV	[redacted] 60-1539 Amendment 1	LC-MS/MS	10 to 5000	[redacted] 60-1566B
		GS-441524			10 to 5000	
	Human PBMC	GS-441524	[redacted] 60N-1576 Amendment 1	LC-MS/MS	4 to 2000[b]	[redacted] 60N-1566C
	Human Plasma	RDV	[redacted] 60-15117 Amendment 6	LC-MS/MS	4 to 4000	[redacted] 60-1566E Amendment 1
		GS-704277			2 to 2000	
		GS-441524			2 to 2000	
	Human Urine	RDV	[redacted] 60-15118 Amendment 2	LC-MS/MS	10 to 5000	[redacted] 60-1566F
		GS-704277			10 to 5000	
		GS-441524			10 to 5000	
	Human PBMC	GS-443902	[redacted] 60-1623 Amendment 4	LC-MS/MS	5 to 2500	[redacted] 60-1566G Amendment 1
	Human Semen	RDV	[redacted] 60-15119 Amendment 2	LC-MS/MS	2 to 200	[redacted] 60-1566H
		GS-704277			2 to 200	
		GS-441524			2 to200	

a The most current versions of the validation reports and sample analysis reports are listed and are cumulative of all previous versions. Validation reports and sample analysis reports cited in the corresponding CSRs were those in effect at the time of sample analysis.
b nmol/L

5.5. Long-Term Storage Stability of RDV, GS-704277, and GS-441524

This table summarizes LTSS data for the proposed commercial product and its metabolites.

Analyte	Matrix	Current LTSS Data (days)	Current Validation Report
RDV	FA-treated Human Plasma	3 at −20°C 392 at −70°C	[redacted] 60-15117 Amendment 6
GS-704277	FA-treated Human Plasma	257 at −70°C	[redacted] 60-15117 Amendment 6
GS-441524	FA-treated Human Plasma	3 at −20°C 392 at −70°C	[redacted] 60-15117 Amendment 6
RDV	FA-treated Human Urine	30 at −20°C 62 at −70°C	[redacted] 60-15118 Amendment 2
GS-704277	FA-treated Human Urine	16 at −20°C 62 at −70°C	[redacted] 60-15118 Amendment 2
GS-441524	FA-treated Human Urine	62 at −20°C 133 at−70°C	[redacted] 60-15118 Amendment 2
RDV	FA-treated Human Semen	268 at −20°C 268 at −70°C	[redacted] 60-15119 Amendment 2
GS-704277	FA-treated Human Semen	91 at −70°C	[redacted] 60-15119 Amendment 2
GS-441524	FA-treated Human Semen	364 at −20°C 364 at−70°C	[redacted] 60-15119 Amendment 2
GS-441524	Human PBMC	127 at −70°C with PBMC pellet 32 at −70ºC in incurred PBMC	[redacted] 60N-1576 Amendment 1
GS-443902	Human PBMC	59 at −70°C in incurred PBMC (thawed at ambient temperature) 87 at −70°C in incurred PBMC (thawed on dry ice)	[redacted] 60-1623 Amendment 4

FA = formic acid; LTSS = long-term storage stability; PBMC = peripheral blood mononuclear cells; RDV = remdesivir (GS-5734™)

5.5.1. Tabular Summary of Long-Term Storage Stability Data for Individual Studies

A tabular summary of LTSS data, study sample collection dates, study sample analysis dates, and transpired time (calculated time between the date of the first sample collection and the date of the last sample analysis) for individual studies is provided below for studies conducted to support the RDV clinical development program. The most current versions of the validation reports and sample analysis reports are listed and are cumulative of all previous versions.

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a] (days)	Supporting LTSS Data (days)	Current Validation/LTSS Report[b]	Sample Analysis Report
GS-US-399-5505	FA-treated Human Plasma	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	119 at −70°C	3 at −20°C 392 at −70°C	[redacted] 60-15117 Amendment 6	[redacted] 60-1955A
		GS-704277				257 at −70°C		
		GS-441524				3 at -20°C 392 at −70°C		
	Human PBMC	GS-443902	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	166 at −70°C[c]	87 at −70°C	[redacted] 60-1623 Amendment 4	[redacted] 60-1955B/C
GS-US-399-4231	FA-treated Human Plasma	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	46 at −70°C	3 at −20°C 392 at −70°C	[redacted] 60-15117 Amendment 6	[redacted] 60-1850A
		GS-704277				257 at −70°C		
		GS-441524				3 at −20°C 392 at −70°C		
	FA-treated Human Urine	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	62 at −70°C	30 at −20°C 62 at −70°C	[redacted] 60-15118 Amendment 2	[redacted] 60-1850B
		GS-704277				16 at −20°C 62 at −70°C		
		GS-441524				62 at −20°C 133 at −70°C		

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a] (days)	Supporting LTSS Data (days)	Current Validation/LTSS Report[b]	Sample Analysis Report
GS-US-399-1954	FA-treated Human Plasma	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	84 at −70°C	85 at −70°C	[redacted] 60-1560 Amendment 1	[redacted] 60-15124A
						3 at −20°C 392 at −70°C	[redacted] 60-15117 Amendment 6[d]	
		GS-704277				257 at −70°C	[redacted] 60-15117 Amendment 6[d]	
		GS-441524				85 at −70°C	[redacted] 60-1560 Amendment 1	
						3 at -20°C 392 at −70°C	[redacted] 60-15117 Amendment 6[d]	
	FA-treated Human Urine	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	97 at −70°C	103 at −70°C	[redacted] 60-1539 Amendment 1[d]	[redacted] 60-15124C
		GS-441524				43 at −20°C 103 at −70°C		
	FA-treated Human Semen	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	108 at −70°C[e]	268 at −20°C 268 at −70°C	[redacted] 60-15119 Amendment 2	[redacted] 60-15124D
		GS-704277				91 at −70°C		
		GS-441524				364 at −20°C 364 at −70°C		
	Human PBMC	GS-441524	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	76 at −70°C[e]	127 at −70°C	[redacted] 60N-1576 Amendment 1	[redacted] 60N-15124E

Study No.	Matrix	Analyte	Sample Collection Dates	Sample Analysis Dates	Sample Maximum Transpired Time[a] (days)	Supporting LTSS Data (days)	Current Validation/LTSS Report[b]	Sample Analysis Report
GS-US-399-1812	FA-treated Human Plasma	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	88 at −70°C[f]	85 at −70°C	[redacted] 60-1560 Amendment 1	[redacted] 60-1566A
		GS-441524			76 at −70°C	85 at −70°C		
	FA-treated Human Urine	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	148 at -70°C[g]	103 at −70°C	[redacted] 60-1539 Amendment 1	[redacted] 601566B
		GS--441524				43 at -20°C 103 at −70°		
	Human PBMC	GS-441524	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	82 at −70°C	127 at −70°C	[redacted] 60N-1576 Amendment 1	[redacted] 60N-1566C
	FA-treated Human Plasma	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	446 at −70°C[h]	3 at −20°C 392 at −70°C	[redacted] 60-15117 Amendment 6	[redacted] 60-1566E Amendment 2
		GS-704277				257 at -70°C		
		GS-441524				3 at −20°C 392 at −70°C		
	FA-treated Human Urine	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	94 at −70°C[i]	30 at −20°C 62 at −70°C	[redacted] 60-15118 Amendment 2	[redacted] 60-1566F
		GS-704277				16 at −20°C 62 at −70°C		
		GS-441524				62 at −20°C 133 at −70°C		
	Human PBMC	GS-443902	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	86 at −70°C[j]	59 at −70°C	[redacted] 60-1623 Amendment 4	[redacted] 60-1566G Amendment 1
	FA-treated Human Semen	RDV	[redacted] 20 through [redacted] 20	[redacted] 20 through [redacted] 20	92 at −70°C[k]	268 at −20°C 268 at −70°C	[redacted] 60-15119 Amendment 2	[redacted] 60-1566H
		GS-704277				91 at −70°C		
		GS-441524				364 at −20°C 364 at −70°C		

FA = formic acid; LTSS = long term storage stability; PBMC = peripheral blood mononuclear cells; RDV = remdesivir (GS-5734™)

a Sample maximum transpired time is the calculated maximum time between the date of the first sample collection and the date of the last sample analysis.

b The most current versions of the validation reports and sample analysis reports are listed and are cumulative of all previous versions. Validation reports and sample analysis reports cited in the corresponding CSRs were those in effect at the time of sample analysis.

c With the exception of 44 samples, all study samples were analyzed within the established LTSS of 87 days at -70˚C. Further supporting LTSS will be generated and reported in a revision to the validation report ([redacted] 60-1623).
d Samples received in December were analyzed using the initial 2-in-1 method ([redacted] 60-1560) for GS-5734 and GS-441524. This method consisted of 1 extraction that was injected separately for each analyte. Subsequently, the 3-in-1 method was used to analyze the same samples for GS-704277 only. The later samples were analyzed with the newer method, [redacted] 60-15117.
e No more than 103 days transpired between sample collection dates and the corresponding extraction dates.
f No more than 42 days transpired between sample collection dates and the corresponding extraction dates.
g No more than 92 days transpired between sample collection dates and the corresponding extraction dates.
h No more than 235 days transpired between sample collection dates and the corresponding extraction dates.
i No more than 35 days transpired between sample collection dates and the corresponding extraction dates.
j No more than 38 days transpired between sample collection dates and the corresponding extraction dates.
k No more than 81 days transpired between sample collection dates and the corresponding extraction dates

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.2—SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

Remdesivir (GS-5734™)

Gilead Sciences

[redacted] 2020

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ΔΔQTcF	time-matched, baseline-adjusted placebo-corrected QTcF
%CV	percentage coefficient of variation
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
AUC_{0-24}	partial area under the concentration versus time curve from time zero to time 24 hours
BMI	body mass index
C_{24}	observed drug concentration at 24 hours post dose
CC_{50}	half-maximal cytotoxic concentration
C_{last}	last observed quantifiable concentration of the drug
CL_r	renal clearance of unchanged drug in a specific interval ($CL_{r\ (interval)}$) or cumulatively over all collection intervals
C_{max}	maximum observed concentration of drug
CoV	coronavirus
COVID-19	coronavirus disease 2019
C-QT	concentration-QT
CRO	contract research organization
CSR	clinical study report
CYP	cytochrome P450 enzyme
DDI	drug-drug interaction
EBOV	Ebola virus
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
ER	extraction ratio
GLP	Good Laboratory Practice
GLSM	geometric least-squares mean
HAE	human airway epithelial

HEK	human embryonic kidney
hERG	human ether-a-go-go-related gene
Huh7	human hepatoma cell line
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IFN-β	interferon-beta
IV	intravenous
LPV	lopinavir
MERS	Middle East respiratory syndrome
MHV	murine hepatitis virus
OATP	organic anion transporting polypeptide
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PTM	placebo-to-match
Q1, Q3	first quartile, third quartile
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RDV	remdesivir (GS 5734™)
RTV	ritonavir
SARS	severe acute respiratory syndrome
SC	subcutaneous
SD	standard deviation
SAE	serious adverse event
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
TP	triphosphate
WHO	World Health Organization

1. BACKGROUND AND OVERVIEW

1.1. Background

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei province, China {Huang 2020}. Sequencing analyses from respiratory tract samples of patients identified a novel coronavirus (CoV), which was named severe acute respiratory syndrome (SARS)-CoV-2 {Zhou 2020}. Cases of the novel infectious disease caused by the SARS-CoV-2 virus, coronavirus disease 2019 (COVID-19), rapidly increased throughout the world. The situation is a major global health emergency, as evident by the International Health Regulations Emergency Committee of the World Health Organization declaration on 30 January 2020 that the SARS-CoV-2 outbreak constitutes a public health emergency of international concern {World Health Organization (WHO) 2020b}. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic {World Health Organization (WHO) 2020c}. As of 08 April 2020, more than 1,353,000 confirmed cases and 79,000 associated deaths were reported worldwide, including more than 720,000 cases and 57,000 deaths in the European Region {World Health Organization (WHO) 2020a}. There are currently no approved therapeutic agents available for the treatment of COVID-19, and the availability of an effective antiviral agent with a favorable benefit-risk profile would address a serious unmet medical need for the treatment of patients with COVID-19.

Remdesivir (RDV, GS-5734™) is a novel antiviral drug that has been evaluated for the treatment of COVID-19. Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate (ATP) that inhibits viral RNA polymerases and has broad-spectrum activity against members of the CoVs (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (eg, Ebola virus [EBOV], Marburg virus), and paramyxoviruses (eg, respiratory syncytial virus, Nipah virus, Hendra virus).

Remdesivir has demonstrated safety and efficacy for the treatment of COVID-19 through clinical evaluation at the proposed dosing regimen, as described in this dossier.

In addition, RDV exhibits potent in vitro and in vivo antiviral activity against SARS-CoV-2. Remdesivir showed potent in vitro activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells (half-maximal effective concentration [EC_{50}] = 0.0099 μM) and also potently inhibited a recombinant chimeric virus expressing the polymerase (nsp12) gene of SARS-CoV-2 in a backbone of SARS-CoV in human hepatoma cell line (Huh7) cells (EC_{50} = 0.0035 μM). In SARS-CoV-2-infected rhesus monkeys, administration of RDV (10 mg/kg for the first dose, followed by 5 mg/kg once daily thereafter) using intravenous (IV) bolus injection initiated 12 hours postinoculation of SARS-CoV-2 resulted in a significant reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals. Remdesivir may provide an effective treatment for patients with COVID-19.

1.2. Overview

Nonclinical characterization of the disposition of RDV across species revealed that RDV was extensively metabolized by hydrolase activity resulting in the formation of the intermediate metabolite, GS-704277. Subsequent cleavage of the phosphoramidate bond results in the formation of the nucleoside analog monophosphate, which is then phosphorylated to the active triphosphate, GS-443902. Dephosphorylation of the nucleoside analog monophosphate results in the formation of the nucleoside analog, GS-441524, that is not efficiently rephosphorylated.

Following IV administration to healthy volunteers, rapid disappearance of RDV ($t_{1/2}$ approximately 1 hour) is followed by transient exposure to the intermediate metabolite GS-704277 and more persistent exposure to the primary circulating nucleoside metabolite GS-441524. Plasma exposures of RDV and its metabolites are considered to be of interest in clinical pharmacology studies for purposes of pharmacokinetics (PK) analyses and interpretation of results.

Clinical studies contributing to the characterization of the PK of RDV and its metabolites (GS-441524 and GS-704277) in plasma, as well as GS-443902 concentrations in peripheral blood mononuclear cells (PBMCs) are discussed in this summary of clinical pharmacology. These studies are further described in Section 1.3.2.

This document is organized as follows:

- An overview of the clinical pharmacology program is outlined in the remainder of Section 1.
- Summaries of individual clinical studies are provided in Section 2.
- The clinical pharmacology of RDV and its metabolites (GS-441524, GS-704277, and GS-443902) are characterized in Section 3.
  - — Section 3.1 to 3.3 presents the absorption, distribution, metabolism, and elimination (ADME) characteristics of RDV as determined through in vitro or nonclinical and clinical studies.
  - — Section 3.4 presents PK across clinical studies, discussion of the potential drug-drug interactions (DDIs) and PK/pharmacodynamics (PD) relationships for safety
- The nonclinical and clinical virology of RDV is characterized in Section 4.

Pharmacokinetic studies related to biopharmaceutics are referenced in this summary and are discussed in detail in the Summary of Biopharmaceutic Studies (m2.7.1).

1.3. Human Biomaterials Studies

Studies pertinent to the PK of RDV using human biomaterials are discussed in detail and in the context of PK data in other species in the Nonclinical Pharmacokinetics Written Summary (m2.6.4). References to using human biomaterials pertinent to clinical PK are included in this summary as appropriate.

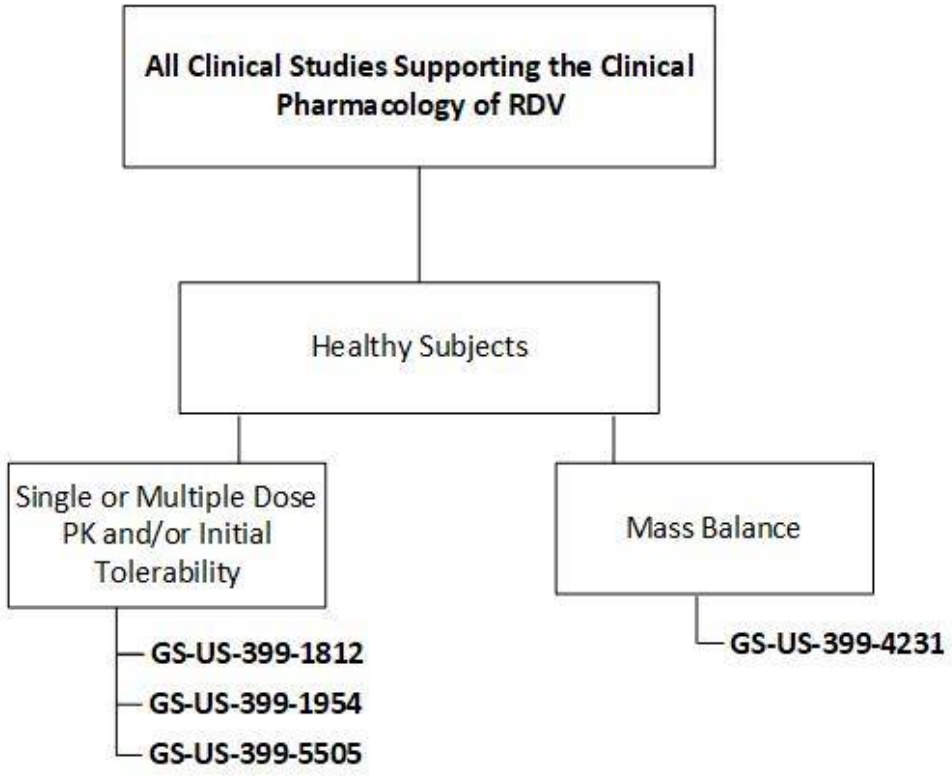
1.3.1. Bioanalytical Methods

The bioanalytical methods used for the determination of plasma or urine concentrations of RDV and its metabolites GS-441524 and GS-704277, and GS-443902 in PBMCs from clinical studies are described in m2.7.1, Section 1.2. An overview of the validated bioanalytical methods used for the determination of plasma or urine concentrations of RDV and its metabolites GS-441524 and GS-704277 in the individual clinical studies is provided in m2.7.1, Appendix 5.3.

1.3.2. Clinical Pharmacology Studies of RDV

Figure 1 and Table 1 summarize the 4 clinical studies that support the characterization of the clinical pharmacology of RDV both with respect to participant population and specific type of clinical pharmacology assessment. Summaries of each of these studies are available in Section 2 and in the tabular summary of clinical pharmacology studies in Appendix 6.1. Information regarding RDV formulations used throughout clinical development is provided in m2.7.1.

Figure 1. Clinical Studies Supporting the Clinical Pharmacology of RDV by Study Type and Study Population



PK = pharmacokinetics; RDV = remdesivir (GS-5734™)

Table 1. Overview of Clinical Studies Contributing to the Characterization of the Clinical Pharmacology of RDV

Study Number/ Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Batch Number)	n[a]	
GS-US-399-1812/ Section 2.2.1	Phase 1 placebo-controlled study to evaluate the safety, tolerability, and PK of single-ascending dose of IV RDV in healthy adult volunteers	RDV solution formulation was a concentrated solution containing 5 mg/mL and was diluted into IV infusion fluid prior to IV infusion. Doses tested were 3, 10, 30, 75, 150, and 225 mg Batch Number: [redacted] RDV lyophilized formulation was supplied as a lyophilized solid containing 150 mg RDV and reconstituted with sterile water for injection and diluted into IV infusion fluid prior to IV infusion Doses tested were 75 and 150 mg Batch Number: [redacted]	96	Placebo-to-match solution formulation Placebo-to match lyophilized formulation
GS-US-399-1954/ Section 2.2.2	Phase 1 placebo-controlled study to evaluate the safety, tolerability, and PK of multiple dose of IV RDV in healthy adult volunteers	RDV solution formulation was a concentrated solution containing 5 mg/mL and was diluted into IV infusion fluid prior to IV infusion. Dose tested was 150 mg Batch Number: [redacted]	24	Placebo-to-match solution formulation
GS-US-399-4231/ Section 2.2.3	Phase 1 mass balance study to evaluate the PK, metabolism, and excretion of a single IV dose of radiolabeled [^{14}C]-RDV in healthy male volunteers	A single dose of RDV 150 mg containing a mixture of both unlabeled and radiolabeled [^{14}C]-RDV (specific activity ≥83 µCi/mg, ≥ 97% radioactivity purity) administered IV over a 0.5-hour period on Day 1. A single dose contained approximately 100 µCi [^{14}C]-RDV (equivalent to 1.2 mg [^{14}C]-RDV) and 148.8 mg of non-radiolabeled RDV as a 30 mL solution diluted with IV fluids (normal saline) prior to infusion. Batch Numbers: [redacted] and [redacted], and [redacted]	8	Not applicable

Study Number/ Location	Study Description	Test Treatment(s)		Reference Treatment(s) Dose and Formulation
		Dose and Formulation (Batch Number)	n[a]	
GS-US-399-5505/ Section 2.2.4	Phase 1 placebo-controlled study to evaluate the safety, tolerability, and PK of multiple doses of IV RDV in healthy adult volunteers	RDV lyophilized formulation was supplied as a lyophilized solid containing 150 mg RDV and reconstituted with sterile water for injection and diluted into IV infusion fluid prior to IV infusion Each cohort received 200 mg RDV loading dose on Day 1 followed by 100 mg RDV daily Batch Number: [redacted]	29	Placebo-to match lyophilized formulation

IV = intravenous; n = number of participants in a population; PK = pharmacokinetics; RDV = remdesivir (GS-5734™)
a Number of participants who were administered any test treatment

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Studies pertinent to the PK of RDV using human biomaterials are discussed in detail and in the context of PK data in other species in the Nonclinical Pharmacokinetics Written Summary (m2.6.4). References to use of human biomaterials pertinent to clinical PK are also included in this summary as appropriate (Section 3).

2.2. Studies in Healthy Volunteers

2.2.1. Study GS-US-399-1812

Study GS-US-399-1812	
Location:	GS-US-399-1812
Title:	A Phase 1, Blinded, Randomized, Placebo-Controlled, First-in-Human, Single-Ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Intravenous GS-5734 in Healthy Adult Volunteers
Primary Objectives:	• To evaluate the safety and tolerability of single ascending IV doses of GS-5734 (solution formulation or lyophilized formulation) compared with placebo in healthy participants • To evaluate the PK of GS-5734 and its metabolites, GS-704277 and/or GS-441524, following single-ascending IV doses of GS-5734 in healthy participants
Study Design and Participant Population:	This was a randomized, blinded, placebo-controlled, Phase 1 study to evaluate the safety and tolerability of single ascending IV doses of GS-5734 compared with placebo and to evaluate the PK of GS-5734 and its metabolites following single ascending IV doses of GS-5734 in healthy volunteers. Nine dose cohorts were evaluated. Following Screening and Day −1 procedures, eligible participants were confined to the study center beginning Day −1. In Cohorts 1-6, eligible participants were randomized 4:1 within each cohort to receive GS-5734 solution formulation at doses ranging from 3 mg to 225 mg (n = 8) or placebo (n = 2) on Day 1. In Cohorts 7-9, eligible participants were randomized 5:1 within each cohort to receive GS-5734 lyophilized formulation at doses ranging from 75 mg to 150 mg (n = 10) or placebo (n = 2) on Day 1. Participants in Cohorts 1-8 received a single dose of study medication administered IV over a 2-hour period, while participants in Cohort 9 received a single dose of study medication administered IV over a 30-minute period. Dose escalation occurred in sequential order. The sponsor could hold dosing for any cohort or stop study enrollment at any time at its discretion. Dose escalation occurred after reviewing safety data through Day 5 and ongoing safety assessments of the previous cohort, and only in the absence of dose-limiting toxicity and/or meeting any prespecified stopping criterion. Dosing in Cohorts 7 and 8 occurred in parallel and was supported by safety data from Cohorts 1-6. Cohort 9 was not initiated until after review of preliminary PK and safety data from Cohorts 7 and 8. Study drug dosing for all participants within an enrolled cohort was to be suspended if either of the following prespecified stopping criteria were met: • The same Grade 3 or 4 confirmed treatment-emergent study drug-related adverse event (AE) or clinically significant laboratory abnormality as defined by the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities occurred in 2 or more participants

- A confirmed decrease in estimated glomerular filtration rate as calculated by the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 50% from Day −1 considered related to study medication in 2 or more participants

Participants were discharged on Day 7 and returned 13 (± 1) days after the last dose for an in-clinic follow up visit. Plasma, PBMCs, urine, and semen were collected for PK assessments at prespecified times during clinic confinement. Safety assessments were performed throughout the study.

Eligible participants were healthy adult males and nonpregnant, nonlactating females of nonchildbearing potential, aged 18 to 55 years (inclusive), with a body mass index (BMI) of 18 to 30 kg/m^2 (inclusive), normal renal function ($eGFR_{CG}$ ≥ 90 mL/min), and normal 12-lead electrocardiogram (ECG).

Summary of Results and Conclusions:

Pharmacokinetics Results:

Single-Dose Plasma Pharmacokinetics of GS-5734 and Metabolites

GS-5734 and GS-441524 exposures, as measured by AUC_{last}, AUC_{inf}, and C_{max}, increased in an apparent dose-proportional manner across the dose range evaluated (3, 10, 30, 75, 150, and 225 mg of GS-5734 solution formulation). Exposures (AUC) of GS-5734, GS-441524, and GS-704277 in the 150-mg dose group were consistent with those obtained following administration of GS-5734 150 mg on Day 1 in the Phase 1 PK Study GS-US-399-1954 that evaluated multiple IV doses of GS-5734. Results of analysis of variance and power model analyses are in agreement, indicating dose-proportional increases in AUC_{last}, AUC_{inf}, and C_{max} after single-dose administration of GS-5734 across the 3 to 225 mg dose range.

GS-5734 Plasma PK Parameter[a]	Cohort 1 GS-5734 3 mg (N = 8)	Cohort 2 GS-5734 10 mg (N = 8)	Cohort 3 GS-5734 30 mg (N = 8)	Cohort 4 GS-5734 75 mg (N = 8)	Cohort 5 GS-5734 150 mg (N = 8)	Cohort 6 GS-5734 225 mg (N = 8)
AUC_{inf} (h•ng/mL)[b]	—	230.0 (28.4)	773.9 (22.9)	1999.6 (27.1)	2976.1 (19.0)	5274.7 (11.6)
AUC_{last} (h•ng/mL)	67.1 (17.2)	230.0 (16.1)	767.5 (23.2)	1989.9 (27.3)	2965.4 (19.1)	5261.7 (11.7)
C_{max} (ng/mL)	57.5 (31.1)	220.8 (31.2)	693.9 (18.6)	1626.0 (38.6)	2280.0 (30.1)	4421.3 (16.0)

%CV = percentage coefficient of variation; PK = pharmacokinetic
a All PK parameters are reported as mean (%CV).
b GS-5734 plasma AUC_{inf} was not estimable for Cohort 1 (GS-5734 3 mg).

GS-441524 Plasma PK Parameter[a]	Cohort 1 GS-5734 3 mg (N = 8)	Cohort 2 GS-5734 10 mg (N = 8)	Cohort 3 GS-5734 30 mg (N = 8)	Cohort 4 GS-5734 75 mg (N = 8)	Cohort 5 GS-5734 150 mg (N = 8)	Cohort 6 GS-5734 225 mg (N = 8)
AUC_{inf} (h•ng/mL)	55.2 (27.6)	264.0 (26.7)	1013.8 (31.1)	2471.8 (22.7)	4642.5 (16.2)	7348.6 (20.7)
AUC_{last} (h•ng/mL)	19.3 (24.8)	180.5 (35.7)	892.9 (33.9)	2374.0 (23.2)	4517.4 (16.4)	7110.7 (20.9)
C_{max} (ng/mL)	3.2 (10.9)	9.4 (28.4)	34.3 (30.9)	85.8 (23.9)	152.0 (23.6)	256.6 (30.2)

%CV = percentage coefficient of variation; PK = pharmacokinetic
a All PK parameters are reported as mean (%CV).

GS-704277 plasma exposures (AUC_{last}, AUC_{inf}, and C_{max}) were similar when GS-5734 75 or 150 mg was administered as the lyophilized formulation compared to the solution formulation. Although the study was not powered or designed for formal equivalence testing of the lyophilized and solution formulations, the results of the statistical analysis comparing 75 and 150 mg doses of GS-5734 show that GS-5734 and GS-441524 plasma exposures were similar with each formulation and that dose proportionality was maintained with the lyophilized formulation.

GS-5734 exposures (AUC_{inf} and AUC_{last}) for participants in Cohort 9 who received a 75-mg, 30-minute infusion of the lyophilized formulation were in the range of those observed in the corresponding group that received the same 75-mg dose of the lyophilized formulation over 2 hours (Cohort 7). As expected, the C_{max} of GS-5734 increased upon shortening of infusion time from 2 hours to 30 minutes. The PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) of GS-441524 and GS-704277 were similar between the lyophilized formulation 75-mg dose groups infused over 30 minutes versus 2 hours.

GS-5734 Plasma PK Parameter[a]	**Cohort 7 GS-5734 75 mg Lyophilized Formulation 2 Hours (N = 10)**	**Cohort 8 GS-5734 150 mg Lyophilized Formulation 2 Hours (N = 10)**	**Cohort 9 GS-5734 75 mg Lyophilized Formulation 30 Minutes (N = 9)**
AUC_{inf} (h•ng/mL)	1839.9 (17.1)	3261.1 (22.2)	1254.7 (19.6)
AUC_{last} (h•ng/mL)	1832.5 (17.1)	3265.4 (21.3)	1245.2 (19.7)
C_{max} (ng/mL)	1722.0 (28.4)	2722.0 (35.0)	2926.7 (29.2)

%CV = percentage coefficient of variation; PK = pharmacokinetic
a All PK parameters are reported as mean (%CV). One participant in Cohort 9 ([redacted]) did not receive the full volume of the intravenous dose; data for this participant were excluded.

GS-441524 Plasma PK Parameter[a]	**Cohort 7 GS-5734 75 mg Lyophilized Formulation 2 Hours (N = 10)**	**Cohort 8 GS-5734 150 mg Lyophilized Formulation 2 Hours (N = 10)**	**Cohort 9 GS-5734 75 mg Lyophilized Formulation 30 Minutes (N = 9)**
AUC_{inf} (h•ng/mL)	2200.1 (18.4)	4330.6 (22.2)	2024.0 (30.9)
AUC_{last} (h•ng/mL)	2091.1 (19.0)	4194.6 (22.2)	1918.1 (32.8)
C_{max} (ng/mL)	77.5 (21.0)	148.1 (26.5)	69.1 (32.8)

%CV = percentage coefficient of variation; PK = pharmacokinetic
a All PK parameters are reported as mean (%CV). One participant in Cohort 9 did not receive the full volume of the intravenous dose; data for this participant were excluded.

Single-Dose Urine Pharmacokinetics of GS-5734 and Metabolites

After single-dose administration of GS-5734 by IV infusion over 2 hours in Cohorts 1-6, the mean CL_r of GS-5734 and GS-441524, and percentage of the GS-5734 dose recovered in urine as unchanged drug over the 48-hour collection period were comparable across the 30 to 225 mg dose groups, indicating dose-linear renal excretion. These results were consistent with GS-5734 and GS-441524 CL_r and percentage of the dose recovered upon administration of GS-5734 150 mg in Study GS-US-399-1954.

	After single-dose administration of the lyophilized formulation of GS-5734 by IV infusion over 2 hours at doses of 75 or 150 mg (Cohorts 7 and 8) or over 30 minutes (75 mg; Cohort 9), the mean CL_r of GS-5734 and GS-441524 and percentage of the dose recovered in urine as unchanged drug over the 48-hour collection period were comparable across Cohorts 7-9. The mean CL_r of GS-5734 and GS-441524 and percentage of the dose recovered in urine in Cohorts 7 and 8 were consistent with the solution formulation. The mean CL_r of GS-704277 and percentage of the dose recovered in urine over the 48-hour collection period were comparable across Cohorts 7-9, indicating that GS-704277 is renally excreted in a dose-linear manner across the 75 to 150 mg dose range. <u>Single-Dose Semen Pharmacokinetics of GS-5734 and Metabolites</u> For Cohorts 7 and 8 (GS-5734 75 and 150 mg lyophilized formulation over 2 hours) and Cohort 9 (GS-5734 75 mg lyophilized formulation over 30 minutes), GS-5734 was detectable in semen in all male participants at 3 hours postdose. As expected, due to the short $t_{1/2}$ of GS-5734, it was undetectable in all participants thereafter. Concentrations were comparable in the 75 mg dose groups infused over 30 minutes and 2 hours. All male participants had detectable semen concentrations of GS-441524 at all collection time points through Day 5, with the exception of 1 participant in each of Cohort 7 and Cohort 9 on Day 5. The majority of male participants had detectable concentrations of GS-704277 at all collection time points through Day 3. As expected, concentrations of GS-5734, GS-441524, and GS-704277 were higher in the 150-mg dose group infused over 2 hours compared to the 75-mg dose group infused over 2 hours. Single-Dose PBMC Pharmacokinetics of GS-441524 and GS-443902 Metabolites After single-dose administration of GS-5734 by IV infusion over 2 hours in Cohorts 1-6, GS-441524 exposures in PBMCs (AUC_{inf}) increased in an apparent dose-proportional manner across the dose range evaluated. Exposures (AUC) of GS-441524 in PBMCs in the 150-mg dose group were consistent with those observed in PBMCs on Day 1 following administration of GS-5734 150 mg in Study GS-US-399-1954. Exposure (AUC_{inf}) of GS-443902 in PBMCs was increased after single-dose IV administration of GS-5734 75 mg lyophilized formulation over 30 minutes compared with 2 hours, and similar to that observed with the GS-5734 150 mg lyophilized formulation administered IV over 2 hours.
	Conclusions: • Following single-dose IV administration over 2 hours of GS-5734 solution formulation at doses ranging from 3 to 225 mg, GS-5734 exhibited a linear PK profile. • Following single-dose IV administration over 2 hours of GS-5734 lyophilized formulation at doses of 75 and 150 mg, plasma PK parameters of GS-5734 were similar to those obtained following administration of the solution formulation at the same doses. • GS-5734 75 mg lyophilized formulation infused IV over 30 minutes provided similar PBMC exposure of GS-443902, the active triphosphate metabolite, as GS-5734 150 mg lyophilized formulation infused IV over 2 hours. • A single-dose IV dose of GS-5734 (ranging from 3 to 225 mg) was well tolerated. No Grade 3 or 4 AEs, serious adverse events (SAEs), AEs leading to study drug or study discontinuation, or deaths were reported during the study. The only AE that was reported for > 1 participant overall was constipation in 3 GS-5734-treated participants. No participant had a graded alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation during the study.

2.2.2. Study GS-US-399-1954

Study GS-US-399-1954	
Location:	GS-US-399-1954
Title:	A Phase 1, Blinded, Randomized, Placebo-Controlled, Multiple-Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Intravenous GS-5734
Primary Objectives:	• To evaluate the safety and tolerability of multiple IV doses of GS-5734 compared with placebo • To evaluate the PK of GS-5734 and its metabolites following multiple IV doses of GS-5734
Study Design and Participant Population:	This was a randomized, blinded, placebo-controlled, Phase 1 study designed to evaluate the safety and tolerability of multiple IV doses of GS-5734 compared with placebo and to evaluate the PK of GS-5734 and its metabolites following multiple IV doses of GS-5734 in healthy adult volunteers. Two dose cohorts were evaluated in the study. Following screening and Day −1 procedures, eligible participants were confined to the study center beginning on Day −1 and were randomized 2:1 within each cohort to receive GS-5734 150 mg or matching placebo, respectively. Each cohort was composed of 2 groups (ie, Groups 1a and 1b for Cohort 1 and Groups 2a and 2b for Cohort 2) of 6 participants each (4 who received GS-5734 and 2 who received placebo). Each participant received study drug administered IV over a 1-hour period once daily for 7 days in Cohort 1 and 14 days in Cohort 2. Participants were discharged on Day 9 for Cohort 1 and Day 16 for Cohort 2. All participants returned 7 days after discharge for an in-clinic follow-up visit. Plasma, PBMCs, urine, and semen were collected for PK assessments at prespecified times during clinic confinement. Safety assessments were performed throughout the study. Group 1a was enrolled first in a blinded fashion. Group 1b was not administered study drug until preliminary safety data through Day 6 were available for Group 1a and demonstrated an acceptable safety profile. Group 2a was enrolled in a blinded fashion and was not administered study drug until preliminary safety data through Day 7 were available for all participants enrolled in Cohort 1 and demonstrated an acceptable safety profile. Group 2b was not administered study drug until preliminary safety data through Day 14 were available for Group 2a and demonstrated an acceptable safety profile. Study drug dosing for all participants within an enrolled cohort was suspended if any prespecified stopping criteria were met: • The same Grade 3 or 4 confirmed treatment-emergent drug-related AE or clinically significant laboratory abnormality as defined by the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities in 2 or more participants • A confirmed decrease in $eGFR_{CG} \geq 50\%$ from Day −1 considered related to study medication in 2 or more participants Eligible participants were healthy adult males and nonpregnant, nonlactating females of nonchildbearing potential, aged 18 to 55 years (inclusive), with a BMI of 18 to 30 kg/m^2 (inclusive), no significant medical history, normal renal function ($eGFR_{CG}$ of ≥ 90 mL/min), and normal 12-lead ECG.

Summary of Results and Conclusions:	**Pharmacokinetics Results:** Following once-daily IV administration of 150-mg doses of GS-5734 for 7 or 14 days, GS-5734 had a median $t_{1/2}$ of approximately 1 hour, and accumulation did not occur, as expected, given the short half-life. The nucleoside analog metabolite GS-441524 had a longer median $t_{1/2}$ of approximately 24.5 hours, with an accumulation ratio for geometric least-squares mean (GLSM) of AUC after multiple daily dosing of approximately 1.9, reaching steady state by Day 4. The intermediate metabolite GS-704277 had a median $t_{1/2}$ of approximately 1.7 hours, and steady state was achieved by Day 1. Accumulation of this metabolite was observed after 7 days of dosing (accumulation ratio for GLSM of AUC of approximately 1.4), and after 14 days of dosing (accumulation ratio of approximately 1.9). Following once-daily dosing of GS-5734 150 mg for 7 days (Cohorts 1 and 2 combined) or 14 days (Cohort 2 only), approximately 10% and 12%, respectively, of the dose was recovered in the urine as unchanged drug, and approximately 45% and 49%, respectively, of the dose was recovered as GS-441524 over the 24-hour collection period. The levels of GS-441524 in the urine persisted throughout the 24 hour-collection period in all participants after 7 and 14 days of dosing. Levels of GS-704277 in urine were not monitored. Due to at least half of all GS-5734-dosed participants having GS-441524 PBMC concentrations that were above the limit of quantitation on Day 7 in Cohort 1 and Day 14 in Cohort 2, the intracellular PK parameters for GS-441524 were presumably underestimated. Trough concentrations (C_{last}) of GS-5734 in semen were below the limit of quantitation at all time points, consistent with the short $t_{1/2}$ of GS-5734 in plasma; at 8 hours postdose, all participants in both cohorts had GS-5734 plasma concentration that was below the limit of quantitation. However, GS-441524 and GS-704277 had detectable trough concentrations in semen with multiple dosing.
	Conclusions: • Following once-daily IV administration of 150-mg doses of GS-5734 for 7 or 14 days, GS-5734 exhibited a PK profile similar to that observed during single-dose administration. By Day 14, the metabolites GS-441524 and GS-704277 accumulated approximately 1.9-fold after daily dosing. • Multiple-dose IV administration of GS-5734 150 mg once daily for 7 or 14 days was generally well tolerated. No Grade 3 or 4 AEs, SAEs, or deaths occurred during the study. One participant discontinued from the study due to treatment-related nausea. Elevations in Grade 1 or 2 ALT and AST were observed, with mild, reversible Grade 1 prothrombin time prolongation in some participants but without other evidence of hepatic effects.

2.2.3. Study GS-US-399-4231

Study GS-US-399-4231	
Location:	GS-US-399-4231
Title:	A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of Remdesivir (GS-5734™) in Healthy Volunteers
Primary Objective:	• To determine the mass balance of RDV following administration of a single, IV dose of radiolabeled [^{14}C]-RDV
Study Design and Participant Population:	This was a Phase 1, single-center, open-label, mass-balance study of RDV administered as a single, IV dose of radiolabeled [^{14}C]-RDV in healthy volunteers. Participants received a single dose of RDV 150 mg containing a mixture of both unlabeled and radiolabeled [^{14}C]- RDV via IV infusion over 0.5 hour. Each dose contained approximately 100 µCi [^{14}C]- RDV (equivalent to approximately 1.2 mg RDV) and approximately 148.8 mg of non-radiolabeled RDV as an approximately 30 mL solution diluted with IV fluids (normal saline) prior to infusion. Eligible participants were healthy adult males aged 18 to 45 years (inclusive), with a BMI of 19 to 30 kg/m^2 (inclusive), no significant medical history, normal renal function ($eGFR_{CG}$ of ≥ 90 mL/min), and normal 12-lead ECG.
Summary of Results and Conclusions:	**Pharmacokinetics Results:** This mass balance study demonstrated that RDV was extensively metabolized and recovery of RDV was primarily from urine relative to feces. The cumulative mean (%CV) recovery of [^{14}C]-radioactivity in urine plus feces was 92.3% (1.83%), with 74.2% (5.833%) recovered from urine and 18.1% (22.837%) recovered from feces. The predominant species detected in urine were GS-441524 (49%), followed by RDV (10%), GS-704277 (2.9%), and 6 other metabolites, accounting for 6% of the total radioactive dose (each less than 2%). In feces, M14 (desamino-hydroxy-GS-441524 metabolite) accounted for 12% of the radioactive dose; all other metabolites were in trace amounts, accounting for approximately 1% of total radioactivity (each less than 0.5%). Systemic exposure was almost exclusively to RDV at the highest radioactivity concentrations (end of 30-minute infusion) and the GS-441524 metabolite, at other times postdose. The whole blood-to-plasma concentration ratio through 168 hours ranged from 0.68 to 1.0, indicating no preferential exclusion of total radioactivity from blood cells. The plasma and urine PK of RDV, GS-441524 and GS-704277 were consistent with previous studies in healthy participants. The biotransformation pathways of RDV were consistent with the established nonclinical profile of RDV.
	Conclusions: • Remdesivir is extensively metabolized and primarily eliminated in urine as the nucleoside metabolite GS-441524. • Following administration of [^{14}C]-RDV, mean total recovery of the radioactive dose was > 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. • A single IV dose of 150 mg RDV, containing a mixture of unlabeled and radiolabeled [^{14}C]-RDV, was generally safe and well tolerated in healthy male participants with no clinically relevant safety findings. No Grade 3 or 4 AEs, SAEs, or deaths occurred during the study. One participant had a Grade 3 laboratory abnormality of increased amylase (Grade 2 at screening).

2.2.4. Study GS-US-399-5505

Study GS-US-399-5505	
Location:	GS-US-399-5505
Title:	A Phase 1, Blinded, Randomized, Placebo-Controlled, Multiple-Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Intravenous Remdesivir in Healthy Volunteers
Primary Objectives:	• To evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo • To evaluate the PK of RDV and its metabolites following multiple IV doses of RDV
Study Design and Participant Population:	This study was a randomized, blinded, placebo-controlled, multiple-dose Phase 1 study to evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo along with the PK of RDV and its metabolites. Three cohorts were planned to be evaluated. Initiation of a multiple-dose administration with longer dosing durations (Cohorts 2 and 3) was to be determined upon evaluation of safety data through 7 days after the last dose from all participants enrolled in the previous dosing cohort(s). The ascending dose cohorts (Cohorts 2 and 3) were planned to be conducted with a sentinel group consisting of 5 participants (4 active and 1 placebo) randomly assigned. Preliminary safety data of the first 5 participants through 7 days after the last dose were reviewed prior to the initiation of the next 20 participants. Sentinel dosing in Cohort 3 was to be implemented only if the duration of treatment in that cohort exceeded that of Cohort 2. Otherwise, all 25 participants (N = 20:5, RDV:placebo) for Cohort 3 were to be dosed together. Cohort 3 was considered optional and would be run only if deemed necessary by the sponsor. The study enrolled only Cohorts 1 and 2. Cohort 3 was not done. Eligible participants were healthy adult males and nonpregnant, nonlactating female participants, aged 18 to 45 years (inclusive), with a BMI of 18 to 30 kg/m^2 (inclusive), no significant medical history, normal renal function ($eGFR_{CG}$ of $\geq$ 90 mL/min), normal 12-lead ECG, and in good health as determined by the investigator at screening.
Summary of Results and Conclusions:	**Pharmacokinetics Results:** The PK of IV RDV administered at a 200-mg loading dose on Day 1, followed by 100 mg maintenance doses for 4 (Cohort 1) and 9 days (Cohort 2) in healthy participants has been examined. Evaluation of RDV PK revealed similar PK of RDV, its GS-441524 and GS-704277 metabolites in plasma, and GS-443902 in PBMCs at Days 5 (Cohort 1) and 10 (Cohort 2). Therefore, the PK data for Cohorts 1 and 2 were combined to present a composite exposure estimate for these doses. Pharmacokinetic data from the single 200-mg and multiple 100-mg RDV dose levels were consistent with historical data. Remdesivir was readily detectable in plasma and reached peak concentrations at the end of infusion. The rapid disappearance of RDV (median $t_{1/2}$ approximately 1 hour) was followed by transient exposure to the intermediate metabolite GS-704277 (median $t_{1/2}$ approximately 1.25 hour) and more persistent plasma exposure to the nucleoside metabolite GS-441524 (median $t_{1/2}$ approximately 27 hours), and PBMC-associated pharmacologically active metabolite GS-443902 (median $t_{1/2}$ approximately 43 hours). The mean volume of distribution of RDV was approximately 93 L, confirming RDV distribution to tissues; and the mean steady-state clearance was approximately 65 L/h demonstrating consistency with historical data.

RDV PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Doses (100 mg) Day 5 and 10 (N = 26)[b]
C_{max} (ng/mL)	4377.9 (23.5)	2228.8 (19.2)
$t_{1/2}$ (h)	0.90 (0.80, 1.03)	0.96 (0.86, 1.08)
AUC_{last} (h•ng/mL)	2850.3 (18.8)	1562.8 (17.0)
AUC[c] (h•ng/mL)	2862.5 (18.6)	1585.3 (16.6)

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

GS-441524 PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Doses (100 mg) Day 5 and 10 (N = 26)
C_{max} (ng/mL)	142.9 (21.5)	145.0 (19.3)
C_{tau} (ng/mL)	--	69.2 (18.2)
$t_{1/2}$ (h)	--	27.36 (25.29, 30.32)
AUC_{last} (h•ng/mL)	2186.4 (19.1)	4189.3 (17.7)
AUC[b] (h•ng/mL)	2191.4 (19.1)	2229.2 (18.4)

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

GS-704277 PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Doses (100 mg) Day 5 and 10 (N = 26)
C_{max} (ng/mL)	370.4 (29.3)	245.5 (33.9)
$t_{1/2}$ (h)	1.27 (1.14, 1.45)	1.23 (1.15, 1.38)
AUC_{last} (h•ng/mL)	688.5 (26.3)	454.4 (31.8)
AUC[b] (h•ng/mL)	697.5 (25.9)	461.5 (31.4)

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

GS-443902 PK Parameter[a]	Single RDV Dose (200 mg) Day 1 (N = 28)	Multiple RDV Dose (100 mg) Day 5 and 10 (N = 26)[b]
C_{max} (µmol)	9.8 (46.6)	14.6 (40.6)
C_{tau} (µmol)	--	10.2 (49.5)
$t_{1/2}$ (h)	--	43.39 (38.70, 48.90)
AUC_{last} (h•µmol)	163.4 (32.1)	596.7 (25.5)
AUC[c] (h•µmol)	157.4 (32.9)	240.0 (25.4)

%CV = percentage coefficient of variation; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)

a Data are presented as mean (%CV), except for T_{max}, T_{last}, and $t_{1/2}$, which are presented as median (Q1, Q3).

b N = 25 for C_{tau} and N= 20 for $t_{1/2}$

c AUC_{0-24} is presented for single RDV dose (200 mg) on Day 1; AUC_{tau} is presented for multiple RDV doses (100 mg) on Days 5 and 10.

Conclusions:

- Pharmacokinetics of RDV and its metabolites observed after a 200-mg loading dose on Day 1, followed by 100-mg maintenance doses for 4 or 9 days, was consistent with previous studies in healthy volunteers.
- High intracellular concentrations of the active triphosphate metabolite GS-443902 were observed.
- Treatment with RDV with a 200 mg loading dose on Day 1, followed by 100 mg maintenance doses for 4 or 9 days, was generally well tolerated. No Grade 3 or 4 AEs, SAEs, deaths, or pregnancies were reported during the study. Reversible, asymptomatic, graded elevations of ALT and AST were noted in the 10-day treatment group.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This section summarizes all available data describing the clinical pharmacology of RDV. All clinical studies supporting the clinical pharmacology for this marketing application at this time are described in Section 1.3.2. Data described in the Nonclinical Pharmacokinetics Written Summary (m2.6.4) and the Summary of Biopharmaceutic Studies (m2.7.1) are also presented in this summary.

3.1. Absorption

3.1.1. Nonclinical Studies

Remdesivir is developed for IV administration as it has insufficient hepatic stability for oral delivery (m2.6.4). Following IV administration, RDV was rapidly eliminated followed by the sequential appearance of GS-704277, GS-441524, and PBMCs associated pharmacologically active metabolite GS-443902.

3.1.2. Clinical Studies

Two IV RDV formulations have been developed and utilized in clinical studies: solution and lyophilized formulation. The absolute bioavailability of both RDV formulations, administered IV, is 100%. Following single IV dose of [^{14}C]-RDV infused over 30 minutes, RDV was readily detectable in blood and plasma, reaching peak concentrations at the end of infusion. Rapid disappearance of RDV ($t_{1/2}$ approximately 1 hour) was followed by transient exposure to the intermediate metabolite GS-704277 and more persistent exposure to the nucleoside metabolite GS-441524. Peak plasma concentrations of GS-704277 and GS-441524 were observed 0.75 hours and 3.00 hours post start of infusion, respectively (Study GS-US-399-4231, Section 2.2.3.). Plasma exposures of RDV and its metabolites are of interest in clinical pharmacology studies for purposes of PK analyses and interpretation of results.

The mean total recovery of the radioactive dose was greater than 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. Predominant species detected in urine were GS-441524 (49%), RDV (10%), GS-704277 (2.9%), and 6 other metabolites, accounting for 6% of total radioactive dose (each less than 2%). In feces, desamino-hydroxy-GS-441524 metabolite accounted for 12% of the radioactive dose; all other metabolites were in trace amounts, accounting for approximately 1% of total radioactivity (each < 0.5%).

3.2. Distribution

Remdesivir had moderate protein binding with free fraction of 8.0%, 14.2%, and 12.1% in rat, monkey, and human plasma, respectively. Protein binding in plasma is low for GS-704277 and GS-441524 (1% to 2% bound; m2.6.4, Section 5.1).

Remdesivir was predominantly distributed to plasma relative to the cellular components of blood with mean whole blood/plasma concentration ratios of 0.71 and 0.76 for monkey and human, respectively. GS 441524 showed some association with the cellular fraction with respective mean blood/plasma ratios of 1.36 and 1.19 for monkey and human (m2.6.4, Section 5.1).

In agreement with these data, after a single IV dose of [^{14}C]-RDV in healthy male participants, the blood-to-plasma ratio of [^{14}C]-radioactivity was 0.68 at 15 minutes from start of infusion and increased over time reaching a ratio of 1.0 at 5 hours, indicating differential distribution of RDV and its metabolites to plasma or cellular components of blood (GS-US-399-4231, Section 2.2.3).

Tissue distribution studies in animals showed [^{14}C]-RDV-derived radioactivity was widely distributed to most tissues (m2.6.4., Section 5.2.). Notably, appreciable levels of radioactivity were also found in lung tissue, which are a target tissue for SARS-CoV-2 replication. Efficient formation of the pharmacologically active triphosphate, GS-443902, was observed in PBMCs and respiratory tissues across various animal species.

The results of nonclinical studies investigating the distribution of RDV are discussed in detail in the Nonclinical Pharmacokinetics Written Summary (m2.6.4).

3.3. Metabolism and Elimination

Remdesivir is a prodrug. The metabolism of RDV, including metabolic routes leading to elimination and activation, was characterized in vitro (in plasma, blood, various hepatic-derived extracts, and cells), in vivo (rat, rabbit, and monkey studies) and in a human mass-balance PK study.

In vitro hepatic stability of RDV in rat, dog, monkey, and human showed that across species, RDV was largely unstable and metabolized primarily via hydrolysis. In all species tested, RDV hydrolysis was associated with appearance of predominantly GS-704277 and to a lesser degree, GS-441524 (m2.6.4, Section 6.1).

Data from in vitro screening assays suggest that pathways involving cytochrome P450 enzyme (CYP) isozymes are not likely to be important in the disposition of RDV or as a mechanism of drug interactions.

The mass balance, PK, and metabolite profile of RDV following administration of a single IV dose of RDV containing [^{14}C]-RDV (100 µCi) in healthy participants were evaluated in Study GS-US-399-4231 (Section 2.2.3). Serial blood (whole blood and plasma), urine, and stool samples were obtained for analysis while participants were confined to the clinic during sample collection, with the exact interval based on the measured recovery of radioactivity. Quantifiable levels of [^{14}C]-radioactivity in whole blood and plasma were observed for up to 48 and 72 hours, respectively (GS-US-399-4231 Clinical Study Report [CSR], Figures 2 and 3).

Following administration of [^{14}C]-RDV, mean total recovery of the radioactive dose was > 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. Elimination through urine was the major elimination pathway for total radioactivity after [^{14}C]-RDV administration (GS-US-399-4231 CSR, Figure 9). Mean recovery of unchanged

prodrug in urine was low (10.3% of dose). Mean clearance and CL_r values for RDV were 1171 and 129 mL/min, respectively, indicating that most of its elimination was potentially via the nonrenal route.

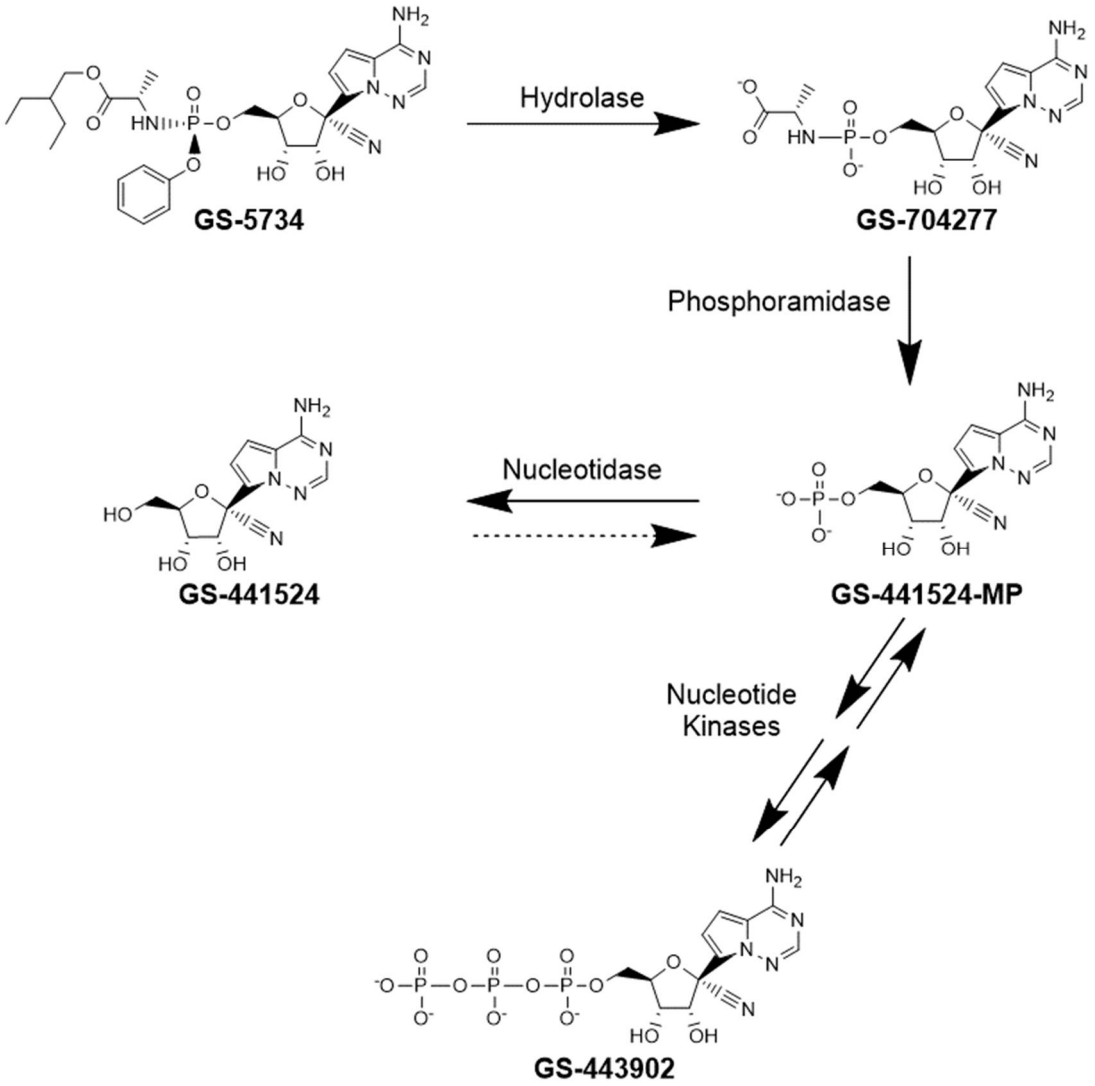
Most of the dose recovered in the urine was as GS-441524 (48.6%) with 10.3% as RDV; confirming that CL_r was a major pathway for elimination of this metabolite. Renal clearance for GS-441524 was estimated as 151 mL/min, approximately 1.2-fold higher than the glomerular filtration rate (120 mL/min), suggesting a role of active secretion in the renal elimination of GS-441524 (Study GS-US-399-4231). The effect of declining renal function on GS-441524 PK has not been studied.

Most of the dose recovered in the feces was as desamino-hydroxy-GS-441524 metabolite (11.9%), and the remaining as [^{14}C]-M15 (GS-441524) (0.46 %) and other unidentified species accounted for a total of 0.84%, each contributing less than 0.5% of the dose.

In plasma, most (44.2%) of the identified radioactivity was attributed to [^{14}C]-M15 (GS-441524); 14.2% was attributed to [^{14}C]-RDV, and 10.6% to unknown metabolite (M27) (could not be identified due to short retention time and coelution with other matrix components) (GS-US-399-4231 CSR, Table 19). Additional analysis is ongoing using accelerator mass spectrometry to further inform on the circulating species of RDV.

Combined results from nonclinical pharmacology and PK studies led to the proposed intracellular metabolic/activation pathway of RDV (Figure 2) (m2.6.4., Section 6.3.). Remdesivir is activated to the pharmacologically active nucleoside analog triphosphate, GS-443902, by a sequential metabolic activation pathway: (i) hydrolase activity removes the ester, resulting in the release of 2-ethyl-butanol; (ii) a chemical step that releases phenol results in formation of the intermediate metabolite, GS-704277; (iii) phosphoramidase activity cleaves the phosphoramidate bond, liberating the nucleoside analog monophosphate and alanine; and (iv) nucleotide kinases likely catalyze the conversion to the active triphosphate, GS-443902. Dephosphorylation of the nucleoside analog monophosphate results in the formation of the nucleoside analog, GS-441524, which is not efficiently rephosphorylated.

Figure 2. Proposed Intracellular Metabolic Pathway of RDV



RDV = remdesivir (GS-5734™)
Source: m2.6.4, Figure 19

3.4. Clinical Pharmacokinetics

3.4.1. Pharmacokinetics of RDV after Single- and Multiple-Dose Administration in Healthy Participants

This section describes available single- and multiple-dose PK data for the solution and lyophilized formulations of RDV in healthy volunteers. Both formulations have been developed to support RDV clinical development. The solution formulation provides a ready-to-use dosage form and does not require reconstitution prior to administration. A lyophilized formulation exhibits improved physiochemical stability, which allows for longer-term storage at room temperate compared with refrigerated storage for the solution formulation (Section 3.2.P.2.1 of Module 3).

Comparison of PK of the solution and lyophilized formulations revealed comparable exposures of RDV and its metabolites (m2.7.1, Section 3), thereby supporting the use of both formulations for treatment of patients with COVID-19.

The PK of the solution formulation has been characterized in early Phase 1 studies (Studies GS-US-399-1812 and GS-US-399-1954). The PK of the lyophilized formulation was subsequently examined in Studies GS-US-399-1812, GS-US-399-5505, and GS-US-399-4231.

In the first-in-human study (Study GS-US-399-1812), the PK of single-ascending doses of the solution formulation of RDV (3, 10, 30, 75, 150, and 225 mg) administered by IV over 2 hours was examined. Following IV administration, RDV plasma concentrations declined rapidly ($t_{1/2}$, 0.66 to 1.05 hours) and were accompanied by sequential appearance of GS-704277 (T_{max}, 1.97 to 2.25 hours; $t_{1/2}$, 0.87 to 1.8 hours) and the nucleoside metabolite GS-441524 (T_{max}, 3.5 to 5.0 hours; $t_{1/2}$, approximately 13 to 31 hours), the predominant plasma metabolite of RDV (Table 2).

The mean CL_r of RDV (48.6 to 78.1 mL/min) and GS-441524 (116 to 154 mL/min), and percentage of the RDV dose recovered in urine as unchanged drug (7.4% to 9.9%) over the 48-hour collection period was comparable across the 30- to 225-mg dose groups.

Table 2. Remdesivir and Metabolites PK Parameters Following a Single Dose of Remdesivir in Healthy Participants

PK Parameter[a]	RDV 30 mg (N = 8)	RDV 75 mg (N = 8)	RDV 150 mg (N = 8)	RDV 225 mg (N = 8)
RDV				
AUC_{inf} (h•ng/mL)	774 (22.9)	2000 (27.1)	2980 (19.0)	5270 (11.6)
C_{max} (ng/mL)	694(18.6)	1630(38.6)	2280 (30.1)	4420(16.0)
T_{max} (h)	2.02 (2.00, 2.03)	2.03 (2.03, 2.05)	2.00 (1.98, 2.04)	1.97 (1.95, 1.98)
$t_{1/2}$ (h)	0.81 (0.61, 0.91)	0.90 (0.82, 1.07)	0.99 (0.92, 1.06)	1.05 (0.96, 1.21)
CL_r (mL/min)	48.6 (17.7)	52.1 (26.4)	78.1 (23.6)	71.4 (25.9)
GS-441524				
AUC_{inf} (h•ng/mL)	1010 (31.1)	2470 (22.7)	4640 (16.2)	7350 (20.7)
C_{max} (ng/mL)	34.3 (30.9)	85.8 (23.9)	152 (23.6)	257 (30.2)
T_{max} (h)	4.00 (3.25, 4.00)	4.50 (3.50, 5.00)	4.00 (3.50, 4.00)	3.50 (3.00, 4.00)
$t_{1/2}$ (h)	27.3 (22.7, 29.6)	26.9 (25.4, 28.9)	27.4 (25.9, 28.8)	30.6 (29.5, 31.1)
CL_r (mL/min)	116 (9.85)	117 (23.4)	127 (12.5)	136 (17.7)
GS-704277				
AUC_{inf} (h•ng/mL)	86.3 (32.8)	270 (49.0)	460 (19.7)	807 (19.8)
C_{max} (ng/mL)	33.7 (31.4)	101 (57.9)	171 (22.3)	315 (19.5)
T_{max} (h)	2.02 (2.00, 2.03)	2.04 (2.03, 2.15)	1.98 (1.98, 2.18)	1.97 (1.96, 1.98)
$t_{1/2}$ (h)	1.09 (0.94, 1.18)	1.48 (1.29, 2.07)	1.81 (1.65, 1.91)	1.77 (1.39, 1.90)

%CV = percentage coefficient of variation; N = number in a population; Q1 = first quartile; Q3 = third quartile; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)

a All PK parameters are reported as mean (%CV) except for T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3); PK parameters are reported to 3 significant figures; CLr for GS-704277 was not estimated due to unavailability of the validated bioanalytical method at the time of sample analysis; Median infusion time length: 1.97 hour for Cohorts 1 to 6 in Study GS-US-399-1812.

Source: Ad Req 10562, Table 5; GS-US-399-1812 CSR, Table 5.3.1 and Table 5.3.3

Remdesivir and its metabolites GS-441524 and GS-704277 exhibit dose-proportional PK. Dose linearity of RDV was evaluated using power model regression analysis in Study GS-US-399-1812. The power model mean slope and 90% CIs indicated dose proportional increases in AUC_{inf} and C_{max} across the evaluated does range (3 to 225 mg) for all analytes (Table 3). Similar results were noted for the lyophilized formulation of RDV (75 mg versus 150 mg) infused over 30 minutes (Studies GS-US-399-1812 and GS-US-399-4231; Ad Req 10562, Table 1).

Table 3 Remdesivir and Metabolites (GS-441524 and GS-704277) PK Parameters Following Single-Dose Administration of Remdesivir (3 to 225 mg) in Healthy Participants

Analyte	PK Parameter	RDV 3 mg (N = 8)	RDV 10 mg (N = 8)	RDV 30 mg (N = 8)	RDV 75 mg (N = 8)	RDV 150 mg (N = 8)	RDV 225 mg (N = 8)	Power Model Mean Slope (90% CI)
RDV	AUC_{inf} (h•ng/mL)	—	230 (28.4)	774 (22.9)	2000 (27.1)	2980 (19.0)	5270 (11.6)	0.95 (0.88, 1.03)
	C_{max} (ng/mL)	57.5 (31.1)	221 (31.2)	694 (18.6)	1630 (38.6)	2280 (30.1)	4420 (16.0)	0.97 (0.92, 1.03)
GS-441524	AUC_{inf} (h•ng/mL)	55.2 (27.6)	264 (26.7)	1010 (31.1)	2470 (22.7)	4640 (16.2)	7350 (20.7)	1.11 (1.06, 1.16)
	C_{max} (ng/mL)	3.2 (10.9)	9.4 (28.4)	34.3 (30.9)	85.8 (23.9)	152 (23.6)	257 (30.2)	1.01 (0.97, 1.06)
GS-704277	AUC_{inf} (h•ng/mL)	11.1 (28.9)	29.5 (20.9)	86.3 (32.8)	270 (49.0)	460 (19.7)	807 (19.8)	1.02 (0.95, 1.08)
	C_{max} (ng/mL)	3.4 (21.1)	11.8 (22.6)	33.7 (31.4)	101 (57.9)	171 (22.3)	315 (19.5)	1.03 (0.97, 1.08)

%CV = percentage coefficient of variation; CI = confidence interval; N = number of participants in a population; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)
Pharmacokinetic parameters are presented as mean (%CV); PK parameters are reported to 3 significant figures.
Median infusion time length: 1.97 hour for Cohorts 1-6 (3 mg to 225 mg) in GS-US-399-1812.
Source: Ad Req 10562, Table 2 and Table 5; GS-US-399-1812, Tables 15, 19, and 22

The multiple-dose PK of RDV, GS-704277, and GS-441524 metabolites was evaluated in 2 Phase 1 studies (Studies GS-US-399-1954 and GS-US-399-5505). Study GS-US-399-1954 evaluated the PK of once-daily 60-minute infusions of an RDV 150-mg solution formulation administered for either 7 or 14 days. Study GS-399-5505 evaluated PK of the lyophilized formulation of RDV 200 mg on Day 1, followed by RDV 100 mg on Days 2 through 4 or Days 2 through 10 (proposed clinical regimen), administered as a 30-minute infusion.

Time to achieve steady state was evaluated using the Helmert transformation testing procedure in Study GS-US-399-1954. Remdesivir and intermediate metabolite, GS-704277, reached steady state by Day 1 and GS-441524 by Day 4. Based on this analysis, evaluation of accumulation ratios was conducted using pooled data (7 days and 14 days). Consistent with its short $t_{1/2}$, RDV did not accumulate upon daily dosing. Accumulation ratios of 51% and 54% for C_{max} and AUC_{tau}, respectively, of GS-704277 were noted; a finding which is not consistent with its short half-life of 0.87 to 1.81 hours. Based on the principle of superpositioning, no accumulation of GS-704277 is expected. Modest accumulation of 68% and 86% for C_{max} and AUC_{tau}, respectively, was observed for GS-441524 (median $t_{1/2}$ of 24.5 hours) (Table 4).

Table 4. Remdesivir and Metabolites PK Parameters Following a Single- or Multiple-Dose Administration of Remdesivir in Healthy Participants

Analyte	PK Parameter	RDV 150 mg Day 1 (N = 16)	RDV 150 mg Days 7 + 14 (N = 15)	Accumulation Ratio
RDV	AUC_{tau} / AUC_{0-24} (h•ng/mL)	2580 (20.1)	2700 (19.1)	1.05 (0.95, 1.17)
	C_{max} (ng/mL)	3170 (24.9)	3220 (20.0)	1.03 (0.91, 1.16)
GS-441524	AUC_{tau} / AUC_{0-24} (h•ng/mL)	1950 (15.7)	3620 (15.1)	1.86 (1.71, 2.02)
	C_{max} (ng/mL)	139 (24.2)	231 (18.6)	1.68 (1.51, 1.88)
GS-704277	AUC_{tau} / AUC_{0-24} (h•ng/mL)	557 (21.3)	880 (31.8)	1.54 (1.33, 1.79)
	C_{max} (ng/mL)	282 (20.7)	435 (29.6)	1.51 (1.30, 1.74)

N = number of participants in a population; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)
Pharmacokinetic parameters are presented as mean (%CV); PK parameters are reported to 3 significant figures.
Median infusion time length: 60 min in GS-US-399-1954.
Source: Ad Req 10562, Table 3 and Table 5

Following a 30-minute IV infusion of the lyophilized formulation of RDV 200 mg on Day 1 and RDV 100 mg once daily on Day 2 through Day 5 (Study GS-US-399-1954) or through Day 10 (Study GS-US-399-5505), plasma concentrations of RDV declined rapidly ($t_{1/2}$, approximately 1 hour) (Table 5). At the 100-mg multiple dose, the peak plasma concentrations of the intermediate metabolite GS-704277 and the predominant plasma metabolite GS-441524 occurred approximately 0.75 and approximately 1.51 hours after the start of infusion, respectively, and declined with $t_{1/2}$ of approximately 1.23 and 27 hours, respectively.

High intracellular concentrations of the active triphosphate metabolite GS-443902 were observed following a single RDV 200-mg dose and multiple doses of RDV 100 mg (GS-US-399-5505).

Table 5. Remdesivir and Metabolites PK Parameters Following Single-Dose Administration of RDV 200 mg on Day 1 and Multiple-Dose Administration of RDV 100 on Days 2 to 10 in Healthy Participants

PK Parameter[a]	Single Dose RDV 200 mg Day 1 (N = 28)	Multiple Dose RDV 100 mg Day 5 and Day 10 Combined (N = 28)[b]
RDV		
AUC (h•ng/mL)	2860 (18.6)	1590 (16.6)[c]
C_{max} (ng/mL)	4380 (23.5)	2230 (19.2)
T_{max} (h)	0.67 (0.25, 0.68)	0.68 (0.25, 0.75)
$t_{1/2}$ (h)	0.90 (0.80, 1.03)	0.96 (0.86, 1.08)[c]
GS-441524		
AUC (h•ng/mL)	2190 (19.1)	2230 (18.4)
C_{max} (ng/mL)	143 (21.5)	145 (19.3)
T_{max} (h)	2.00 (1.50, 4.00)	1.51 (1.50, 2.00)
C_{24} (ng/mL)	64.8 (20.8)	69.2 (18.2)
$t_{1/2}$ (h)	—	27.4 (25.3, 30.3)
GS-704277		
AUC (h•ng/mL)	698 (25.9)	462 (31.4)
C_{max} (ng/mL)	370 (29.3)	246 (33.9)
T_{max} (h)	0.75 (0.67, 0.75)	0.75 (0.75, 0.78)
$t_{1/2}$ (h)	1.27 (1.14, 1.45)	1.23 (1.15, 1.38)
GS-443902		
AUC (h•µmol)	157 (32.9)[c]	240 (25.4)
C_{max} (µmol)	9.80 (46.6)	14.6 (40.6)
T_{max} (h)	6.00 (1.00, 12.02)	6.00 (1.00, 12.00)
C_{24} (µmol)	6.90 (45.8)	10.2 (49.5)[c]
$t_{1/2}$ (h)	—	43.4 (38.7, 48.9)[d]

CV = coefficient of variation; N = number of participants in a population; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)

AUC_{0-24} presented for Day 1 and AUC_{tau} presented for Day 5 and Day 10; C_{24} presented for Day 1 and C_{tau} presented for Day 5 and Day 10

a All PK parameters are reported as mean (%CV) except for T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3); PK parameters are reported to 3 significant figures

b N = 26 (number of participants who completed study drug)

c N = 25

d N = 20

Source: GS-US-399-5505 CSR, Tables 15.10.1.1.6.1 to 15.10.1.1.6.4

3.4.2. Intrinsic Factors

Pharmacokinetic data of RDV in patients with COVID-19 are not available. The PK of RDV in healthy adult participants is expected to be generalizable to SARS-CoV-2 infected patients with normal renal or hepatic function. The impact of COVID-19-mediated kidney or liver disfunction on the PK of RDV is currently unknown. The effect of demographics on the PK of RDV has not been examined.

3.4.2.1. Pediatrics

The PK of RDV in pediatric patients have not been evaluated. The safety and efficacy of adolescent patients (12 years and older) weighing ≥ 40 kg are being evaluated in the ongoing Studies GS-US-540-5773 and GS-US-540-5774. The disposition of RDV is expected to be similar in adults and adolescents; thus, the PK in adult patients is expected to be generalizable to adolescents.

3.4.3. Extrinsic Factors

Clinical studies to examine the effect of extrinsic factors on the PK of RDV have not been conducted. This section includes mathematical prediction of the DDI liability of RDV using in vitro data and available Phase 1 data in healthy volunteers {Kirby 2010}.

3.4.3.1. Food Effect

Remdesivir is being developed for IV administration. The effect of food was not evaluated.

3.4.3.2. Drug Interaction Potential

3.4.3.2.1. Potential for RDV to Affect Other Drugs

In vitro, RDV was identified as a weak inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 (IC_{50} ranging from 55 to 78μM), and slightly more potent against CYP3A4 (IC_{50} = 11.0 μM and 1.6 μM, testosterone, and midazolam as substrates, respectively) in vitro (m2.6.4, Section 8). It also inhibited UGT1A1 activity with an IC_{50} of 9.78 μM which is above the clinically observed concentrations (200 mg, C_{max} = 7.3 μM). Remdesivir also inhibited organic anion transporting polypeptide (OATP)1B1- and OATP1B3-dependent transport of Fluo-3, with IC_{50} values of 2.8 and 2.1 μM, respectively. Further in vitro analysis showed that there was no evidence for RDV to be a mechanism-based inhibitor of CYP3A using the most sensitive activity. Evaluation of inhibitory effects of GS-702477 and GS-441524 is ongoing. Remdesivir, GS-441524, or GS-704277 are not inducers of CYP enzymes. The potential of RDV to be the perpetrator of clinically significant drug-drug interactions is further limited by its rapid clearance.

3.4.3.2.2. Potential for Other Drugs to Affect RDV

Remdesivir is a substrate of CYP2C8, 2D6, and 3A4 in vitro. However, coadministration with inhibitors of these CYP isoforms is unlikely to markedly increase RDV levels as its metabolism is likely to be predominantly mediated by hydrolase activity. Remdesivir is a substrate of OATP1B1 and P-glycoprotein (P-gp).

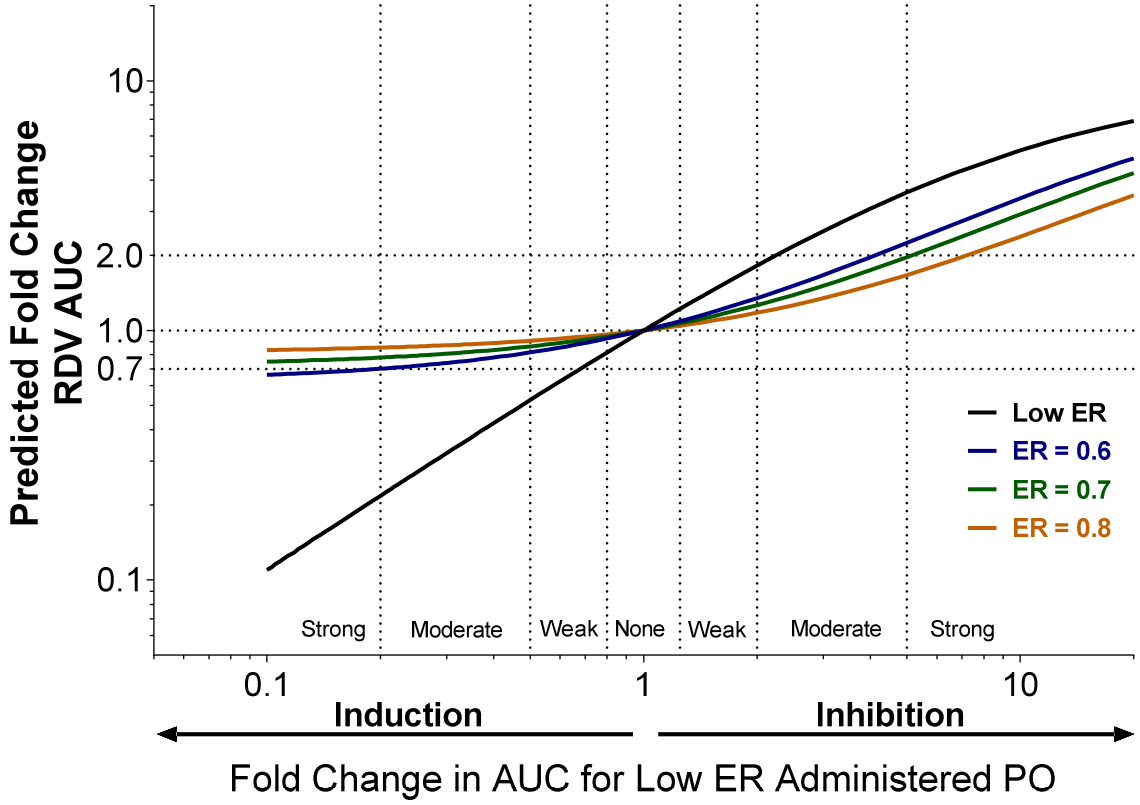
Clinical DDI studies of RDV have not been conducted. The effect of inhibitors or inducers of hepatic transport on RDV exposure has been predicted using available Phase 1 data in healthy volunteers.

Non-compartmental PK analysis of single dose IV administration of RDV to healthy volunteers in Study GS-US-399-1812 resulted in RDV plasma clearance ranging from 40 to 52 L/hr. Based on a blood-to-plasma ratio of 0.7 (GS-US-399-4231 CSR, Section 10.3) a standard human liver blood flow of 97 L/hr, and assumption that CL_r accounts for 10% of systemic clearance (GS-US-399-4231 CSR, Section 10.4.2.1), the hepatic extraction ratio for RDV is estimated to be 0.6 to 0.8, which is considered moderate-to-high extraction.

Because of the moderate-to-high hepatic extraction of RDV, the approximate 11% contribution of renal clearance to systemic clearance (GS-US-399-4231 CSR, Section 10.4.2.1), and its administration via the IV route, the effect of inhibition or induction of hepatic transporters on RDV PK will be attenuated compared with what would be expected if RDV had a low hepatic extraction ratio (ER) {Kirby 2010}. Figure 3 below highlights this attenuation by presenting the expected fold change in AUC of RDV administered IV under scenarios of weak, moderate, and strong inhibition or induction of hepatic intrinsic clearance (transport or metabolism) assuming a range of ER from 0.6 to 0.8 compared with that expected for RDV if it were a low ER compound. These data highlight that the effect of strong induction of hepatic intrinsic clearance is substantially attenuated across the range of ER from 0.6 to 0.8 with maximum reduction in RDV AUC of approximately 30%. Additionally, weak or moderate inhibition of hepatic intrinsic clearance is expected to elicit only modest changes in RDV AUC (approximate 2-fold increase or less). These simulations were carried out under a worst-case scenario, assuming that the intrinsic clearance mechanism being augmented by inhibition or induction accounted for the entirety of hepatic clearance (ie, $F_m = 1.0$).

Based on available data, extra-hepatic esterase-mediated clearance cannot be ruled out and may alter the characterization of induction liability of RDV. As such, Gilead plans to evaluate the potential for a DDI between rifampin and RDV in a future Phase 1 study.

Figure 3. Hepatic Extraction Ratio Attenuation of Predicted Fold Change in RDV AUC with Inhibition or Induction of Hepatic Transporters.



ER = extraction ratio; PO = oral administration; RDV = remdesivir (GS-5734™)
Source: Ad Req 10584, Listing 1

3.4.3.2.3. Management of Known and Potential Drug-Drug Interactions

In vitro, RDV is a substrate of CYP2C8, 2D6, and 3A4; the impact of metabolizing enzymes on RDV disposition is expected to be minimal since RDV metabolism is predominantly mediated by hydrolase activity. Remdesivir is a substrate of OATP1B1and P-gp. The effect of inhibition or induction of hepatic transporters on RDV PK will be attenuated because of moderate-to-high hepatic extraction of RDV and its administration via the IV route.

Remdesivir has been identified as a weak inhibitor of CYP3A, OATP1B1, and OATP1B3. Due to the short half-life, the inhibitory effects are predicted to be transient. Evaluation of inhibitory effects of GS-704277 and GS-441524 is ongoing.

Clinical DDI studies of RDV have not been conducted. Based on available data, weak to moderate inhibition or strong induction are expected to result in only modest alteration in RDV exposure.

Remdesivir may be administered with weak to moderate inducers or strong inhibitors of CYP450, OATP, or P-gp. Since extra-hepatic esterase-mediated clearance cannot be ruled out, the use of RDV with known strong inducers of P-gp (eg, rifampin or herbal medications) is not recommended.

3.5. Dose Selection

The proposed clinical regimen for the treatment of patients weighing ≥ 40 kg with COVID-19 is as follows: single RDV 200 mg IV loading dose on Day 1 followed by RDV 100 mg IV once-daily maintenance doses from Day 2 (for a total treatment duration of either 5 days or 10 days).

Selection of this dosing regimen is based on the PK bridge from animal data to human doses and efficacy using the results of in vivo efficacy studies conducted in SARS-CoV-2- and MERS-CoV-infected rhesus monkeys, and available PK data in healthy rhesus monkeys and Phase 1 studies in healthy participants.

Remdesivir showed therapeutic efficacy in SARS-CoV-2-infected rhesus monkeys and prophylactic and therapeutic efficacy in MERS-CoV-infected rhesus monkeys. Administration of RDV 10/5 mg/kg (RDV 10 mg/kg first dose, followed by RDV 5 mg/kg once daily thereafter for 6 days) using IV bolus injection initiated 12 hours postinoculation with SARS-CoV-2 resulted in a significant reduction of clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals (Study PC-540-2004).

In MERS-CoV-infected monkeys, prophylactic 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 significant reduction of clinical scores, clinical signs of respiratory disease, and viral RNA levels compared with vehicle-treated animals. Therapeutic RDV treatment of 5 mg/kg once daily using IV bolus injection initiated 12 hours postinoculation also resulted in reduced clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions (Study PC-399-2038; {De Wit 2020}).

For the treatment of COVID-19, the approach has been to target exposures (plasma and PBMC) associated with efficacy at 10 mg/kg and 5 mg/kg in the SARS-CoV-2- and MERS-CoV-infected rhesus monkeys. Using allometric scaling, the proposed clinical maintenance dose of daily 100 mg provides systemic exposure of RDV in plasma and GS-443902 (active triphosphate) in PBMCs similar with that observed in rhesus monkeys at 5 mg/kg IV dose of RDV (Study AD-399-2030, Study GS-US-399-5505) (Table 6).

Table 6. Pharmacokinetics of RDV in Plasma and Nucleoside Triphosphate Metabolite GS-443902 (PBMCs) following Repeat RDV Doses (30-minute IV Infusion) to Healthy Rhesus Monkeys (5 mg/kg) and Healthy Humans (100 mg)

PK Parameter (Mean [SD])	Mean (SD)	
	Healthy Rhesus Monkeys	Healthy Human Participants
	RDV 5 mg/kg (N = 8)	RDV 100 mg (N = 26)
Plasma RDV		
AUC[a] (h•ng/mL)	1430 (230)	1590 (264)
C_{max} (ng/mL)	3350 (390)	2230 (427)
PBMC GS-443902		
C_{24} (µM)	7.1 (6.7)	10.2 (5.05)[b]

N = number in a population; PBMC = peripheral blood mononuclear cell; RDV = remdesivir (GS-5734™); SD = standard deviation
a AUC: healthy rhesus monkeys AUC_{0-24}; healthy human participants AUC_{tau}; PK data reported to 3 significant figures
b N = 25
Source: AD-399-2030, Tables 8 and 10, GS-US-399-5505 CSR, Tables 15.10.1.1.6.1, 15.10.1.1.6.4, and 16

To target efficacy seen at 10 mg/kg loading dose in infected rhesus monkeys requires a loading dose of 200 mg in humans. As shown in Table 7, PK of a single dose of 200-mg RDV in healthy participants is similar to the expected exposure in rhesus monkeys at 10 mg/kg (AUC 5 mg/kg × 2 due to dose proportionality; AD-399-2002).

High intracellular trough concentrations of the active triphosphate metabolite GS-443902 have been observed in human PBMCs following a single RDV 200 mg dose or multiple IV doses of RDV 100 mg (Study GS-399-5505). These concentrations are approximately 1000-fold above the in vitro EC_{50} (half-maximal effective concentration) against SARS-CoV-2 (clinical isolate; EC_{50} = 0.0099 µM) and SARS-CoV in primary human airway epithelial cells (EC_{50} = 0.0066 µM) (m2.6.2, Section 3.1, PC-540-2003). These concentrations are also comparable with those observed in rhesus monkeys receiving RDV 5 mg/kg doses for 7 days, and the doses associated with efficacy in SARS-CoV-2 and MERS-CoV infected rhesus monkey models (m2.6.2, Section 3.2.).

Table 7. Pharmacokinetics of Plasma RDV and Nucleoside Triphosphate Metabolite GS-443902 (PBMCs) following a 200 mg Single Dose of RDV to Healthy Volunteers

PK Parameter (Mean [%CV])	Mean (%CV) Healthy Human Participants RDV 200 mg (N = 28)
Plasma RDV	
AUC_{0-24} (h•ng/mL)	2860 (18.6)
C_{max} (ng/mL)	4380 (23.5)
PBMC GS-443902	
C_{24} (μM)	6.9 (45.8)

CV = coefficient of variation; N = number in a population; PBMC = peripheral blood mononuclear cell; RDV = remdesivir (GS-5734™)
Source: GS-US- 399-5505 CSR, Table 15.10.1.1.6.1 and Table 15.10.1.1.6.4

Dose selection of RDV in pediatric patients was informed by a physiologically based pharmacokinetic (PBPK) model developed to characterize the PK of RDV and the primary circulating nucleoside metabolite, GS-441524, in adults ([redacted] v.17, [redacted]). The adult PBPK model was subsequently used to predict pediatric patient exposure, accounting for age-dependent changes in organ volume or size (liver and kidney), esterase expression, plasma protein binding, and organ blood flow. Simulations indicated that use of the adult dosage regimen in pediatric participants ≥ 40 kg is predicted to maintain RDV and GS-441524 exposures generally within the expected adult steady-state exposure range following the adult dosage regimen. The PBPK modeling and simulation methods and results are described in a PBPK report (m5.3.5.3).

These simulations did not account for possible diminished liver or kidney function due to SARS-CoV-2 infection because the impact of infection on the PK of RDV and GS-441524 is currently unknown.

The efficacy of the proposed clinical regimen is currently being evaluated in patients with COVID-19 and is supported by clinical safety data in approximately 500 individuals who have received RDV to date in Phase 1 studies, non-Gilead-sponsored studies, and on an expanded-access basis for multiple indications.

3.6. Pharmacokinetic-Pharmacodynamic Relationship for Safety

3.6.1. Healthy Participants

Nonclinical and clinical data demonstrated that RDV exhibits a low potential to prolong QTc interval. In the in vitro human ether-a-go-go-related gene (hERG) study, IC_{50} value was 28.9 μM, approximately 33-fold above the estimated free drug concentration at C_{max} concentrations of the proposed highest clinical dose of 200 mg. In a safety pharmacology cardiovascular study with telemetry-instrumented conscious cynomolgus monkeys, there were no

RDV-related effects on any ECG parameters and the IV dose of 10 mg/kg (the highest dose tested) was considered to be the no observed effect level (m2.6.2, Section 5.1). In agreement with nonclinical data, no cardiac-related AEs were reported following administration of a single dose (3 mg to 225 mg) or multiple doses (150 mg once daily up to 14 days or 200 mg on Day 1 and 100 mg once daily up to Day 10) in Phase 1 studies.

A concentration-QT (C-QT) analysis was conducted in lieu of a thorough QT study using Phase 1 data in heathy volunteers who received daily 60-minute infusions of RDV for 7 or 14 days (Study GS-US-399-1954). The exposures achieved in this study represent therapeutic exposures at the proposed clinical regimen. An assessment of the supratherapeutic concentrations on the QTc interval could not be conducted as RDV administration to healthy participants is limited to a single dose of 200 mg or multiple doses of 100 mg (IND 125566 Continue Partial Clinical Hold letter dated [redacted] 20[redacted]).

The statistical approach used in the RDV C-QT analysis is described in the C-QT Technical Report and is consistent with the International Council for Harmonisation (ICH) E14 guidance and the scientific white paper {Garnett 2018, ICH 2012}.

The predicted mean time-matched, baseline-adjusted, placebo-corrected QTcF (ΔΔQTcF) and corresponding 2-sided 90% CI were estimated for all relevant concentrations of RDV, GS-441524, and GS-704277, which showed upper bounds below the 10 msec threshold. Two sensitivity analyses were conducted to examine the robustness of the results from the final model. The sensitivity analyses evaluated results from a 2-way combination of the analytes models with the lowest Akaike Information Criterion, and models with a single analyte. Results from all sensitivity analyses and the results from the final model were similar and showed consistently upper 2-sided 90% CI bounds to be below the 10 msec threshold, indicating that RDV, GS-441524 and GS-704277 do not cause QT interval corrected for heart rate using the Fridericia formula (QTcF) interval prolongation at therapeutic concentrations.

3.7. PK and PK/PD Conclusions

The PK of the solution and lyophilized formulations has been characterized in Phase 1 studies in healthy volunteers. Phase 1 studies included single- and multiple-dose evaluations and a single-dose ADME study. Evaluation of intrinsic or extrinsic factors on the PK of RDV was not performed. This assessment of the DDI liability of RDV was based on in vitro data and available Phase 1 data in healthy volunteers. The data are summarized as follows:

3.7.1. Absorption

Remdesivir is developed for IV administration. The absolute bioavailability of the solution and lyophilized RDV formulations administered IV is 100%. Following IV administration, RDV is rapidly detectable in plasma, reaching peak concentrations at the end of infusion. Remdesivir elimination ($t_{1/2}$ approximately 1 hour) is followed by the sequential appearance of GS-704277, GS-441524, and PBMCs-associated pharmacologically active metabolite, GS-443902.

Following IV administration of a proposed clinical regimen of a single RDV 200 mg IV loading dose on Day 1 followed by RDV 100 mg IV once-daily maintenance doses on Days 2-10 in healthy participants, peak plasma concentrations of GS-704277 and GS-441524 are observed 0.75 hours and at 1.51 to 2.00 hours post start of infusion, respectively. High intracellular concentrations of the active triphosphate metabolite are observed

Remdesivir and its plasma metabolites exhibit dose-proportional PK over the dose range of 3 mg to 225 mg.

3.7.2. Distribution

Remdesivir had moderate protein binding (approximately 88% bound) in human plasma. Protein binding in plasma is low for GS-704277 and GS-441524 (1% to 2% bound; m2.6.4, Section 5.1). After a single IV dose of [^{14}C]-RDV in healthy male participants, the blood-to-plasma ratio of [^{14}C]-radioactivity was 0.68 at 15 minutes from start of infusion, increased over time reaching a ratio of 1.0 at 5 hours, indicating differential distribution of RDV and its metabolites to plasma or cellular components of blood.

3.7.3. Metabolism

Remdesivir is extensively metabolized into the pharmacologically active nucleoside analog triphosphate GS-443902. The metabolic activation pathway involves hydrolysis by esterases which leads to the formation of the intermediate metabolite, GS-704277. Phosphoramidate cleavage followed by phosphorylation forms the active triphosphate, GS-443902. Dephosphorylation results in the formation of nucleoside metabolite GS-441524 that is not efficiently rephosphorylated.

3.7.4. Elimination

Following administration of [^{14}C]-RDV, mean total recovery of the radioactive dose was > 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. Elimination through urine was the major elimination pathway for total radioactivity after [^{14}C]-RDV administration.

The majority of the RDV dose recovered in urine was GS-441524 (48.6%) while 10.3% was recovered as RDV. These data indicate that renal clearance is the major elimination pathway for GS-441524. Most of RDV elimination is via the nonrenal route.

After a single 30-minute infusion of [^{14}C]-RDV in healthy participants, the median terminal half-lives of RDV, GS-704277, and GS-441524 were approximately 1, approximately 1.3, and 27 hours, respectively.

3.7.5. Effect of Intrinsic Factors

Pharmacokinetic data of RDV in adult and pediatric patients with COVID-19 are not available. The PK of RDV in healthy adult participants is expected to be generalizable to SARS-CoV-2 infected patients with normal renal or hepatic function. The effect of intrinsic factors, including the effect of organ dysfunction and the effect of demographics on the PK of RDV have not been examined. The disposition of RDV is expected to be similar in adults and adolescents; thus, the PK in adult patients is expected to be generalizable to adolescents.

3.7.6. Effect of Extrinsic Factors

Clinical studies to examine the effect of extrinsic factors on the PK of RDV have not been conducted. This assessment of the DDI liability of RDV was based on in vitro data and available Phase 1 data in healthy volunteers

In vitro, RDV is a substrate of CYP2C8, 2D6, and 3A4; the impact of metabolizing enzymes on RDV disposition is expected to be minimal since RDV metabolism is predominantly mediated by hydrolase activity. Remdesivir is a substrate of OATP1B1and P-gp. The effect of inhibition or induction of hepatic transporters on RDV PK will be attenuated because of moderate-to-high hepatic extraction of RDV and its administration via the IV route.

Remdesivir has been identified as a weak inhibitor of CYP3A, OATP1B1, and OATP1B3. Due to the short half-life, the inhibitory effects are predicted to be transient. Evaluation of inhibitory effects of GS-704277 and GS-441524 is ongoing.

Based on available data, weak to moderate inhibition or strong induction are expected to result in only modest alteration in RDV exposure.

Remdesivir may be administered with weak to moderate inducers or strong inhibitors of CYP450, OATP, or P-gp. Since extra-hepatic esterase-mediated clearance cannot be ruled out, the use of RDV with known inducers of P-gp (eg, rifampin or herbal medications) is not recommended.

3.7.7. Clinical Pharmacokinetics/Pharmacodynamics

Selection of the proposed clinical dosing regimen (200 mg on Day 1 followed by 100 mg once daily from Day 2 [for a total treatment duration of either 5 days or 10 days]) is selected based on the PK bridge from animal data to human doses and efficacy using the results of in vivo efficacy studies conducted in SARS-CoV-2- and MERS-CoV-infected rhesus monkeys, and available PK data in healthy rhesus monkeys and Phase 1 studies in healthy volunteers. This regimen is currently being evaluated in patients with COVID-19 and is supported by safety data in approximately 500 individuals who have received RDV to date in Phase 1 studies and non-Gilead-sponsored studies.

A C-QT analysis conducted to evaluate the effect of RDV on QTc interval showed no impact at therapeutic concentrations of RDV, GS-774277, or GS-441524.

4. VIROLOGY

Nonclinical and clinical virology studies are discussed in the following sections.

4.1. Nonclinical Virology

Remdesivir shows potent in vitro and in vivo activity against SARS-CoV-2 and multiple genetically diverse CoVs. Remdesivir inhibits the human pathogenic CoVs SARS-CoV-2, SARS-CoV, and MERS-CoV in human cell types relevant for viral infection. Remdesivir also exhibits broad in vitro antiviral activity against filoviruses, including EBOV and Marburg virus, as well as other RNA viruses such as pathogenic paramyxoviruses (eg, Nipah and Hendra viruses).

The primary mechanism of inhibition by RDV is the incorporation of the triphosphate form of RDV, GS-443902, into nascent RNA chains by the viral RNA-dependent RNA polymerase, causing delayed RNA chain termination during viral replication. Delayed chain termination has been shown to be the mechanism of action of RDV inhibition of the SARS-CoV-2, SARS-CoV, and MERS-CoV polymerases.

In vitro resistance profiling of RDV using the rodent CoV murine hepatitis virus (MHV) demonstrated a high barrier to resistance development and identified 2 mutations in the viral polymerase at residues conserved across CoVs that conferred low-level (5.6-fold) reduced susceptibility to RDV. The mutant viruses showed reduced viral fitness in vitro and introduction of the corresponding mutations into SARS-CoV resulted in attenuated SARS-CoV pathogenesis in a mouse model.

Importantly, RDV exhibits in vivo prophylactic and/or therapeutic efficacy in multiple animal models of CoV infection. Remdesivir exhibits in vivo therapeutic efficacy against SARS-CoV-2 in rhesus monkeys and prophylactic and therapeutic efficacy MERS-CoV infection in rhesus monkeys as well as SARS-CoV and MERS-CoV infection in mice. In these animal studies, RDV treatment resulted in a significant reduction in clinical scores, signs of respiratory disease, and viral RNA levels compared to vehicle-treated animals.

A summary of nonclinical virology is provided in the following sections, and a full description of nonclinical virology is provided in m2.6.2. A tabular listing of nonclinical virology studies is provided in Appendix 6.3.

4.1.1. Primary Pharmacodynamics

Remdesivir is a diastereomerically pure monophosphoramidate prodrug of a modified adenine nucleoside analog GS-441524. In multiple cell types relevant for CoV replication, RDV undergoes efficient conversion to the pharmacologically active triphosphate GS-443902 (m2.6.4, Section 6.1.3). Remdesivir shows potent in vitro activity against SARS-CoV-2 and multiple genetically diverse CoVs. Remdesivir inhibits the human pathogenic CoVs SARS-CoV-2, SARS-CoV, and MERS-CoV in human cell types relevant for viral infection.

4.1.1.1. In Vitro Studies

Remdesivir inhibited the in vitro replication of a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with an average EC_{50} value of 0.0099 µM (m2.6.3, Section 2.1, PC-540-2003). Similarly, RDV potently inhibited a recombinant chimeric virus expressing the polymerase (nsp12) gene of SARS-CoV-2 in a backbone of SARS-CoV with a luciferase reporter in Huh7 cells with an EC_{50} of 0.0035 µM (m2.6.3, Section 2.1, PC-540-2002). Remdesivir also inhibits the human pathogenic CoVs SARS-CoV and MERS-CoV in multiple human cell types relevant for viral infection with EC_{50} values ranging from 0.0066 to 0.52 µM (m2.6.2, Section 3.1.1).

Biochemical studies have demonstrated that RDV is a selective inhibitor of viral RNA-dependent RNA polymerases. The nucleoside triphosphate GS-443902 acts as an analog of ATP and competes with the natural ATP substrate to become incorporated into nascent RNA chains by the viral RNA-dependent RNA polymerase. This process results in delayed RNA chain termination during replication of the viral RNA. Delayed chain termination has been shown to be the mechanism of action of RDV inhibition of the SARS-CoV-2, SARS-CoV, and MERS-CoV polymerases (m2.6.3, Section 2.1, PC-540-2005) {Gordon 2020}. In contrast, host RNA and DNA polymerases, including mitochondrial polymerases, are not inhibited by RDV-triphosphate at concentrations as high as 200 µM (m2.6.3, Section 3.1, PC-399-2017).

The in vitro development of resistance to RDV in CoVs has been assessed by cell culture passaging of MHV in the presence of the RDV nucleoside analog GS-441524. After 23 passages, 2 mutations were selected in the nsp12 polymerase at residues conserved across CoVs: F476L and V553L. Compared with wild-type virus, recombinant MHV containing the F476L mutation showed 2.4-fold reduced susceptibility to RDV, and MHV containing V553L demonstrated 5-fold reduced susceptibility, while the double mutant conferred 5.6-fold reduced susceptibility to RDV in vitro. The mutant viruses were unable to compete with wild-type virus in coinfection experiments in the absence of RDV, demonstrating a viral fitness cost associated with these mutations. Introduction of the MHV resistance mutations into the corresponding residues of SARS-CoV (F480L and V557L) resulted in the same in vitro susceptibility changes and attenuated pathogenesis in a mouse model {Agostini 2018}. These results suggest that mutations at these conserved residues across divergent CoVs may affect conserved functions of nsp12 and potentially imply common pathways to resistance across CoVs.

4.1.1.2. In Vivo Studies

Remdesivir exhibits prophylactic and/or therapeutic efficacy in multiple animal models of CoV infection. Remdesivir demonstrated therapeutic efficacy in a study of RDV treatment in rhesus macaques inoculated with a clinical isolate of SARS-CoV-2 (m2.6.3, Section 2.2, PC-540-2004). Remdesivir was administered at 10 mg/kg via IV bolus injection 12 hours postinoculation followed by additional once-daily doses at 5 mg/kg through 6 days post-inoculation. Animals treated with RDV showed significantly reduced clinical signs of SARS-CoV-2 infection and reduced severity of pulmonary infiltrates as assessed by radiography compared to the vehicle control group. Upon scheduled necropsy at 7 days postinoculation, RDV-treated animals had

significantly reduced gross lung lesions and lower viral RNA levels in lung tissue compared to vehicle-treated animals.

Remdesivir also demonstrated prophylactic and therapeutic efficacy in a mouse model of SARS-CoV pathogenesis. Administration of 25 mg/kg RDV subcutaneously (SC) twice daily beginning 1 day before or 1 day after SARS-CoV inoculation resulted in significantly reduced lung viral load and improved clinical signs of disease as well as lung function {Sheahan 2017}.

Similarly, in a mouse model of MERS-CoV pathogenesis, both prophylactic and therapeutic administration of 25 mg/kg RDV SC twice daily improved pulmonary function and reduced lung viral loads and severe lung pathology. In contrast, prophylactic lopinavir/ritonavir and interferon-beta (LPV/RTV-IFN-β) slightly reduced viral loads without impacting other disease parameters. Therapeutic LPV/RTV-IFNβ improved pulmonary function but did not reduce virus replication or severe lung pathology {Sheahan 2020}.

Remdesivir showed prophylactic and therapeutic efficacy in MERS-CoV-infected rhesus monkeys. Administration of RDV at 10 mg/kg (m2.6.3, Section 2.2, PC-399-2038) or 5 mg/kg {De Wit 2020} once daily for 7 days using IV bolus injection beginning 1 day prior to MERS-CoV inoculation resulted in a significant reduction of clinical scores, clinical signs of respiratory disease, and viral RNA levels compared to vehicle-treated animals (m2.6.3, Section 2.2, PC-399-2038). Therapeutic RDV treatment of 5 mg/kg once daily using IV bolus injection initiated 12 hours postinoculation also resulted in reduced clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions {De Wit 2020}.

4.1.2. Secondary Pharmacodynamics

Remdesivir exhibits broad in vitro antiviral activity against filoviruses, including EBOV and Marburg virus, as well as other RNA viruses such as pathogenic paramyxoviruses (Nipah virus and Hendra virus) with EC_{50} values ranging from 0.018 to 0.79 μM (m2.6.2, Section 4.2)

Remdesivir and the nucleoside analog GS-441524 were profiled for in vitro cytotoxicity and mitochondrial toxicity in multiple relevant cell types (m2.6.2., Section 4.2 and 4.3). Remdesivir exhibited selectivity values > 170 (half-maximal cytotoxic concentration [CC_{50}]/EC_{50} against SARS-CoV-2 in HAE cells) in in vitro toxicity assays. Data from in vitro studies with liver cell culture systems demonstrated that human hepatocytes are susceptible to RDV-mediated toxicity, likely due to high cellular permeability and effective intracellular metabolism of the drug. While GS-704277 and GS-441524 are in vivo metabolites, and can be readily detected in plasma, these metabolites are unlikely to contribute significantly to changes in liver enzymes observed in humans treated with repeated doses of RDV, due to their low systemic exposure and minimal in vitro effects on hepatocytes. A relatively narrow in vitro cytotoxicity margin (ie, ratio of CC_{50} and clinical C_{max}), for a 200-mg IV infusion, of approximately 1-fold was determined for RDV in primary human hepatocytes following a 5-day incubation, which may be informative in further understanding the liver transaminase elevations observed in healthy human participants following multiple doses of RDV. It should be noted in this context that systemic clinical exposures to RDV concentrations within the range of the hepatocyte cytotoxicity margin are transient, lasting only for the duration of drug administration due to the rapid systemic clearance of RDV.

Molecular target screening studies with GS-441524 and GS-466547 (diastereomeric mixture) showed no significant binding (> 50%) at 10 μM (m2.6.3, Section 3.1, PC-399-2002 and PC-399-2001).

4.2. Clinical Virology

4.2.1. Sequence Analyses of SARS-CoV-2 from Clinical Isolates

Since SARS-CoV-2 emerged at the end of 2019, the number of infected cases has been growing exponentially through human-to-human transmission. This rapid spread of SARS-CoV-2 in the human population worldwide may result in viral diversification from the original common ancestor strain despite the proofreading activity provided by viral exoribonuclease nsp14. The genetic variation of nsp12 polymerase across circulating clinical isolates was assessed using publicly available SARS-CoV-2 sequences from the ongoing pandemic and evaluated the prevalence of amino acid substitutions in clinical isolates from December 2019 to March 2020. Specifically, the prevalence of substitutions at positions previously identified to cause reduced susceptibility to RDV was investigated.

4.2.1.1. SARS-CoV-2 Sequences

SARS-CoV-2 sequences were obtained from GISAID EpiCov database on 27 March 2020. These sequences were submitted to the database from 26 December 2019 through 27 March 2020 {Elbe 2017}. Sequences with ambiguous bases (N) were excluded or trimmed.

4.2.1.2. Sequence Alignment and Variant Analyses

Sequences were aligned to Wuhan-Hu-1 viral isolate (NC_ 045512) using the Mafft Multiple Sequence Aligner {Katoh 2003}. The nsp12 sequences were adjusted for the ribosomal slippage at nucleotide position 13468. Amino acid changes from reference Wuhan-Hu-1 viral isolate (NC_ 045512) were tabulated. Amino acid residues F476 and V553 of MHV nsp12 were identified to correspond to F480 and V557 SARS-CoV-2 nsp12, respectively {Agostini 2018}.

4.2.1.3. Characteristics of SARS-CoV-2 Clinical Isolates Analyzed

Similar to other betacoronaviruses, the genome of SARS-CoV-2 has a long ORF1ab polyprotein at the 5′ end encoding nonstructural proteins including nsp12 RdRp, followed by 4 major structural proteins, including the spike surface glycoprotein, small envelope protein, matrix protein, and nucleocapsid protein. To assess the genetic variation of nsp12, publicly available SARS-CoV-2 sequences from the ongoing pandemic were downloaded. A total of n = 1993 sequences with full or near-full genomes were selected and aligned to the reference strain Wuhan-Hu-1 viral isolate (NC_ 045512). The number of sequences obtained, and months and countries of sample collections are summarized in Table 8. The sequences were obtained from 52 countries and were mostly collected in February and March 2020.

Table 8. Number of SARS-CoV-2 Sequences Analyzed

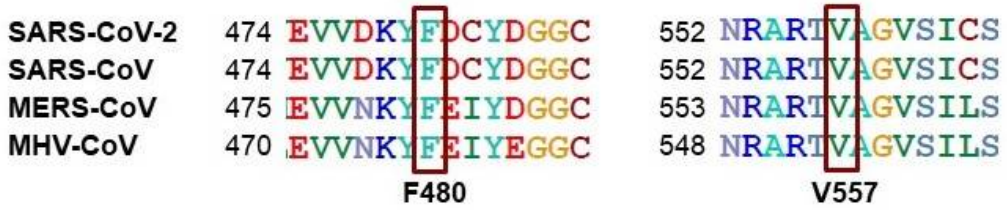
	December 2019	January 2020	February 2020	March 2020	Total[a]
USA	—	14	77	387	479
Iceland	—	—	1	322	323
China	17	108	105	1	231
Netherlands	—	—	8	163	186
UK	—	2	30	161	193
Japan	—	8	73	2	83
France	—	8	8	59	75
Australia	—	9	10	45	64
Belgium	—	—	2	42	44
Switzerland	—	—	21	10	31
Germany	—	1	11	14	26
Hong Kong	—	8	18	-	26
Other[b]	—	27	62	143	232
Total	17	185	426	1349	1993

CoV = coronavirus; SARS = severe acute respiratory syndrome; UK = United Kingdom; USA = United States of America
a N = 16 sequences did not have sample collection date available
b Other category included countries with less than 20 sequences and included the following countries: Brazil, Canada, Taiwan, Italy, Singapore, Finland, South Korea, Spain, Georgia, Luxembourg, Denmark, Malaysia, New Zealand, Norway, Chile, Congo, Ireland, Vietnam, Kuwait, Slovakia, Czech Republic, Saudi Arabia, Hungary, India, Portugal, Thailand, Cambodia, Colombia, Ecuador, Lithuania, Mexico, Nepal, Nigeria, Pakistan, Panama, Peru, Poland, Russia, South Africa, and Sweden
Source: PC-540-2006

4.2.1.4. Evaluation of Pre-existing Resistance to RDV in the SARS-CoV-2 Pandemic

Sequence alignments demonstrate that nsp12 of SARS-CoV-2 reference strain (Wuhan-Hu-1 viral isolate, NC_ 045512) exhibits 96% sequence identity with SARS-CoV, 71% with MERS-CoV, and 66% with MHV. The nsp12 amino acid substitutions in MHV associated with reduced susceptibility to RDV (F480 and V557) are also conserved across all these CoVs (Figure 4).

Figure 4. Conservation of F480 and V557 Residues in SARS-CoV-2 nsp12



CoV = coronavirus; MERS = Middle East respiratory syndrome; MHV = murine hepatitis virus; SARS = severe acute respiratory syndrome
Source: PC-540-2006

Among n = 1993 SARS-CoV-2 clinical isolates from December 2019 to March 2020 obtained from 52 countries, no amino acid substitutions were detected at the nsp12 residues F480 and V557 that are associated with reduced susceptibility to RDV in vitro (Table 9). This observation suggests a low probability of pre-existing resistance to RDV among circulating clinical isolates of SARS-CoV-2.

Table 9. Number of Substitutions Observed in SARS-CoV-2 Clinical Isolates at nsp12 Residues with In Vitro Resistance to RDV

SARS-CoV-2 nsp12 Amino Acid	Number of SARS-CoV-2 Isolates with Substitutions at the Residue per Number of Isolates Sequenced (n/N)
F480	0/1993
V557	0/1993

CoV = coronavirus; RDV = remdesivir (GS-5734™); SARS = severe acute respiratory syndrome
Source PC-540-2006

4.2.1.5. Identification of Amino Acid Substitutions at the Residues That Are Located in Close Proximity to the Binding Site of RDV

Available sequences of SARS-CoV-2 clinical isolates were also examined to identify amino acid substitutions at residues located in close proximity to the binding site of RDV. These residues were identified from the model of an elongating SARS-CoV-2 RdRp complex as previously described (PC-540-2005). In brief, a SARS-CoV-2 homology model was built based on the 3.1Å cryo-electron microscopy structure of the apo SARS-CoV RdRp complex, composed of the viral proteins nsp7, nsp8, and nsp12 (PDB 6NUR, {Kirchdoerfer 2019}. To this, primer and template RNA strands, catalytic Mg^{++} ions and an incoming RDV triphosphate (RDV-TP) were modeled. This structure was then used to identify amino acids in nsp12 that directly interact with the metal

ions or RDV-TP or may contribute to the inhibitor's delayed chain termination. No amino acid substitutions were observed at any of these identified residues in nsp12 that directly interact with the metal ions or RDV-TP or may contribute to the inhibitor's delayed chain termination (Table 10).

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 1 substitution (A547V) within 10Å of the active site was observed in 1 sequence of 1993 clinical isolates investigated.

Table 10. Amino Acid Residues Located in Close Proximity to the Active Site on SARS-CoV-2 nsp12 Polymerase

Category	SARS-CoV-2 nsp12 Amino Acid Residues	Number of SARS-CoV-2 Isolates with Substitutions at the Listed Residues per Number of Isolates Sequenced (n/N)
Residues that directly interact with the metal ions or RDV-TP or may contribute to the inhibitor's delayed chain termination		
Metal binding	D760, D761, D618	**0/1993**
Triphosphate interaction	R555, R553, K798, K621	**0/1993**
2' pocket	D623, T680, S682, N691	**0/1993**
1' pocket	T687, A688	**0/1993**
Base interaction	G683, K545	**0/1993**
Chain termination	S681, E857	**0/1993**
Other residues that are located within 5Å, 10Å of the active site and 7Å of primer C1'		
Residues within 5Å	545, 553, 555, 557, 618, 619, 620, 621, 622, 623, 624, 680, 682, 683, 687, 688, 691, 759, 760, 761, 798	**0/1993**
Residues within 10Å	166, 452, 455, 456, 458, 497, 543, 544, 545, 546, 547, 548, 549, 550, 551, 553, 554, 555, 556, 557, 558, 559, 560, 589, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 631, 662, 663, 676, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 757, 758, 759, 760, 761, 762, 786, 790, 792, 793, 794, 795, 798, 799, 811, 812, 813, 814, 836	**1/1993**[a]
Residues with 7Å of primer C1'	513, 593, 688, 691, 758, 759, 760, 761, 813, 814, 815, 836, 848, 853, 854, 857, 858, 859, 861, 862, 865	**0/1993**

CoV = coronavirus; RDV = remdesivir (GS-5734™); SARS = severe acute respiratory syndrome; TP = triphosphate
a A547V substitution was observed in clinical isolate from USA collected in March 2020
Source: PC-540-2006

4.2.1.6. Genetic Drift of nsp12 and Full Genome SARS-CoV-2 between December 2019 and March 2020

With only 1 amino acid substitution observed within 10Å of the active site of nsp12 SARS-CoV-2 clinical isolates, other amino acid substitutions within nsp12 and the overall genetic drift across full genome sequences at the nucleotide level were evaluated.

Amino acid substitutions in nsp12 were observed at other residues in 874/1993 (44%) clinical isolates. The most prevalent nsp12 substitution was P323L, which was observed in 812/1993 (41%) clinical isolates from 37 of 52 countries. All other variants were observed in less than 1% of clinical isolates each.

In addition, the number of nucleotide changes relative to the reference strain Wuhan-Hu-1 viral isolate (NC_ 045512) across the full genome for each clinical isolate was calculated. There were on average 8 nucleotide changes from the reference for 1993 SARS-CoV-2 clinical isolates from December 2019 to March 2020.

4.2.1.7. SARS-CoV-2 Sequence Analysis Conclusions

SARS-CoV-2 full genome sequences of 1993 clinical isolates from 52 countries collected between December 2019 and March 2020 were downloaded from public databases and compared. Sequence alignments of the nsp12 polymerases from SARS-CoV-2, SARS-CoV, MERS-CoV, and MHV demonstrate significant amino acid conservation across these CoVs. Among circulating clinical isolates of SARS-CoV-2, no amino acid substitutions were observed at the highly conserved nsp12 amino acid residues F480 and V557 previously shown to be associated with reduced susceptibility of CoVs to RDV in vitro or for any other residues that directly interact with the metal ions or RDV-TP or may contribute to the inhibitor's delayed chain termination. These data provide evidence supporting a lack of pre-existing resistance to RDV and high conservation of nsp12 among circulating SARS-CoV-2 clinical isolates.

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6. APPENDIX

6.1. Tabular Summary of Clinical Pharmacology Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-399-1812	To evaluate the safety and tolerability of single-ascending IV doses of RDV (solution formulation or lyophilized formulation) compared with placebo in healthy subjects To evaluate the PK of RDV and its metabolites, GS-704277 and/or GS-441524, following single-ascending IV doses of RDV in healthy subjects	Phase 1, blinded, randomized, placebo-controlled, first-in-human, single-ascending dose study	• Cohort 1: RDV 3 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 2: RDV 10 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 3: RDV 30 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 4: RDV 75 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 5: RDV 150 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 6: RDV 225 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 7: RDV 75 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 8: RDV 150 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 9: RDV 75 mg or placebo lyophilized formulation over 30 minutes as an IV infusion	1 day	Enrolled: 96 Completed: 96	Healthy adults	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-399-1954	To evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo To evaluate the PK of RDV and its metabolites following multiple IV doses of RDV	Phase 1, blinded, randomized, placebo-controlled, multiple-dose study	• Cohort 1: RDV 150 mg or placebo administered IV, QD • Cohort 2: RDV 150 mg or placebo administered IV, QD	Cohort 1: 7 days Cohort 2: 14 days	Enrolled: 24 Completed: 22	Healthy adults	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-399-4231	To determine the mass balance of RDV following administration of a single, IV dose of radiolabeled [^{14}C]-RDV	Phase 1, single-center, open-label, mass balance study	• Single dose of RDV 150 mg containing a mixture of both unlabeled and radiolabeled [^{14}C]-RDV administered via IV infusion over 0.5 hour on the morning of Day 1	1 day	Enrolled: 8 Completed: 8	Healthy male adults	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-399-5505	To evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo To evaluate the PK of RDV and its metabolites following multiple IV doses of RDV	Phase 1, blinded, randomized, placebo-controlled, multiple-dose study	• Cohort 1: RDV 200 mg or placebo administered IV, QD for the first day, followed by 100 mg RDV or placebo administrated IV QD, for 4 days • Cohort 2: RDV 200 mg or placebo administered IV, QD for the first day, followed by 100 mg RDV or placebo administrated IV QD, for 9 days • Cohort 3 (optional): RDV 200 mg or placebo administered IV, QD for the first day, followed by 100 mg RDV or placebo administrated IV QD, for up to 13 days. Cohort 3 was not enrolled.	Cohort 1: 5 days Cohort 2: 10 days Cohort 3: up to 14 days (not enrolled)	Enrolled: 36 Completed: 30	Healthy adults	Study completed; Final CSR

CSR = clinical study report; IV = intravenous; PK = pharmacokinetics; QD = once daily; RDV = remdesivir (GS-5734™);

6.2. Pharmacokinetic/Pharmacodynamic Ad Hoc Analyses

Additional outputs with numbering beginning with "Ad Req" present data from analyses that were not prespecified in a statistical analysis plan.

6.3. Tabular Summary of Applicable Nonclinical Studies

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No. (CRO Study No.)
Primary Pharmacodynamics					
In Vitro Antiviral Activity of Remdesivir against SARS-CoV-2 and SARS-CoV in Primary Human Airway Epithelial Cells	No	Primary HAE cell cultures infected with SARS-CoV-2 or SARS-CoV	In vitro	[redacted], USA	PC-540-2003
In Vitro Antiviral Activity of Remdesivir against SARS-CoV and SARS-CoV-2 in Huh7 Cells	No	Human transformed hepatocyte cell line (Huh7) cultures infected with SARS-CoV-2 or SARS-CoV	In vitro	[redacted], USA	PC-540-2002
In Vitro Antiviral Activity of Remdesivir against SARS-CoV-2 RNA-dependent RNA polymerase	No	In vitro biochemical enzyme activity assays	In vitro	[redacted], Canada	PC-540-2005
Efficacy of Remdesivir Treatment in the Rhesus Macaque Model of SARS-CoV-2	No	SARS-CoV-2-infected rhesus macaques	In vivo	[redacted], USA	PC-540-2004
Prophylactic Efficacy of 10 mg/kg Remdesivir (GS-5734) Treatment in the Rhesus Macaque Model of MERS-CoV Infection	No	MERS-CoV-infected rhesus macaques	In vivo	[redacted], USA	PC-399-2038

Type of Study/Description	GLP[a]	Test System	Method of Administration	Testing Facility	Gilead Study No. (CRO Study No.)
Secondary Pharmacodynamics					
Interaction of GS-443902, the Active Nucleoside Triphosphate Metabolite of Remdesivir, with Host RNA and DNA Polymerase Enzymes	No	In vitro biochemical enzyme activity assays	In vitro	Gilead Sciences, Foster City, California, USA	PC-399-2017
Molecular Target Screen of GS-441524	No	Human, rabbit, rat, hamster, guinea pig, pig, and mouse receptors	In vitro	[redacted], Taiwan, [redacted]	PC-399-2001 [redacted]
Molecular Target Screen of GS-466547	No	Human, rabbit, rat, hamster, guinea pig, pig, and mouse receptors	In vitro	[redacted], Taiwan, [redacted]	PC-399-2002 [redacted]
Distribution					
Repeat Dose Pharmacokinetics	No	Rhesus monkey	In vivo	[redacted], USA	AD-399-2030

CRO = contract research organization; GLP = Good Laboratory Practice; HAE = human airway epithelial; HEK = human embryonic kidney; Huh7 = human hepatoma cell line; IV = intravenous

a An entry of "Yes" indicates that the study includes a GLP or regulatory compliance statement.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.3—SUMMARY OF CLINICAL EFFICACY

REMDESIVIR
(GS-5734™)

Gilead Sciences

[redacted] **2020**

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTT	Adaptive COVID-19 Treatment Trial
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CSR	clinical study report
EC_{50}	half-maximal effective concentration
ECMO	extracorporeal membrane oxygenation
FAS	Full Analysis Set
Gilead	Gilead Sciences
HR	hazard ratio
IQR	interquartile range
ITT	intent-to-treat
IV	intravenous
KM	Kaplan-Meier
m	Module
MERS	Middle East respiratory syndrome
NIAID	National Institute of Allergy and Infectious Diseases
NIPPV	noninvasive positive pressure ventilation
OR	odds ratio
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
Q1	first quartile
Q3	third quartile
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
RRR	recovery rate ratio
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SD	standard deviation
SOC	standard of care
SpO_2	peripheral oxygen saturation
TEAE	treatment-emergent adverse event

TESAE	treatment-emergent serious adverse event
UK	United Kingdom
ULN	upper limit of normal
US, USA	United States, United States of America
WHO	World Health Organization

1. BACKGROUND AND OVERVIEW

1.1. Background

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei province, China {Huang 2020}. Sequencing analyses from respiratory tract samples of patients identified a novel coronavirus (CoV), which was named severe acute respiratory syndrome (SARS)-CoV-2 {Zhou 2020b}. Cases of the novel infectious disease caused by the SARS-CoV-2 virus, coronavirus disease 2019 (COVID-19), rapidly increased throughout the world. The situation is a major global health emergency, as evident by the International Health Regulations Emergency Committee of the World Health Organization declaration on 30 January 2020 that the SARS-CoV-2 outbreak constitutes a Public Health Emergency of International Concern {World Health Organization (WHO) 2020b}. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic {World Health Organization (WHO) 2020c}. As of 26 June 2020, a total of 9,473,214 confirmed cases and 484,249 associated deaths were reported worldwide, including 2,414,870 cases and 124,325 deaths in the United States (US) and 2,619,753 cases and 195,535 deaths in Europe {Centers for Disease Control and Prevention (CDC) 2020, World Health Organization (WHO) 2020a}.

Remdesivir (RDV, GS-5734™) is a novel antiviral treatment developed by Gilead Sciences (Gilead) that has been evaluated for the treatment of COVID-19. Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad-spectrum activity against members of the CoVs (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (eg, Ebola virus, Marburg virus), and paramyxoviruses (eg, respiratory syncytial virus, Nipah virus, Hendra virus).

Remdesivir exhibits potent in vitro and in vivo antiviral activity against SARS-CoV-2. Remdesivir showed potent in vitro activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells (half-maximal effective concentration [EC_{50}] = 0.0099 μM) and also potently inhibited a recombinant chimeric virus expressing the polymerase (nsp12) gene of SARS-CoV-2 in a backbone of SARS-CoV in Huh7 cells (EC_{50} = 0.0035 μM). In SARS-CoV-2-infected rhesus monkeys, administration of RDV (10 mg/kg for the first dose, followed by 5 mg/kg once daily thereafter) using intravenous (IV) bolus injection initiated 12 hours postinoculation of SARS-CoV-2 resulted in a significant reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals.

On 01 May 2020, based on early data from clinical studies, the US Food and Drug Administration issued an emergency use authorization for RDV for the treatment of COVID-19 in patients with severe disease, on the basis that RDV may be effective in treating COVID-19 and given the available information supporting the benefit-risk profile of RDV for use in this population {U. S. Food and Drug Administration (FDA) 2020}.

Remdesivir has demonstrated safety and efficacy for the treatment of COVID-19 through clinical evaluation at the proposed dosing regimen, as described in this dossier. Remdesivir was first approved by the Japanese Pharmaceuticals and Medical Devices Agency on 07 May 2020 for the treatment of patients with severe COVID-19 and has since been approved in a number of additional territories globally.

1.2. Overview of Clinical Efficacy

1.2.1. Primary Studies Supporting the Clinical Efficacy of Remdesivir

The proposed indication for RDV is primarily based on results from a National Institute of Allergy and Infectious Diseases (NIAID)–sponsored Phase 3 study in hospitalized participants with COVID-19 (Study CO-US-540-5776; Adaptive COVID-19 Treatment Trial [ACTT]-1); Part A (Day 28) of a Gilead-sponsored Phase 3 study in participants with severe COVID-19 (Study GS-US-540-5773); and Part A (Day 11) of a Gilead-sponsored Phase 3 study in participants with moderate COVID-19 (Study GS-US-540-5774). Information on the study designs and populations for these studies is presented in Table 1.

Table 1. Overview of Primary Studies Supporting the Clinical Efficacy of Remdesivir

Study	Study Design	Treatment Regimen	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
CO-US-540-5776 (ACTT-1) {Beigel 2020}	Phase 3, adaptive, randomized, double-blind, placebo-controlled, multicenter study to evaluate available investigational treatments for COVID-19, including RDV (sponsored by NIAID)	• Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg once daily for a total of up to 10 days • Treatment Group 2: continued SOC therapy together with placebo to match	RDV 10-day: N = 531 Placebo: N = 517	Adult participants hospitalized with COVID-19 Efficacy and safety data through 28 April 2020	Section 2.1.1 CO-US-540-5776 Preliminary CSR
GS-US-540-5773 {Goldman 2020}	Phase 3, randomized, open-label, multicenter study conducted in 2 parts: Part A, a randomized, open-label, multicenter part; Part B, a 2-group, multicenter part	• Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10	RDV 5-day: N = 200 RDV 10-day: N = 197	Participants with severe COVID-19 who were hospitalized; participants in Part A were not to be mechanically ventilated at screening Final efficacy and safety data for Part A	Section 2.1.2 GS-US-540-5773 Interim (Final Part A) CSR

Study	Study Design	Treatment Regimen	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
GS-US-540-5774	Phase 3, randomized, open-label study conducted in 2 parts: Part A, a randomized, open-label, multicenter part; Part B, a single-group, multicenter part	• Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Treatment Group 3: continued SOC therapy	RDV 5-day: N = 191 RDV 10-day: N = 193 SOC only: N = 200[b]	Participants with moderate COVID-19 who were hospitalized Efficacy and safety data through Day 11 of Part A	Section 2.1.3 GS-US-540-5774 Interim 1 (Part A Day 11) CSR

a Participants who received at least 1 dose of study treatment.
b Participants who completed the protocol-specified Day 1 visit.

Study CO-US-540-5776 is an ongoing Phase 3, adaptive, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of RDV versus placebo in hospitalized adult participants with COVID-19. Eligible participants were male or nonpregnant female adults aged ≥ 18 years who had been admitted to the hospital with symptoms suggestive of COVID-19, had laboratory-confirmed SARS-CoV-2 infection, and had illness of any duration and at least 1 of the following: radiographic infiltrates by imaging (chest x-ray, computed tomography scan, etc), peripheral oxygen saturation (SpO_2) ≤ 94% on room air, requirement for supplemental oxygen, or requirement for mechanical ventilation. Participants with evidence of severe hepatic impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 5 × the upper limit of normal [ULN]) or severe renal impairment (estimated glomerular filtration rate < 30 mL/min, including participants receiving hemodialysis or hemofiltration) were excluded. Randomization was stratified by site and disease severity (mild-to-moderate versus severe). Severe disease was defined as requiring mechanical ventilation, requiring oxygen, having SpO_2 ≤ 94% on room air, or having tachypnea (respiratory rate ≥ 24 breaths/minute). Mild-to-moderate disease was defined as having SpO_2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen.

This summary document provides the results of the preliminary analyses of data from participants randomized to either RDV or placebo as of the 28 April 2020 data cut date, at which point the prespecified number of recoveries was achieved for the purposes of the primary analysis.

Study GS-US-540-5773 is an ongoing Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of 5- and 10-day regimens of RDV in participants with severe COVID-19. Eligible participants were males or nonpregnant females aged ≥ 18 years or aged ≥ 12 and < 18 years and weighing ≥ 40 kg who had polymerase chain reaction (PCR)–confirmed SARS-CoV-2 infection, were hospitalized with SpO_2 ≤ 94% on room air or required supplemental oxygen, and had radiographic evidence of pulmonary infiltrates. Participants who had evidence of severe hepatic impairment (ALT or AST > 5 × ULN) or creatinine clearance (CrCl) < 50 mL/min were excluded. Participants in Part A must not have been mechanically ventilated at screening.

Study GS-US-540-5774 is an ongoing Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of 5- and 10-day regimens of RDV compared with standard of care (SOC) alone in participants with moderate COVID-19. Eligible participants were males or nonpregnant females aged ≥ 18 years or aged ≥ 12 and < 18 years and weighing ≥ 40 kg who had PCR-confirmed SARS-CoV-2 infection, were hospitalized with SpO_2 > 94% on room air, and had radiographic evidence of pulmonary infiltrates. Participants who had evidence of severe hepatic impairment (ALT or AST > 5 × ULN) or CrCl < 50 mL/min were excluded.

This summary document provides the final results for Part A (Day 28) for Study GS-US-540-5773 and the results from the primary analysis of Part A (Day 11) for Study GS-US-540-5774.

1.2.1.1. Efficacy Endpoints

The primary efficacy endpoint for Study CO-US-540-5776 was time to recovery, defined as the elapsed time from randomization to the earliest day on which a participant was discharged or achieved a clinical status of recovery. The study was powered to detect a 40% increase in the rate of recovery from RDV across the population of all eligible participants. The key secondary efficacy endpoint was the distribution of clinical status (8-point ordinal scale) on Day 15. The secondary efficacy endpoint of 14-day mortality was also analyzed for this preliminary analysis.

The primary efficacy endpoint for Studies GS-US-540-5773 and GS-US-540-5774 was clinical status assessed by a 7-point ordinal scale on Day 14 (Study GS-US-540-5773) or Day 11 (Study GS-US-540-5774). Study GS-US-540-5773 was powered to detect an odds ratio (OR) of 1.75, indicating an improvement in clinical status comparing 10 days versus 5 days of RDV treatment, while Study GS-US-540-5774 was powered to detect an OR of 1.8, indicating an improvement in clinical status comparing 10 days or 5 days of RDV treatment versus SOC. Other efficacy endpoints of interest presented for Studies GS-US-540-5773 and GS-US-540-5774 in this summary document include recovery, all-cause mortality, shift in oxygen support status, and clinical improvement.

The ordinal scale is an assessment of the clinical status of a participant on a given study day (Table 2). The 7-point ordinal scale utilized for Studies GS-US-540-5773 and GS-US-540-5774 was similar to the 8-point ordinal scale used for Study CO-US-540-5776 except that the scale was reversed, with death defined as an ordinal score of 1, and with no distinction between nonhospitalized participants with limitations on activities versus those without limitations on activities. On the 7-point ordinal scale, recovery was defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7 or an improvement from a baseline score of 6 to a score of 7. On the 8-point ordinal scale, recovery was defined as an improvement from a baseline score of 4 through 7 to a score of 1, 2, or 3.

Table 2. Ordinal Scales (7- and 8-Point)

7-Point Ordinal Scale (Studies GS-US-540-5773 and GS-US-540-5774)	8-Point Ordinal Scale (Study CO-US-540-5776)
1. Death	8. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO	7. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices	6. Hospitalized, on noninvasive ventilation or high-flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen	5. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care (other than per-protocol RDV administration)	3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care
7. Not hospitalized	2. Not hospitalized, limitation on activities and/or requiring home oxygen
	1. Not hospitalized, no limitations on activities

Statistical methods are presented in the clinical study report (CSR) for Study CO-US-540-5776 (CO-US-540-5776 Preliminary CSR, Section 7.7) and in the statistical analysis plans for Studies GS-US-540-5773 and GS-US-540-5774 (GS-US-540-5773 Interim [Final Part A] CSR, Appendix 16.1.9; GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Appendix 16.1.9).

1.2.2. Other Data Supporting the Clinical Efficacy of Remdesivir

Supportive efficacy data are provided from an investigator-sponsored Phase 3 study conducted in China in adult participants with severe COVID-19 (Study CO-US-540-5758) and from a cohort of adult patients with confirmed COVID-19 who were treated with RDV under the single-patient compassionate use program (Study IN-US-540-5755) (Table 3).

Table 3. Overview of Other Data Supporting the Clinical Efficacy of Remdesivir

Study	Design	Treatment Regimen	Number of Patients or Participants by Treatment Regimen	Patient or Participant Population and Data Presented	Location of Narrative and Report
CO-US-540-5758	Phase 3, randomized, double-blind, placebo-controlled, multicenter study (sponsored by investigator)	Single loading dose of IV RDV 200 mg or placebo on Day 1, followed by once-daily maintenance doses of IV RDV 100 mg or placebo for 9 days	RDV: N = 155[a] Placebo: N = 78[a]	Hospitalized patients with severe COVID-19 Available efficacy and safety data as of the data cutoff date, as study was stopped prematurely because of the control of the outbreak in Wuhan and on the basis of the termination criteria specified in the protocol	Section 2.2.1 {Wang 2020}
IN-US-540-5755[b]	Single-patient compassionate use	Single loading dose of IV RDV 200 mg on Day 1, followed by once-daily maintenance doses of IV RDV 100 mg for up to 9 days	RDV: N = 163[c]	Patients with PCR-confirmed COVID-19 who were hospitalized with substantial clinical symptoms where the benefits of treatment with an investigational agent outweighed the risks Efficacy and safety data from 163 patients through [redacted] 20[redacted]	Section 2.2.2 IN-US-540-5755 Interim 1 Summary Report

a Participants who received at least 1 dose of study treatment
b As of [redacted] 20[redacted], Study IN-US-540-5755 shifted from an investigator-sponsored single-patient compassionate use program to a Gilead-sponsored expanded access program (Study GS-US-540-5821; NCT04323761/2020-001453-49) to accelerate the emergency use of RDV for severely ill adult patients. The single-patient compassionate use program (Study IN-US-540-5755) is currently accepting pediatric patients < 18 years of age and pregnant women with confirmed COVID-19.
c Patients who received at least 1 dose of RDV on or prior to [redacted] 20[redacted] through the compassionate use program, per data entered in electronic case report forms as of 10:00 AM Pacific Daylight Time on [redacted] 20[redacted].

Supportive efficacy data are provided from an investigator-sponsored Phase 3, randomized, double-blind, placebo-controlled, multicenter study of RDV in participants with severe COVID-19 in Wuhan, Hubei, China, which was stopped prematurely because there were no new cases of COVID-19 at the study sites (Study CO-US-540-5758) {Wang 2020}. Eligible participants were males or nonpregnant females aged ≥ 18 years who were admitted to the hospital with laboratory-confirmed SARS-CoV-2 infection, had pneumonia confirmed by chest imaging, had $SpO_2 \leq 94\%$ on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg, and were within 12 days of symptom onset. The primary efficacy endpoint was time to clinical improvement. Secondary efficacy endpoints presented for Study CO-US-540-5758 in this summary document are duration of invasive mechanical ventilation and Day 28 mortality.

Access to RDV for the treatment of COVID-19 was also available through investigator-sponsored single-patient protocols under a compassionate use program (Study IN-US-540-5755). The details of each individual clinical case were provided by the treating physician. Patients who had COVID-19 confirmed by PCR, required oxygen support, and were hospitalized with substantial clinical symptoms where the benefits of treatment with an investigational agent outweighed the risks were eligible to participate in the program. Patients who had evidence of severe renal impairment (CrCl < 30 mL/min) or hepatic impairment (ALT > 5 × ULN) were excluded. Efficacy data from Study IN-US-540-5755 are presented in this summary, including overall mortality and live discharge.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. Primary Studies Supporting the Clinical Efficacy of Remdesivir

2.1.1. Study CO-US-540-5776

Location:	CO-US-540-5776 Preliminary CSR
Title:	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults
Primary and Key Secondary Objectives:	The primary objective of this study was as follows: • To evaluate the clinical efficacy, as assessed by time to recovery, of RDV compared with the control arm in adults hospitalized with COVID-19 The key secondary objective of this study was as follows: • To evaluate the clinical efficacy of RDV relative to the control arm in adults hospitalized with COVID-19 according to clinical status (8-point ordinal scale) at Day 15
Study Design and Participant Population:	This is an ongoing Phase 3, adaptive, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. The first novel therapeutic agent tested in this study was RDV, with placebo as the comparator. Participants were randomized in a 1:1 ratio to receive either active product or placebo. The study initially had 2 treatment groups: • RDV 10-day group: RDV was administered as a 200-mg IV loading dose on Day 1, followed by a 100-mg once-daily IV maintenance dose while hospitalized for up to a 10-day total course. If a participant was no longer hospitalized, then infusions were no longer administered. — The total course was not to exceed 10 calendar days even if an infusion was missed. • Placebo group: a matching placebo was given at an equal volume at the same schedule. Randomization was stratified by site and disease severity (mild-to-moderate versus severe). Eligible participants were male and nonpregnant female adults aged ≥ 18 years who had been admitted to the hospital with symptoms suggestive of COVID-19, had laboratory-confirmed SARS-CoV-2 infection, and had illness of any duration and at least 1 of the following: radiographic infiltrates by imaging (chest x-ray, computed tomography scan, etc), $SpO_2 \leq 94\%$ on room air, requirement for supplemental oxygen, or requirement for mechanical ventilation. Participants with evidence of severe hepatic impairment (ALT or AST > 5 × ULN) or severe renal impairment (estimated glomerular filtration rate < 30 mL/min, including participants receiving hemodialysis or hemofiltration) were excluded. The preliminary CSR describes the results of the preliminary analyses of efficacy and safety data from participants randomized to either RDV or placebo as of the 28 April 2020 data cut date, at which point the prespecified number of recoveries was achieved for the purposes of the primary analysis. A total of 1107 participants were screened for this study, of whom 1062 were randomized, and 1048 received at least 1 dose of study treatment. A total of 14 randomized participants did not receive study treatment due to not meeting the eligibility criteria or withdrawal of consent. A total of 408 participants (RDV 10-day group 201 participants; placebo group 207 participants) received all 10 doses of study treatment, and 592 participants (RDV 10-day group 310 participants; placebo group 282 participants) received < 10 doses of study treatment. The most common reasons for receiving < 10 doses of study treatment were recovery (RDV 10-day group 163 participants; placebo group 118 participants), intermittent missed doses (RDV 10-day group 80 participants; placebo group 82 participants), and discontinuation of

	study product due to adverse event (AE) or serious adverse event (SAE) other than death (RDV 10-day group 36 participants; placebo group 36 participants). As of the 28 April 2020 data cut, a total of 412 participants in the RDV 10-day group and 362 participants in the placebo group had completed the study through Day 29, recovered, or died. A total of 15 participants (RDV 10-day group 9 participants; placebo group 6 participants) discontinued the study before Day 29. A total of 110 participants in the RDV 10-day group and 149 participants in the placebo group had not recovered and had not completed the Day 29 follow-up visit. Demographics and baseline characteristics were similar between the 2 treatment groups. The majority of participants in the study were male (64.4%). The mean (SD) age was 58.9 (15.0) years; the majority of participants were white (53.3%), and 23.5% were Hispanic or Latino. Most participants (89.5%, 950 of 1062 participants) were in the severe disease stratum. The median number of days between symptom onset and randomization was 9 days for both the RDV 10-day and placebo groups. Baseline clinical status (8-point ordinal scale) was similar between the 2 treatment groups. A total of 282 participants (26.6%) had a clinical status of 7 (hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO]), 200 participants (18.8%) had a clinical status of 6 (hospitalized, on noninvasive ventilation or high-flow oxygen devices), 434 participants (40.9%) had a clinical status of 5 (hospitalized, requiring supplemental oxygen), and 135 participants (12.7%) had a clinical status of 4 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise]).
Summary of Results and Conclusions:	• Remdesivir administered for up to 10 days to hospitalized adult participants with COVID-19 resulted in significantly shorter times to recovery, as well as better odds of clinical improvement compared with those in the placebo group. — A statistically significant shorter median time to recovery was observed for participants in the RDV 10-day group (10 days [95% CI: 9 to 11]) compared with those in the placebo group (14 days [95% CI: 12 to 17]) (recovery rate ratio [RRR] 1.31; 95% CI: 1.12 to 1.53; $p < 0.001$). — The odds of improvement in the ordinal score at Day 15 were significantly higher in the RDV 10-day group compared with the placebo group (OR for improvement 1.46; 95% CI: 1.15 to 1.86; $p = 0.002$). Higher proportions of Day 15 ordinal scores of 1, 2, and 3 were observed in participants in the RDV 10-day group compared with the placebo group. • The risk of death at 14 days was numerically lower (by 27%) in the RDV 10-day group compared with the placebo group (hazard ratio [HR] 0.73; 95% CI: 0.50 to 1.07). • Remdesivir was safe and well tolerated, with a safety profile similar to placebo, in hospitalized participants with COVID-19. — The incidence and types of common AEs were generally similar between the 2 treatment groups. Similar percentages of participants in the RDV 10-day and placebo groups had nonserious Grade 3 or 4 AEs (29.9% versus 32.9%, respectively) or SAEs (21.1% versus 26.9%, respectively).

2.1.2. Study GS-US-540-5773

Location:	GS-US-540-5773 Interim (Final Part A) CSR
Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Primary Objective:	To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14
Study Design and Participant Population:	This Phase 3 study of RDV therapy in participants with severe COVID-19 is being conducted in 2 parts. Part A of this study was a randomized, open-label, multicenter study of RDV in participants with severe COVID-19. Part B is a 2-group, multicenter study of RDV in participants with severe COVID-19. In Part A, participants who met all eligibility criteria and who were not mechanically ventilated were randomized in a 1:1 ratio into 1 of the following 2 treatment groups: • Treatment Group 1 (hereafter referred to as the RDV 5-day group): continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2 (hereafter referred to as the RDV 10-day group): continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Part B enrolled participants on mechanical ventilation and, after enrollment to Part A was complete, any additional participants. In Part B, participants who met all of the eligibility criteria were assigned, based on whether they were mechanically ventilated at enrollment, to receive the following: • Mechanically Ventilated Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Eligible participants were males or nonpregnant females aged ≥ 18 years or aged ≥ 12 and < 18 years and weighing ≥ 40 kg who had PCR-confirmed SARS-CoV-2 infection, were hospitalized with $SpO_2 \leq 94\%$ on room air or required supplemental oxygen, and had radiographic evidence of pulmonary infiltrates. Participants who had evidence of severe hepatic impairment (ALT or AST > 5 × ULN) or CrCl < 50 mL/min were excluded. Participants in Part A must not have been mechanically ventilated at screening. The interim CSR provides the final results for participants in Part A. All data for Part A collected by the data finalization date ([redacted] 20[redacted]) were included in this interim analysis. A total of 407 participants were screened, of whom 401 were randomized, and 397 received at least 1 dose of study treatment in Part A of the study. Four randomized participants did not receive any study treatment (2 were enrolled in violation of the study protocol, 1 withdrew consent, and 1 was withdrawn due to investigator's discretion). Of the 397 participants treated in Part A, 35.0% of participants (139 participants) prematurely discontinued study treatment (RDV 5-day group 14.0%, 28 participants; RDV 10-day group 56.3%, 111 participants), and 16.4% of participants (65 participants) prematurely discontinued from the study (RDV 5-day group 16.0%, 32 participants; RDV 10-day group 16.8%, 33 participants). The most common reasons for premature discontinuation of study treatment were hospital discharge (RDV 5-day group 8.0%, 16 participants; RDV 10-day group 34.0%, 67 participants), AE (RDV 5-day group 4.5%, 9 participants; RDV 10-day group 11.2%, 22 participants), and death (RDV 5-day group 0 participants; RDV 10-day group 6.1%, 12 participants).

	Demographic and baseline characteristics were similar between the 2 treatment groups. The majority of the participants in the Safety Analysis Set were male (63.7%). The median age was 61 years (range: 20 to 98); the majority of participants were white (75.0%), and the majority were not Hispanic or Latino (78.0%). Although treatment groups were balanced in demographics, they were not balanced in baseline disease characteristics. A better (higher score) baseline clinical status was observed in participants in the RDV 5-day group compared with those in the RDV 10-day group; this difference was statistically significant (p = 0.0230). There were also statistically significant differences between the treatment groups in baseline oxygen support status, which was derived from the 7-point ordinal scale used to assess clinical status, with better status in the RDV 5-day group compared with the RDV 10-day group (p = 0.0175). The median duration of symptoms prior to first dose of RDV (9 days) and the median duration of hospitalization prior to first dose of RDV (2 days) were similar between the treatment groups.
Summary of Results and Conclusions:	• Remdesivir administered for 5 days or 10 days to participants with severe COVID-19 resulted in similar improvements in clinical status at Day 14, as assessed by a 7-point ordinal scale, after adjustment for imbalances in baseline clinical status (p = 0.1563). • Patients on invasive mechanical ventilation may benefit from a treatment duration longer than 5 days. — Treatment with RDV beyond 5 days among participants on invasive mechanical ventilation on Day 5 appeared to be associated with improvement in oxygen support status and fewer deaths at Day 14. For participants who were on invasive mechanical ventilation or ECMO on Day 5, those in the RDV 10-day group appeared to have better outcomes than those in the RDV 5-day group. A lower proportion of participants in the RDV 10-day group than the RDV 5-day group died on or before Day 14 (7 of 41 participants [17.1%] versus 10 of 25 participants [40.0%], respectively), and a higher proportion had improvements in oxygen support status on Day 14 (11 participants [26.8%] versus 5 participants [20.0%], respectively). • Remdesivir administered for 5 days or 10 days was generally safe and well tolerated in participants with severe COVID-19. — Similar percentages of participants in the RDV 5-day and 10-day groups had AEs during the study (RDV 5-day group 71.5%, 143 of 200 participants; RDV 10-day group 75.1%, 148 of 197 participants). The incidence and types of common AEs reported were generally similar between the 2 treatment groups, with the exception of a lower frequency of acute kidney injury in the RDV 5-day group compared with the RDV 10-day group (RDV 5-day group 2.0%, 4 participants; RDV 10-day group 8.1%, 16 participants). The most commonly reported AEs were nausea, constipation, and acute respiratory failure in the RDV 5-day group and acute respiratory failure, nausea, and acute kidney injury in the RDV 10-day group. Overall, there was no identifiable difference in safety between the RDV 5-day and 10-day groups, and safety outcomes were consistent with underlying severe COVID-19.

2.1.3. Study GS-US-540-5774

Location:	GS-US-540-5774 Interim 1 (Part A Day 11) CSR
Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment
Primary Objective:	To evaluate the efficacy of 2 RDV regimens compared to SOC with respect to clinical status assessed by a 7-point ordinal scale on Day 11
Study Design and Participant Population:	This Phase 3 study of RDV therapy in participants with moderate COVID-19 is being conducted in 2 parts. Part A of this study was a randomized, open-label, multicenter study of RDV in participants with moderate COVID-19. Part B is a single-group, multicenter study of RDV in participants with moderate COVID-19. In Part A, participants who met all eligibility criteria were randomized in a 1:1:1 ratio into 1 of the following 3 treatment groups: • Treatment Group 1 (hereafter referred to as the RDV 5-day group): continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2 (hereafter referred to as the RDV 10-day group): continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Treatment Group 3 (hereafter referred to as the SOC only group): continued SOC therapy Part B enrolled participants meeting eligibility criteria (Extension Treatment Group) after enrollment to Part A was complete. In Part B, participants who met all of the eligibility criteria were assigned to receive the following: • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1, followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Eligible participants were males or nonpregnant females aged ≥ 18 years or aged ≥ 12 and < 18 years and weighing ≥ 40 kg who had PCR-confirmed SARS-CoV-2 infection, were hospitalized with SpO_2 > 94% on room air, and had radiographic evidence of pulmonary infiltrates. Participants who had evidence of severe hepatic impairment (ALT or AST > 5 × ULN) or CrCl < 50 mL/min were excluded. The interim CSR provides the results for participants in Part A through Day 11. All data for Part A collected by the data finalization date ([redacted] 20[redacted]) were included in this interim analysis. A total of 612 participants were screened, of whom 596 were randomized, 384 received at least 1 dose of study treatment (RDV groups: RDV 5-day group 191 participants; RDV 10-day group 193 participants), and 200 completed the protocol-specified Day 1 visit (SOC only group) in Part A of the study. Twelve randomized participants did not receive study treatment (8 withdrew consent, 3 were enrolled in violation of the study protocol, and 1 was withdrawn due to investigator's discretion). Of the 384 participants treated with RDV in Part A, 24.1% of participants (46 participants) prematurely discontinued study treatment in the RDV 5-day group, and 62.2% of participants (120 participants) prematurely discontinued study treatment in the RDV 10-day group. Of the 584 participants in the Safety Analysis Set, 7.9% of participants (46 participants) prematurely discontinued from the study (RDV 5-day group 6.3%, 12 participants; RDV 10-day group 8.3%, 16 participants; SOC only group 9.0%, 18 participants), and 53.1% of participants (310 participants) were still in the study at the data cut date (RDV 5-day group 53.9%, 103 participants; RDV 10-day group 52.8%, 102 participants; SOC only group 52.5%, 105 participants). The most common reasons for premature discontinuation of study treatment

	were hospital discharge (RDV 5-day group 18.3%, 35 participants; RDV 10-day group 50.8%, 98 participants), subject decision (RDV 5-day group 2.6%, 5 participants; RDV 10-day group 3.6%, 7 participants), and AE (RDV 5-day group 2.1%, 4 participants; RDV 10-day group 3.6%, 7 participants). Participants in the SOC only group were not receiving RDV and could not prematurely discontinue study treatment. Demographic and baseline characteristics were similar between the 3 treatment groups. The majority of the participants in the Safety Analysis Set were male (61.1%). The median age was 57 years (range: 12 to 95); the majority of participants were white (61.3%), and the majority were not Hispanic or Latino (81.9%). Treatment groups were balanced in other baseline disease characteristics. There were no statistically significant differences in baseline clinical status (7-point ordinal scale) between the treatment groups. There were also no statistically significant differences between the treatment groups in baseline oxygen support status derived from the 7-point ordinal scale used to assess clinical status. Most participants were on room air (not requiring oxygen support) across all treatment groups (RDV 5-day group 83.8%, 160 participants; RDV 10-day group 87.6%, 169 participants; SOC only group 81.0%, 162 participants). The median duration of symptoms prior to first dose of RDV (8 days) (or Study Day 1 for the SOC only group [9 days]) and the median duration of hospitalization prior to first dose of RDV (2 days) (or Study Day 1 for the SOC only group [2 days]) were similar across treatment groups.
Summary of Results and Conclusions:	• Remdesivir administered for 5 days to participants with moderate COVID-19 resulted in significantly better odds of improvement in clinical status at Day 11, as assessed by a 7-point ordinal scale, compared with those who received only SOC treatment ($p = 0.0174$). — After excluding participants on oxygen support at baseline, odds of improved clinical status on Day 11 were greater in the RDV 5-day group versus the SOC only group ($p = 0.0483$). • Remdesivir administered for 5 days or 10 days was generally safe and well tolerated, with a similar safety profile as SOC in participants with moderate COVID-19. — Numerically higher percentages of participants in the RDV 5-day and 10-day groups had AEs during the study compared with the SOC only group (RDV 5-day group 50.8%, 97 of 191 participants; RDV 10-day group 54.9%, 106 of 193 participants; SOC only group 45.0%, 90 of 200 participants). The incidence and types of common AEs were generally similar between treatment groups, except for nausea, which was reported in higher percentages of participants in the RDV 5-day and 10-day groups compared with the SOC only group (RDV 5-day group 9.9%, 19 participants; RDV 10-day group 9.3%, 18 participants; SOC only group 3.0%, 6 participants). The most commonly reported AEs were nausea, diarrhea, and headache in the RDV 5-day group; nausea, hypokalemia, diarrhea, and headache in the RDV 10-day group; and diarrhea, constipation, pyrexia, and insomnia in the SOC only group.

2.2. Other Data Supporting the Clinical Efficacy of Remdesivir

2.2.1. Study CO-US-540-5758

Location:	{Wang 2020}
Title:	Remdesivir in Adults with Severe COVID-19: A Randomised, Double-Blind, Placebo-Controlled, Multicentre Trial. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Lancet 2020; 395(10236):1569-78
Primary Objective:	To evaluate the efficacy and safety of RDV in hospitalized adult participants with severe COVID-19
Study Design and Participant Population:	This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of RDV in hospitalized adult participants with severe COVID-19. Eligible participants were randomized in a 2:1 ratio to receive either IV RDV (200 mg on Day 1 followed by 100 mg on Days 2 through 10 in single daily infusions) or the same volume of placebo infusions for a total of 10 days. Randomization was stratified by level of oxygen support (no oxygen support or oxygen support with nasal duct or mask; or high-flow oxygen, noninvasive ventilation, invasive ventilation, or ECMO). Eligible participants were males or nonpregnant females aged ≥ 18 years who were admitted to the hospital with laboratory-confirmed SARS-CoV-2 infection, had pneumonia confirmed by chest imaging, had $SpO_2 \leq 94\%$ on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 300 mm Hg, and were within 12 days of symptom onset. Available efficacy and safety data as of the data cutoff date are summarized, as the study was stopped prematurely due to control of the outbreak in Wuhan and on the basis of the termination criteria specified in the protocol. Of the 255 participants screened, 237 participants were randomized to study treatment (RDV group 158 participants; placebo group 79 participants). Three participants in the RDV group did not start their assigned treatment, and 1 participant in the placebo group did not receive study treatment due to withdrawal of consent. Five participants in the RDV group and 2 participants in the placebo group received study treatment for < 5 days. Demographic and baseline characteristics were similar between the 2 treatment groups. Overall, the majority of participants were male (59%), and the median age was 65 years (interquartile range [IQR]: 56 to 71). The majority of participants were in category 3 of the 6-point ordinal scale of clinical status at baseline (hospital admission, requiring supplemental oxygen); however, a higher proportion of participants in the RDV group required higher levels of oxygen support at baseline compared with the placebo group (28 of 158 participants [18%] versus 10 of 78 participants [13%], respectively). Median time from symptom onset to starting study treatment was 10 days (IQR: 9 to 12), and the proportion of participants who started treatment > 10 days after symptom onset was numerically higher in the RDV group compared with the placebo group (84 of 155 participants [54%] versus 31 of 78 participants [40%], respectively).

Summary of Results and Conclusions:	• Because there were no new cases of COVID-19 at the study sites, the study was stopped prematurely with a total of only 148 events of clinical improvement. Because the study was underpowered and utilized a 2:1 randomization, it was unable to demonstrate any statistically significant clinical benefits of RDV. The time to clinical improvement was numerically shorter in the RDV group compared with the placebo group. • In the context of COVID-19, the safety profile of RDV was similar to that of placebo. • Adverse events were reported in 66% of participants (102 of 155 participants) in the RDV group and 64% of participants (50 of 78 participants) in the placebo group. Grade 3 or 4 AEs were reported in 8% of participants (13 participants) in the RDV group and 14% of participants (11 participants) in the placebo group. The most common Grade 3 or 4 AEs (reported in > 1% of participants in either treatment group) were thrombocytopenia (RDV group 3%; placebo group 4%) and anemia (RDV group 1%; placebo group 3%). • Serious adverse events were reported in 18% of participants (28 participants) in the RDV group and 26% of participants (20 participants) in the placebo group. The most common SAEs (reported in > 1% of participants in either treatment group) were respiratory failure or acute respiratory distress syndrome (RDV group 10%; placebo group 5%), cardiopulmonary failure (RDV group 5%; placebo group 9%), and multiple organ dysfunction syndrome (RDV group 1%; placebo group 3%). • More participants in the RDV group than the placebo group discontinued study treatment due to AEs (RDV group 12%; placebo group 5%). The most common AEs leading to study treatment discontinuation (reported in > 1% of participants in either treatment group) were secondary infection (RDV group 3%; placebo group 9%), respiratory failure or acute respiratory distress syndrome (RDV group 5%; placebo group 1%), and cardiopulmonary failure (RDV group 2%; placebo group 1%). (Note the error carried over from {Wang 2020}: the percentage of placebo-treated participants who discontinued study treatment due to secondary infection [9%] is higher than the total percentage of placebo-treated participants who discontinued study treatment due to any AE [5%]). • All deaths during the observation period were judged by the site investigators to be unrelated to study treatment.

2.2.2. Study IN-US-540-5755

Location:	IN-US-540-5755 Interim 1 Summary Report
Title:	Summary of Single-Patient Compassionate Use: Remdesivir (RDV; GS-5734™) for the Treatment of Selected Coronavirus (CoV) Infection: Single Patient Protocol
Primary Objective:	To provide RDV for single-patient compassionate use for the treatment of COVID-19
Study Design and Patient Population:	In the US, single-patient compassionate use requests were fulfilled under investigator-sponsored, single-patient emergency investigational new drug applications. Outside of the US, these requests were fulfilled in accordance with the applicable compassionate use mechanism available in that country. Adult patients received a single loading dose of IV RDV 200 mg (infused over 30 to 120 minutes) on Day 1 followed by once-daily maintenance doses of IV RDV 100 mg (infused over 30 to 120 minutes) for up to 9 days. Each case was assessed individually based on complete medical history and COVID-19 status as provided by the physician and using the specific eligibility criteria in effect at the time of the request. Eligible patients had COVID-19 confirmed by PCR, required oxygen support, and were hospitalized with substantial clinical symptoms where the benefits of treatment with an investigational agent outweighed the risks. Patients with evidence of severe renal impairment (CrCl < 30 mL/min) or hepatic impairment (ALT > 5 × ULN) were excluded. Available results for a cohort of patients through a data cutoff date of 7:30 PM Pacific Daylight Time on [redacted] 20[redacted] are summarized. A total of 163 adult patients met eligibility criteria, received at least 1 dose of RDV on or prior to [redacted] 20[redacted], per data entered in electronic case report forms as of 10:00 AM Pacific Daylight Time on [redacted] 20[redacted]. Overall, 71.2% of patients (116 of 163 patients) received RDV for 10 days, 19.6% of patients (32 patients) received RDV for 5 to 9 days, and 9.2% of patients (15 patients) received RDV for < 5 days. The patients included in this report were treated at hospitals in the following countries: Italy (84 patients [51.5%]); the US (46 patients [28.2%]); Japan (9 patients [5.5%]); France (5 patients [3.1%]); Switzerland (4 patients [2.5%]); Austria and the United Kingdom (UK) (3 patients [1.8%] each); Germany, Ireland, and Spain (2 patients [1.2%] each); and Canada, Greece, and the Netherlands (1 patient [0.6%] each). The median (first quartile [Q1], third quartile [Q3]) age was 63 (51, 71) years overall, with a similar median, range, and percentage of patients ≥ 70 years of age across the country subgroups; however, the Italy subgroup had fewer patients < 50 years of age. Overall, 79.6% of patients (129 patients) were male, with similar percentages of male patients across the country subgroups. Overall, at baseline, 63.8% of patients (104 patients) were on invasive oxygen support (ECMO or invasive mechanical ventilation) and 35.6% of patients (58 patients) were on noninvasive oxygen support (noninvasive positive pressure ventilation [NIPPV], high- or low-flow oxygen, or room air).

Summary of Results and Conclusions:	• Overall mortality was 20.2% (33 of 163 patients). Outcomes were better among patients treated outside Italy (compared with those treated in Italy) and among those on noninvasive baseline oxygen support (compared with those on invasive baseline oxygen support). Among patients treated outside Italy, none on noninvasive baseline oxygen support died during the observation period. • Overall, 47.2% of patients (77 patients) showed any clinical improvement, 41.1% of patients (67 patients) showed ≥ 2-point clinical improvement, and 30.1% of patients (49 patients) were discharged. The overall median time to ≥ 2-point clinical improvement or discharge was 19.0 days (95% CI: 16.0 to 25.0). — Among patients on noninvasive baseline oxygen support, 67.2% of patients (39 of 58 patients) showed any clinical improvement, and 62.1% of patients (36 patients) showed ≥ 2-point clinical improvement and were discharged, with a median time to ≥ 2-point clinical improvement or discharge of 14.0 days (95% CI: 11.0 to 16.0). Among patients on invasive baseline oxygen support, 36.5% of patients (38 of 104 patients) showed any clinical improvement, 28.8% of patients (30 patients) showed ≥ 2-point clinical improvement, and 11.5% of patients (12 patients) were discharged, with a median time to ≥ 2-point clinical improvement or discharge of 25.0 days (95% CI: 18.0 to 28.0). • Fewer patients on noninvasive oxygen support at baseline had treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) compared with patients on invasive oxygen support at baseline (41.4% versus 55.8% for TEAEs; 15.5% versus 27.9% for TESAEs). Most TEAEs were reported in the system organ classes of Investigations (including elevations in liver function tests); Respiratory, Thoracic and Mediastinal Disorders (including respiratory failure and acute respiratory distress syndrome); Infections and Infestations (including CoV infection and septic shock); and Renal and Urinary Disorders (including acute kidney injury, renal failure, and renal impairment). A total of 20 patients (12.3%) had hepatic TEAEs, 19 of which had TEAEs of elevated liver function tests. • Overall, 13 patients (8.0%) prematurely discontinued RDV due to AEs. Most of these patients prematurely discontinued RDV due to AEs associated with renal dysfunction (4 patients) or elevated liver function tests (5 patients). Two patients discontinued due to multiple organ failure, 1 patient due to systolic dysfunction, and 1 patient due to respiratory distress. The following AEs were also reported as leading to discontinuation of RDV: maculopapular rash in a patient with transaminase elevations; rash in a patient with elevated transaminases; and hypotension in a patient with creatinine renal clearance abnormal and renal failure. • Median ALT, AST, and serum creatinine remained near baseline through Day 10. Overall, 41.7% of patients (60 of 144 patients) had increases in ALT and 47.8% of patients (65 of 136 patients) had increases in AST. Most ALT and AST increases were Grade 1 or 2. Grade 3 ALT increases were reported in 5.6% of patients (8 patients), and there were no Grade 4 ALT increases. Grade 3 AST increases were reported in 6.6% of patients (9 patients), and a Grade 4 AST increase was reported in 0.7% of patients (1 patient). Nearly all of the Grade 3 or 4 ALT or AST increases occurred in patients with invasive baseline oxygen support. • In summary, among these 163 patients with severe COVID-19 who received compassionate use RDV beginning on or before [redacted] 20[redacted], approximately 80% survived and nearly half showed clinical improvement during the observation period. No new safety findings were observed.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Study Populations

3.1.1. Primary Studies Supporting the Clinical Efficacy of Remdesivir

Analysis populations, participant disposition, and demographic and other baseline characteristics are presented by study for Studies CO-US-540-5776, GS-US-540-5773, and GS-US-540-5774.

Detailed results are presented in the individual CSRs (CO-US-540-5776 Preliminary CSR, Section 8; GS-US-540-5773 Interim [Final Part A] CSR, Section 8; GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Section 8).

3.1.1.1. Study CO-US-540-5776

3.1.1.1.1. Analysis Populations

A total of 1062 participants (RDV 10-day group 541 participants; placebo group 521 participants) were randomized into Study CO-US-540-5776 and were included in the Intent-to-Treat (ITT) Population. A total of 1048 randomized participants (RDV 10-day group 531 participants; placebo group 517 participants) received any study treatment infusion, even if the infusion was halted or slowed, and were included in the Treated Population.

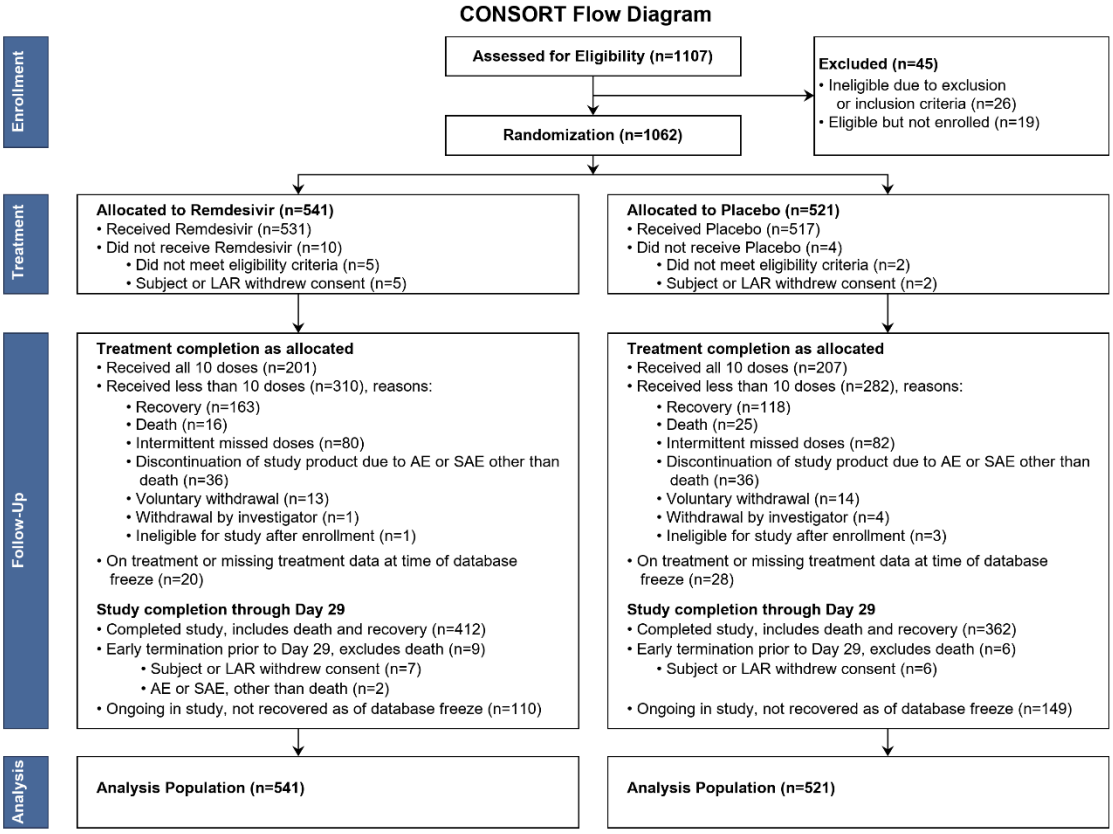
3.1.1.1.2. Participant Disposition

Participants in Study CO-US-540-5776 were enrolled and treated at a total of 60 main study sites in the US, Denmark, the UK, Greece, Germany, the Republic of Korea, Mexico, Spain, Japan, and Singapore. A total of 1107 participants were screened, of whom 1062 were randomized, and 1048 received at least 1 dose of study treatment (Figure 1). A total of 14 randomized participants did not receive study treatment due to not meeting the eligibility criteria or withdrawal of consent.

A total of 408 participants (RDV 10-day group 201 participants; placebo group 207 participants) received all 10 doses of study treatment, and 592 participants (RDV 10-day group 310 participants; placebo group 282 participants) received < 10 doses of study treatment. The most common reasons for receiving < 10 doses of study treatment were recovery (RDV 10-day group 163 participants; placebo group 118 participants), intermittent missed doses (RDV 10-day group 80 participants; placebo group 82 participants), and discontinuation of study product due to AE or SAE other than death (RDV 10-day group 36 participants; placebo group 36 participants).

As of the 28 April 2020 data cut, a total of 412 participants in the RDV 10-day group and 362 participants in the placebo group had completed the study through Day 29, recovered, or died. A total of 15 participants (RDV 10-day group 9 participants; placebo group 6 participants) discontinued the study before Day 29. A total of 110 participants in the RDV 10-day group and 149 participants in the placebo group had not recovered and had not completed the Day 29 follow-up visit.

Figure 1. CO-US-540-5776: Disposition of Participants (All Screened Participants)



LAR = legally authorized representative
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Figure 1

3.1.1.1.3. Demographic and Other Baseline Characteristics

3.1.1.1.3.1. Demographic and General Baseline Characteristics

Demographics and baseline characteristics were similar between the 2 treatment groups (Table 4). The majority of participants in the study were male (64.4%). The mean (SD) age was 58.9 (15.0) years; the majority of participants were white (53.3%), and 23.5% were Hispanic or Latino. The mean (SD) body mass index (BMI) was 30.6 (7.6) kg/m^2.

Table 4. CO-US-540-5776: Demographic and Baseline Characteristics of the Study Population

Characteristic	All Subjects (N = 1062)	RDV 10-Day (N = 541)	Placebo (N = 521)
Age (Years), Mean (± SD)	58.9 (15.0)	58.6 (14.6)	59.2 (15.4)
18 to 39 years, No. (%)	119 (11.2)	59 (10.9)	60 (11.5)
40 to 64 years, No. (%)	559 (52.6)	295 (54.5)	264 (50.7)
65+ years, No. (%)	384 (36.2)	187 (34.6)	197 (37.8)
Male Sex, No. (%)	684 (64.4)	352 (65.1)	332 (63.7)
Race			
American Indian or Alaska Native, No. (%)	7 (0.7)	4 (0.7)	3 (0.6)
Asian, No. (%)	135 (12.7)	79 (14.6)	56 (10.7)
Native Hawaiian or Other Pacific Islander, No. (%)	4 (0.4)	2 (0.4)	2 (0.4)
Black or African American, No. (%)	225 (21.2)	109 (20.1)	116 (22.3)
White, No. (%)	566 (53.3)	279 (51.6)	287 (55.1)
Multiracial, No. (%)	3 (0.3)	2 (0.4)	1 (0.2)
Unknown, No. (%)	122 (11.5)	66 (12.2)	56 (10.7)
Ethnicity			
Not Hispanic or Latino, No. (%)	754 (71.0)	381 (70.4)	373 (71.6)
Hispanic or Latino, No. (%)	250 (23.5)	134 (24.8)	116 (22.3)
Not Reported, No. (%)	29 (2.7)	15 (2.8)	14 (2.7)
Unknown, No. (%)	29 (2.7)	11 (2.0)	18 (3.5)
Body Mass Index (kg/m^2), Mean (± SD)[a]	30.6 (7.6)	30.7 (7.6)	30.5 (7.5)
Region/Country			
Asia, No. (%)	52 (4.9)	26 (4.8)	26 (5.0)
Europe, No. (%)	163 (15.3)	84 (15.5)	79 (15.2)
North America, No. (%)	847 (79.8)	431 (79.7)	416 (79.8)

a Body mass index data were missing for 151 subjects.
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Table 1

3.1.1.1.3.2. Other Baseline Characteristics

Most participants (89.5%, 950 of 1062 participants) were in the severe disease stratum (Table 5). The median number of days between symptom onset and randomization was 9 days for both the RDV 10-day and placebo groups.

Most participants had 1 (26.9%, 249 participants) or 2 or more (55.2%, 512 participants) of the 13 prespecified comorbidities at enrollment. The most commonly reported comorbidities were hypertension (51.1%, 475 participants), obesity (45.0%, 418 participants), and type 2 diabetes mellitus (30.8%, 286 participants); the distribution of comorbidities was similar between the 2 treatment groups. Baseline clinical status (8-point ordinal scale) was also similar between the treatment groups. A total of 282 participants (26.6%) had a clinical status of 7 (hospitalized, on invasive mechanical ventilation or ECMO), 200 participants (18.8%) had a clinical status of 6 (hospitalized, on noninvasive ventilation or high-flow oxygen devices), 434 participants (40.9%) had a clinical status of 5 (hospitalized, requiring supplemental oxygen), and 135 participants (12.7%) had a clinical status of 4 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19 related or otherwise]).

Table 5. CO-US-540-5776: Other Baseline Characteristics of the Study Population

Characteristic	All Subjects (N = 1062)	RDV 10-Day (N = 541)	Placebo (N = 521)
Days from Symptom Onset to Randomization (Median, IQR)[a]	9 (6, 12)	9 (6, 12)	9 (7, 13)
Disease Severity			
Mild-to-moderate disease, No. (%)	112 (10.5)	57 (10.5)	55 (10.6)
Severe disease, No. (%)	950 (89.5)	484 (89.5)	466 (89.4)
Summary of Comorbidities[b]			
None, No. (%)	166 (17.9)	80 (17.1)	86 (18.8)
1, No. (%)	249 (26.9)	127 (27.1)	122 (26.6)
2 or More, No. (%)	512 (55.2)	262 (55.9)	250 (54.6)
Comorbidities[b]			
Hypertension, No. (%)	475 (51.1)	237 (50.4)	238 (51.7)
Coronary artery disease, No. (%)	112 (12.0)	63 (13.4)	49 (10.7)
Congestive heart failure, No. (%)	46 (4.9)	23 (4.9)	23 (5.0)
Chronic respiratory disease (emphysema), No. (%)	72 (7.7)	34 (7.2)	38 (8.3)
Chronic oxygen requirement, No. (%)	18 (1.9)	14 (3.0)	4 (0.9)
Asthma, No. (%)	108 (11.6)	60 (12.8)	48 (10.4)
Chronic liver disease (chronic hepatitis, cirrhosis), No. (%)	20 (2.2)	10 (2.1)	10 (2.2)
Chronic kidney disease, No. (%)	57 (6.1)	33 (7.0)	24 (5.2)
Diabetes I, No. (%)	8 (0.9)	6 (1.3)	2 (0.4)
Diabetes II, No. (%)	286 (30.8)	147 (31.3)	139 (30.2)
Obesity, No. (%)	418 (45.0)	217 (46.3)	201 (43.8)
Cancer, No. (%)	73 (7.8)	41 (8.7)	32 (7.0)
Immune deficiency (acquired or innate), No. (%)	65 (7.0)	28 (6.0)	37 (8.0)
Ordinal Scale			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19 related or otherwise), No. (%)	135 (12.7)	74 (13.7)	61 (11.7)
5. Hospitalized, requiring supplemental oxygen, No. (%)	434 (40.9)	231 (42.7)	203 (39.0)
6. Hospitalized, on noninvasive ventilation or high-flow oxygen devices, No. (%)	200 (18.8)	99 (18.3)	101 (19.4)
7. Hospitalized, on invasive mechanical ventilation or ECMO, No. (%)	282 (26.6)	129 (23.8)	153 (29.4)
Missing at baseline, No. (%)	11 (1.0)	8 (1.5)	3 (0.6)

a Symptom onset data were missing for 3 subjects.
b Comorbidities data were missing for 132 subjects and incomplete for 3 subjects.
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Table 1

3.1.1.2. Study GS-US-540-5773

3.1.1.2.1. Analysis Populations

Overall, 397 participants (RDV 5-day group 200 participants; RDV 10-day group 197 participants) were randomized into Part A of Study GS-US-540-5773, received at least 1 dose of study treatment, and were included in the Safety Analysis Set and Full Analysis Set (FAS) (Table 6). A total of 401 participants (RDV 5-day group 201 participants; RDV 10-day group 200 participants) were randomized into Part A of the study and were included in the All Randomized Analysis Set.

Table 6. GS-US-540-5773: Analysis Sets for Part A (All Randomized Analysis Set)

	RDV 5 Days	RDV 10 Days	Total
All Randomized Analysis Set	201	200	401
Subjects in Safety Analysis Set	200 (99.5%)	197 (98.5%)	397 (99.0%)
Subjects in Full Analysis Set	200 (99.5%)	197 (98.5%)	397 (99.0%)

Subjects in the Safety Analysis Set were summarized according to randomized treatment group.
The denominator for percentages is the number of subjects in the All Randomized Analysis Set.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.8.5

3.1.1.2.2. Participant Disposition

For Part A of Study GS-US-540-5773, participants were enrolled and treated at a total of 55 study sites in Germany, Hong Kong, Italy, Korea, Singapore, Spain, Taiwan, and the US. A total of 407 participants were screened, of whom 401 were randomized, and 397 received at least 1 dose of study treatment in Part A of the study (Table 7). Four randomized participants did not receive any study treatment (2 were enrolled in violation of the study protocol, 1 withdrew consent, and 1 was withdrawn due to investigator's discretion) (GS-US-540-5773 Interim [Final Part A] CSR, Listing 16.2.1.3).

Of the 397 participants treated in Part A, 35.0% of participants (139 participants) prematurely discontinued study treatment (RDV 5-day group 14.0%, 28 participants; RDV 10-day group 56.3%, 111 participants), and 16.4% of participants (65 participants) prematurely discontinued from the study (RDV 5-day group 16.0%, 32 participants; RDV 10-day group 16.8%, 33 participants).

The most common reasons for premature discontinuation of study treatment were hospital discharge (RDV 5-day group 8.0%, 16 participants; RDV 10-day group 34.0%, 67 participants), AE (RDV 5-day group 4.5%, 9 participants; RDV 10-day group 11.2%, 22 participants), and death (RDV 5-day group 0 participants; RDV 10-day group 6.1%, 12 participants).

Table 7. GS-US-540-5773: Disposition of Participants (All Screened Participants)

	RDV 5 Days	RDV 10 Days	Total
Subjects Screened			407
Screen Failure Subjects Who Were Not Randomized			5
Subjects Met All Eligibility Criteria and Not Randomized[a]			1
Subjects Randomized	201	200	401
Subjects Randomized and Never Treated	1	3	4
Subjects in Safety Analysis Set	200	197	397
Subjects in Full Analysis Set	200	197	397
Subjects Completed Study Drug	172 (86.0%)	86 (43.7%)	258 (65.0%)
Subjects Prematurely Discontinuing Study Drug	28 (14.0%)	111 (56.3%)	139 (35.0%)
Reasons for Prematurely Discontinuing Study Drug			
Adverse Event	9 (4.5%)	22 (11.2%)	31 (7.8%)
Death	0	12 (6.1%)	12 (3.0%)
Hospital Discharge	16 (8.0%)	67 (34.0%)	83 (20.9%)
Investigator's Discretion	0	5 (2.5%)	5 (1.3%)
Protocol Violation	1 (0.5%)	1 (0.5%)	2 (0.5%)
Subject Decision	2 (1.0%)	4 (2.0%)	6 (1.5%)
Subjects Completed Study	168 (84.0%)	164 (83.2%)	332 (83.6%)
Subjects Prematurely Discontinuing from Study	32 (16.0%)	33 (16.8%)	65 (16.4%)
Reasons for Prematurely Discontinuing from Study			
Adverse Event	2 (1.0%)	1 (0.5%)	3 (0.8%)
Death	21 (10.5%)	28 (14.2%)	49 (12.3%)
Withdrew Consent	1 (0.5%)	0	1 (0.3%)
Lost to Follow-Up	8 (4.0%)	4 (2.0%)	12 (3.0%)

a One subject met all eligibility criteria and was not randomized due to other reason (investigator's discretion).
The denominator for percentages is the number of subjects in the Safety Analysis Set.
The number of screen failures is counted by unique subject based on rescreening information entered into the electronic case report form.
All available case report form data as of [redacted] 20[redacted] are included.
Screen failure subjects are the subjects who did not meet all eligibility criteria.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.8.1.2

3.1.1.2.3. Demographic and Other Baseline Characteristics

3.1.1.2.3.1. Demographic and General Baseline Characteristics

Demographic and baseline characteristics were similar between the 2 treatment groups (Table 8). The majority of the participants in the Safety Analysis Set were male (63.7%). The median age was 61 years (range: 20 to 98); the majority of participants were white (75.0%), and the majority were not Hispanic or Latino (78.0%). The median (Q1, Q3) BMI was 28.7 (25.3, 33.5) kg/m^2.

Demographic and baseline characteristics are presented for the country subgroups United States of America (USA), Italy, and ex-Italy in the GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.8.3.1.1, 15.8.3.1.2, and 15.8.3.1.3, respectively. Demographic and baseline characteristics were similar between the 2 treatment groups in each subgroup.

Table 8. GS-US-540-5773: Demographic and Baseline Characteristics (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)	RDV 5 Days vs RDV 10 Days P-Value
Age (Years)				
N	200	197	397	0.7953
Mean (SD)	60 (15.1)	60 (14.4)	60 (14.8)	
Median	61	62	61	
Q1, Q3	50, 69	50, 71	50, 70	
Min, Max	20, 98	21, 93	20, 98	
Age Categories (Years)				
< 50	50 (25.0%)	49 (24.9%)	99 (24.9%)	0.9609
≥ 50 to < 65	66 (33.0%)	64 (32.5%)	130 (32.7%)	
≥ 65 to < 75	52 (26.0%)	53 (26.9%)	105 (26.4%)	
≥ 75	32 (16.0%)	31 (15.7%)	63 (15.9%)	
Sex at Birth				
Male	120 (60.0%)	133 (67.5%)	253 (63.7%)	0.1200
Female	80 (40.0%)	64 (32.5%)	144 (36.3%)	
Race				
American Indian or Alaska Native	2 (1.1%)	0	2 (0.5%)	0.4302
Asian	20 (10.8%)	25 (13.7%)	45 (12.2%)	
Black	21 (11.3%)	23 (12.6%)	44 (12.0%)	
Native Hawaiian or Pacific Islander	1 (0.5%)	0	1 (0.3%)	
White	142 (76.3%)	134 (73.6%)	276 (75.0%)	
Not Permitted	0	5	5	
Other	14	10	24	
Ethnicity				
Hispanic or Latino	47 (23.6%)	38 (20.2%)	85 (22.0%)	0.4193
Not Hispanic or Latino	152 (76.4%)	150 (79.8%)	302 (78.0%)	
Not Permitted	1	9	10	
Baseline Body Mass Index (kg/m^2)				
N	197	192	389	0.9716
Mean (SD)	30.1 (7.35)	29.7 (6.02)	29.9 (6.72)	
Median	28.7	28.6	28.7	
Q1, Q3	25.0, 34.0	25.4, 33.0	25.3, 33.5	
Min, Max	15.5, 63.0	17.4, 50.1	15.5, 63.0	

max = maximum; min = minimum; vs = versus
For race and ethnicity, "Not Permitted" and "Other" were excluded from the percentage calculation and p-value calculation.
Not Permitted = local regulators did not allow collection of race/ethnicity information. All but 1 value of "Other" are unknown, not specified, etc.
For categorical data, p-value was from the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data and row means score differ for ordinal data). For continuous data, p-value was from the Wilcoxon rank sum test.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.8.3.1

3.1.1.2.3.2. Other Baseline Characteristics

Other baseline characteristics are presented by treatment group in Table 9 and for the country subgroups USA, Italy, and ex-Italy in the GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.8.3.2.1, 15.8.3.2.2, and 15.8.3.2.3, respectively.

Although treatment groups were balanced in demographics, they were not balanced in baseline disease characteristics. A better (higher score) baseline clinical status (7-point ordinal scale) was observed in participants in the RDV 5-day group compared with those in the RDV 10-day group; this difference was statistically significant (p = 0.0230).

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

Median baseline ALT was similar between the treatment groups; however, participants in the RDV 5-day group had significantly lower median (Q1, Q3) baseline AST than participants in the RDV 10-day group (RDV 5-day group 41 [29, 58] U/L; RDV 10-day group 46 [34, 67] U/L; p = 0.0081). There were no statistically significant differences between the treatment groups in median baseline serum creatinine or CrCl by Cockcroft-Gault (GS-US-540-5773 Interim [Final Part A] CSR, Tables 15.11.6.1.9 and 15.11.6.1.10).

When analyzed by country subgroup, a worse (lower score) baseline clinical status was observed in participants in the Italy subgroup compared with the ex-Italy subgroup; 71.4% of participants (55 of 77 participants) in the Italy subgroup had a clinical status of 3 compared with 16.6% of participants (53 of 320 participants) in the ex-Italy subgroup. In addition, in the Italy subgroup, participants in the RDV 5-day group had significantly lower median (Q1, Q3) AST than participants in the RDV 10-day group (RDV 5-day group 39 [26, 55] U/L; RDV 10-day group 51 [36, 70] U/L; p = 0.0300). In contrast, median baseline AST was similar between the treatment groups for the USA and ex-Italy subgroups.

The median duration of symptoms prior to first dose of RDV (9 days) and the median duration of hospitalization prior to first dose of RDV (2 days) were similar between the treatment groups.

Medical history was reported in 89.0% of participants (178 of 200 participants) in the RDV 5-day group and 90.9% of participants (179 of 197 participants) in the RDV 10-day group (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.8.3.3). The 3 most commonly reported medical history preferred terms in the RDV 5-day and 10-day groups were hypertension (46.0%, 92 participants and 47.2%, 93 participants, respectively), pyrexia (31.5%, 63 participants and 37.1%, 73 participants, respectively), and cough (26.5%, 53 participants and 27.9%, 55 participants, respectively).

Concomitant medications during the study are presented by treatment group and preferred drug name in the GS-US-540-5773 Interim (Final Part A) CSR, Table 15.11.7.3.

Table 9. GS-US-540-5773: Other Baseline Characteristics (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)	RDV 5 Days vs RDV 10 Days P-Value
Clinical Status (7-Point Ordinal Scale)				
2 - Hospitalized, on invasive mechanical ventilation or ECMO[a]	4 (2.0%)	9 (4.6%)	13 (3.3%)	0.0230
3 - Hospitalized, on noninvasive ventilation or high-flow oxygen devices	49 (24.5%)	59 (29.9%)	108 (27.2%)	
4 - Hospitalized, requiring low-flow supplemental oxygen	113 (56.5%)	108 (54.8%)	221 (55.7%)	
5 - Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care	34 (17.0%)	21 (10.7%)	55 (13.9%)	
6 - Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care	0	0	0	
Duration of Hospitalization Prior to First Dose of RDV (Days)				
N	200	197	397	0.9364
Mean (SD)	3 (2.2)	3 (3.2)	3 (2.7)	
Median	2	2	2	
Q1, Q3	1, 3	1, 3	1, 3	
Min, Max	0, 11	0, 35	0, 35	
Duration of Symptoms Prior to First Dose of RDV (Days)				
N	198	194	392	0.6715
Mean (SD)	9 (4.3)	9 (4.6)	9 (4.4)	
Median	9	9	9	
Q1, Q3	6, 11	7, 12	7, 11	
Min, Max	2, 32	2, 43	2, 43	
ALT (U/L)				
N	200	195	395	0.1950
Mean (SD)	42 (33.3)	45 (31.1)	44 (32.2)	
Median	32	36	34	
Q1, Q3	22, 50	23, 58	22, 56	
Min, Max	6, 198	6, 165	6, 198	

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)	RDV 5 Days vs RDV 10 Days P-Value
AST (U/L)				
N	195	194	389	0.0081
Mean (SD)	47 (26.0)	54 (30.1)	51 (28.3)	
Median	41	46	43	
Q1, Q3	29, 58	34, 67	31, 63	
Min, Max	15, 140	7, 156	7, 156	
Oxygen Support Status				
Invasive Mechanical Ventilation	4 (2.0%)	9 (4.6%)	13 (3.3%)	0.0175
High-Flow Oxygen	49 (24.5%)	59 (29.9%)	108 (27.2%)	
Low-Flow Oxygen	113 (56.5%)	108 (54.8%)	221 (55.7%)	
Room Air	34 (17.0%)	21 (10.7%)	55 (13.9%)	

max = maximum; min = minimum; vs = versus
a A requirement for mechanical ventilation developed between screening and the beginning of treatment for these participants, or they were on mechanical ventilation at enrollment and were designated as representing protocol deviations.
For Clinical Status: Category 5 includes medical care (COVID-19 related or otherwise); Category 6 excludes per-protocol RDV administration. Category 7 (Not Hospitalized) and Category 1 (Death) are not included in this table.
For oxygen support status, p-value was from the Cochran-Mantel-Haenszel test (row mean scores differ statistic). For clinical status and continuous data, p-value was from the Wilcoxon rank sum test.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.8.3.2

3.1.1.3. Study GS-US-540-5774

3.1.1.3.1. Analysis Populations

Overall, 584 participants (RDV 5-day group 191 participants; RDV 10-day group 193 participants; SOC only group 200 participants) were randomized into Part A of the study, received at least 1 dose of study treatment (RDV groups) or completed the Day 1 visit (SOC only group), and were included in the Safety Analysis Set and FAS (Table 10). A total of 596 participants (RDV 5-day group 199 participants; RDV 10-day group 197 participants; SOC only group 200 participants) were randomized into Part A of the study and were included in the All Randomized Analysis Set.

Table 10. GS-US-540-5774: Analysis Sets for Part A (All Randomized Analysis Set)

	RDV 5 Days	RDV 10 Days	SOC	Total
Subjects in All Randomized Analysis Set	199	197	200	596
Subjects in Safety Analysis Set	191 (96.0%)	193 (98.0%)	200 (100.0%)	584 (98.0%)
Subjects in Full Analysis Set	191 (96.0%)	193 (98.0%)	200 (100.0%)	584 (98.0%)

Subjects in the Safety Analysis Set were summarized according to randomized treatment group.
The denominator for percentages is the number of subjects in the All Randomized Analysis Set.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.8.5

3.1.1.3.2. Participant Disposition

For Part A of the study, participants were enrolled and treated at a total of 105 study sites in France, Germany, Hong Kong, Italy, Korea, Netherlands, Singapore, Spain, Switzerland, Taiwan, the UK, and the US. A total of 612 participants were screened, of whom 596 were randomized, 384 received at least 1 dose of study treatment (RDV groups: RDV 5-day group 191 participants; RDV 10-day group 193 participants), and 200 completed the protocol-specified Day 1 visit (SOC only group) in Part A of the study (Table 11). Twelve randomized participants did not receive study treatment (8 withdrew consent, 3 were enrolled in violation of the study protocol, and 1 was withdrawn due to investigator's discretion) (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Listing 16.2.1.3).

Of the 384 participants treated with RDV in Part A, 24.1% of participants (46 participants) prematurely discontinued study treatment in the RDV 5-day group, and 62.2% of participants (120 participants) prematurely discontinued study treatment in the RDV 10-day group.

Of the 584 participants in the Safety Analysis Set, 7.9% of participants (46 participants) prematurely discontinued from the study (RDV 5-day group 6.3%, 12 participants; RDV 10-day group 8.3%, 16 participants; SOC only group 9.0%, 18 participants), and 53.1% of participants (310 participants) were still in the study at the data cut date (RDV 5-day group 53.9%, 103 participants; RDV 10-day group 52.8%, 102 participants; SOC only group 52.5%, 105 participants).

The most common reasons for premature discontinuation of study treatment were hospital discharge (RDV 5-day group 18.3%, 35 participants; RDV 10-day group 50.8%, 98 participants), subject decision (RDV 5-day group 2.6%, 5 participants; RDV 10-day group 3.6%, 7 participants), and AE (RDV 5-day group 2.1%, 4 participants; RDV 10-day group 3.6%, 7 participants). Participants in the SOC only group were not receiving RDV and could not prematurely discontinue study treatment.

Table 11. GS-US-540-5774: Disposition of Participants (All Screened Participants)

	RDV 5 Days	RDV 10 Days	SOC	Total
Subjects Screened				612
Screen Failure Subjects Who Were Not Randomized				13
Subjects Met All Eligibility Criteria and Not Randomized[a]				3
Subjects Randomized	199	197	200	596
Subjects Randomized and Never Treated	8	4	0	12
Subjects in Safety Analysis Set	191	193	200	584
Subjects in Full Analysis Set	191	193	200	584
Subjects Completed Study Drug	145 (75.9%)	73 (37.8%)	NA	218 (37.3%)
Subjects Prematurely Discontinuing Study Drug	46 (24.1%)	120 (62.2%)	NA	166 (28.4%)
Reasons for Prematurely Discontinuing Study Drug				
Adverse Event	4 (2.1%)	7 (3.6%)		11 (1.9%)
Death	0	1 (0.5%)		1 (0.2%)
Hospital Discharge	35 (18.3%)	98 (50.8%)		133 (22.8%)
Investigator's Discretion	1 (0.5%)	4 (2.1%)		5 (0.9%)
Noncompliance with Study Drug	0	1 (0.5%)		1 (0.2%)
Protocol Violation	0	2 (1.0%)		2 (0.3%)
Subject Decision	5 (2.6%)	7 (3.6%)		12 (2.1%)
Lost to Follow-Up	1 (0.5%)	0		1 (0.2%)
Subjects Still on Study up to the Data Cut Date	103 (53.9%)	102 (52.8%)	105 (52.5%)	310 (53.1%)
Subjects Completed Study	76 (39.8%)	75 (38.9%)	77 (38.5%)	228 (39.0%)
Subjects Prematurely Discontinuing from Study Prior to the Data Cut Date	12 (6.3%)	16 (8.3%)	18 (9.0%)	46 (7.9%)
Reasons for Prematurely Discontinuing from Study				
Death	2 (1.0%)	2 (1.0%)	4 (2.0%)	8 (1.4%)
Noncompliance with Study Drug	0	1 (0.5%)	0	1 (0.2%)
Protocol Violation	0	0	1 (0.5%)	1 (0.2%)
Withdrew Consent	2 (1.0%)	2 (1.0%)	5 (2.5%)	9 (1.5%)
Lost to Follow-Up	8 (4.2%)	11 (5.7%)	8 (4.0%)	27 (4.6%)

NA = not applicable
a Three subjects met all eligibility criteria and were not randomized due to withdrawal of consent.
The denominator for percentages is the number of subjects in the Safety Analysis Set.
The number of screen failures is counted by unique subject based on rescreening information entered into the electronic case report form.
All available case report form data as of [redacted] 20[redacted] are included.
Screen failure subjects are the subjects who did not meet all eligibility criteria.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.8.1.2

3.1.1.3.3. Demographic and Other Baseline Characteristics

3.1.1.3.3.1. Demographic and General Baseline Characteristics

Demographic and baseline characteristics were similar between the 3 treatment groups (Table 12). The majority of the participants in the Safety Analysis Set were male (61.1%). The median age was 57 years (range: 12 to 95); the majority of participants were white (61.3%), and the majority were not Hispanic or Latino (81.9%).

Demographic and baseline characteristics are presented for the country subgroups USA, Italy, and ex-Italy in the GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.8.3.1.1, 15.8.3.1.2, and 15.8.3.1.3, respectively. Demographic and baseline characteristics were similar between the 3 treatment groups in each subgroup.

Table 12. GS-US-540-5774: Demographic and Baseline Characteristics (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	Total (N = 584)	P-Value
Age (Years)					
N	191	193	200	584	0.7607
Mean (SD)	56 (14.6)	55 (15.5)	55 (15.1)	56 (15.1)	
Median	58	56	57	57	
Q1, Q3	48, 66	45, 66	45, 66	46, 66	
Min, Max	12, 90	20, 94	23, 95	12, 95	
Age Categories (Years)					
< 50	58 (30.4%)	67 (34.7%)	65 (32.5%)	190 (32.5%)	0.9832
≥ 50 to < 65	84 (44.0%)	74 (38.3%)	77 (38.5%)	235 (40.2%)	
≥ 65 to < 75	31 (16.2%)	26 (13.5%)	38 (19.0%)	95 (16.3%)	
≥ 75	18 (9.4%)	26 (13.5%)	20 (10.0%)	64 (11.0%)	
Sex at Birth					
Male	114 (59.7%)	118 (61.1%)	125 (62.5%)	357 (61.1%)	0.8500
Female	77 (40.3%)	75 (38.9%)	75 (37.5%)	227 (38.9%)	
Race					
American Indian or Alaska Native	2 (1.1%)	0	1 (0.6%)	3 (0.6%)	0.8317
Asian	34 (18.8%)	31 (17.6%)	37 (20.8%)	102 (19.1%)	
Black	35 (19.3%)	37 (21.0%)	27 (15.2%)	99 (18.5%)	
Native Hawaiian or Pacific Islander	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (0.6%)	
White	109 (60.2%)	107 (60.8%)	112 (62.9%)	328 (61.3%)	
Not Permitted	5	5	7	17	
Other	5	12	15	32	
Ethnicity					
Hispanic or Latino	25 (13.4%)	42 (22.6%)	34 (18.3%)	101 (18.1%)	0.0691
Not Hispanic or Latino	162 (86.6%)	144 (77.4%)	152 (81.7%)	458 (81.9%)	
Not Permitted	4	7	13	24	
- Missing -	0	0	1	1	
Baseline Body Mass Index (kg/m^2)					
N	185	183	191	559	0.2373
Mean (SD)	27.8 (6.51)	28.9 (6.77)	28.2 (6.65)	28.3 (6.64)	
Median	26.7	27.6	26.7	27.1	
Q1, Q3	23.8, 30.4	24.5, 32.2	23.5, 31.1	24.1, 31.1	
Min, Max	17.2, 76.9	16.1, 63.2	15.9, 53.9	15.9, 76.9	

max = maximum; min = minimum
For race and ethnicity, "Not Permitted," "Missing," and "Other" were excluded from the percentage calculation and p-value calculation.
Not Permitted = local regulators did not allow collection of race/ethnicity information. All but 3 values of "Other" are unknown, not specified, etc.
For categorical data, p-value was from the Cochran-Mantel-Haenszel test (general association statistic for nominal data and row mean scores differ statistic for ordinal data). For continuous data, p-value was from the Kruskal-Wallis test.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.8.3.1

3.1.1.3.3.2. Other Baseline Characteristics

Other baseline characteristics are presented by treatment group in Table 13 and for the country subgroups USA, Italy, and ex-Italy in the GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.8.3.2.1, 15.8.3.2.2, and 15.8.3.2.3, respectively.

Treatment groups were balanced in other baseline disease characteristics. There were no statistically significant differences in baseline clinical status (7-point ordinal scale) between the treatment groups. For the country subgroups USA, Italy, and ex-Italy, there were no statistically significant differences in baseline clinical status (7-point ordinal scale) between the treatment groups.

There were no statistically significant differences between the treatment groups in baseline oxygen support status derived from the 7-point ordinal scale used to assess clinical status. Most participants were on room air (not requiring oxygen support) across all treatment groups (RDV 5-day group 83.8%, 160 participants; RDV 10-day group 87.6%, 169 participants; SOC only group 81.0%, 162 participants). For the country subgroups USA, Italy, and ex-Italy, there were no statistically significant differences between the treatment groups in baseline oxygen support status; however, a low-flow oxygen requirement was more common in participants in Italy than in ex-Italy.

Median baseline ALT, AST, serum creatinine, and CrCl by Cockcroft-Gault were similar between the treatment groups (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Tables 15.11.6.1.9 and 15.11.6.1.10).

Median duration of symptoms prior to first dose of RDV (8 days) (or Study Day 1 for the SOC only group [9 days]) and the median duration of hospitalization prior to first dose of RDV (2 days) (or Study Day 1 for the SOC only group [2 days]) were similar across treatment groups.

Medical history was reported in 90.1% of participants (172 of 191 participants) in the RDV 5-day group, 91.7% of participants (177 of 193 participants) in the RDV 10-day group, and 87.0% of participants (174 of 200 participants) in the SOC only group (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.8.3.3). The 3 most commonly reported medical history preferred terms by treatment group were as follows:

- RDV 5-day group: hypertension (40.3%, 77 participants), pyrexia (16.2%, 31 participants), and cough (15.7%, 30 participants)
- RDV 10-day group: hypertension (37.8%, 73 participants), hyperlipidemia (20.2%, 39 participants), and pneumonia and pyrexia (each 14.0%, 27 participants)
- SOC only group: hypertension (39.0%, 78 participants), cough (14.5%, 29 participants), and pyrexia and type 2 diabetes mellitus (each 13.0%, 26 participants)

Concomitant medications during the study are presented by treatment group and preferred drug name in the GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.11.7.3.

Table 13. GS-US-540-5774: Other Baseline Characteristics (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	Total (N = 584)	P-Value
Clinical Status (7-Point Ordinal Scale)					
2 - Hospitalized, on invasive mechanical ventilation or ECMO	0	0	0	0	0.0781
3 - Hospitalized, on noninvasive ventilation or high-flow oxygen devices[a]	2 (1.0%)	1 (0.5%)	2 (1.0%)	5 (0.9%)	
4 - Hospitalized, requiring low-flow supplemental oxygen[a]	29 (15.2%)	23 (11.9%)	36 (18.0%)	88 (15.1%)	
5 - Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care	160 (83.8%)	163 (84.5%)	160 (80.0%)	483 (82.7%)	
6 - Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care	0	6 (3.1%)	2 (1.0%)	8 (1.4%)	
Duration of Hospitalization Prior to Study Day 1 (Days)					
N	191	193	199	583	0.6273
Mean (SD)	3 (4.4)	3 (4.6)	3 (3.6)	3 (4.2)	
Median	2	2	2	2	
Q1, Q3	1, 3	1, 3	1, 3	1, 3	
Min, Max	0, 36	0, 30	0, 33	0, 36	
Duration of Symptoms Prior to Study Day 1 (Days)					
N	191	189	197	577	0.0253
Mean (SD)	9 (6.5)	8 (5.7)	9 (5.2)	9 (5.8)	
Median	8	8	9	8	
Q1, Q3	5, 11	5, 11	6, 11	5, 11	
Min, Max	1, 48	1, 40	1, 34	1, 48	
ALT (U/L)					
N	191	193	200	584	0.8702
Mean (SD)	39 (31.3)	40 (35.4)	42 (35.5)	40 (34.1)	
Median	30	28	30	29	
Q1, Q3	19, 51	21, 47	19, 49	19, 50	
Min, Max	6, 221	4, 229	5, 289	4, 289	

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	Total (N = 584)	P-Value
AST (U/L)					
N	186	187	193	566	0.9772
Mean (SD)	42 (28.2)	41 (29.5)	42 (30.9)	42 (29.5)	
Median	32	34	34	33	
Q1, Q3	25, 48	23, 48	24, 49	24, 49	
Min, Max	8, 147	9, 215	8, 229	8, 229	
Baseline Oxygen Support Status					
Invasive Mechanical Ventilation	0	0	0	0	0.2070
High-Flow Oxygen	2 (1.0%)	1 (0.5%)	2 (1.0%)	5 (0.9%)	
Low-Flow Oxygen	29 (15.2%)	23 (11.9%)	36 (18.0%)	88 (15.1%)	
Room Air	160 (83.8%)	169 (87.6%)	162 (81.0%)	491 (84.1%)	

max = maximum; min = minimum
a Either enrolled under the original protocol which allowed participants to be included if they were receiving supplemental oxygen but had SpO_2 > 94% on room air or had a requirement for supplemental oxygen develop between screening and the beginning of treatment, or were on supplemental oxygen at enrollment and were designated as representing important protocol deviations
For Clinical Status: Category 5 includes medical care (COVID-19 related or otherwise); Category 6 excludes per-protocol RDV administration. Category 7 (Not Hospitalized) and Category 1 (Death) are not included in this table.
Baseline was the last available value recorded on or prior to dosing for RDV groups and Study Day 1 for SOC. For clinical status for SOC, baseline was the electronic case report form record labeled "Day 1 Predose."
For oxygen support status, p-value was from the Cochran-Mantel-Haenszel test (row mean scores differ statistic). For clinical status and continuous data, p-value was from the Kruskal-Wallis test.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.8.3.2

3.1.2. Other Data Supporting the Clinical Efficacy of Remdesivir

3.1.2.1. Study CO-US-540-5758

3.1.2.1.1. Analysis Population

Overall, 236 randomized participants (RDV group 158 participants; placebo group 78 participants) were included in the ITT Population {Wang 2020}. A total of 233 randomized participants (RDV group 155 participants; placebo group 78 participants) started their assigned treatment and were included in the Safety Population.

3.1.2.1.2. Demographic and Other Baseline Characteristics

Participants were enrolled and treated at a total of 10 study sites in China {Wang 2020}. Demographic and baseline characteristics were similar between the 2 treatment groups. Overall, the majority of participants were male (59%), and the median age was 65 years (IQR: 56 to 71). The most common comorbidity was hypertension (43%), followed by diabetes (24%) and coronary heart disease (7%). The majority of participants were in category 3 of the 6-point ordinal scale of clinical status at baseline (hospital admission, requiring supplemental oxygen); however, a higher proportion of participants in the RDV group required higher levels of oxygen

support at baseline compared with the placebo group (28 of 158 participants [18%] versus 10 of 78 participants [13%], respectively). Median time from symptom onset to starting study treatment was 10 days (IQR: 9 to 12), and the proportion of participants who started treatment > 10 days after symptom onset was numerically higher in the RDV group compared with the placebo group (84 of 155 participants [54%] versus 31 of 78 participants [40%], respectively).

3.1.2.2. Study IN-US-540-5755

3.1.2.2.1. Analysis Population

Per data entered in electronic case report forms as of 10:00 AM Pacific Daylight Time on [redacted] 20[redacted], a total of 163 adult patients received at least 1 dose of RDV on or prior to 20[redacted] and were included in the Compassionate Use Analysis Set for this interim analysis.

3.1.2.2.2. Baseline Characteristics and Intake Information

Baseline characteristics and intake information are presented in the IN-US-540-5755 Interim 1 Summary Report, Section 3.1.

Patients were treated at hospitals in the following countries: Italy (84 of 163 patients [51.5%]); the US (46 patients [28.2%]); Japan (9 patients [5.5%]); France (5 patients [3.1%]); Switzerland (4 patients [2.5%]); Austria and the UK (3 patients [1.8%] each); Germany, Ireland, and Spain (2 patients [1.2%] each); and Canada, Greece, and the Netherlands (1 patient [0.6%] each).

The median (Q1, Q3) age was 63 (51, 71) years overall, with a similar median, range, and percentage of patients ≥ 70 years of age across the country subgroups; however, the Italy subgroup had fewer patients < 50 years of age (Table 14). Overall, 79.6% of patients (129 patients) were male, with similar percentages of male patients across the country subgroups. Overall, comorbidities were reported as follows: hypertension (28.2%), diabetes (20.2%), history of respiratory disease (14.7%), hyperlipidemia (13.5%), history of cardiac disorder (11.7%), history of malignancy (8.0%), and smoker (1.8%).

Median (Q1, Q3) duration of symptoms prior to initiation of RDV was 13 (10, 16) days overall, with a slightly longer duration of symptoms in Italy (13 [11, 17] days) compared with outside Italy (11 [8, 14] days).

Overall, at baseline, 63.8% of patients (104 patients) were on invasive oxygen support (ECMO or invasive mechanical ventilation), and 35.6% of patients (58 patients) were on noninvasive oxygen support (NIPPV, high- or low-flow oxygen, or room air). The Italy subgroup had the lowest percentage of patients on invasive oxygen support of any kind (57.1% [48 patients]) and no patients on ECMO. Median (Q1, Q3) duration of invasive oxygen support was 5 (3, 8) days in Italy and 2 (1, 5) days outside Italy.

Table 14. IN-US-540-5755: Baseline Characteristics by Country Subgroup - All Patients (Compassionate Use Analysis Set)

	Italy (N = 84)	Outside Italy (N = 79)	All Countries (N = 163)
Median (Q1, Q3) Age (Years)	64 (57, 73)	63 (46, 71)	63 (51, 71)
Age Categories (Years), n (%)			
< 50	9 (10.7%)	24 (30.4%)	33 (20.2%)
≥ 50 to < 60	23 (27.4%)	14 (17.7%)	37 (22.7%)
≥ 60 to < 70	26 (31.0%)	15 (19.0%)	41 (25.2%)
≥ 70	26 (31.0%)	26 (32.9%)	52 (31.9%)
Male, n (%)	68 (81.0%)	61 (78.2%)	129 (79.6%)
Reported Comorbidities, n (%)			
Hypertension[a]	25 (29.8%)	21 (26.6%)	46 (28.2%)
Diabetes[b]	14 (16.7%)	19 (24.1%)	33 (20.2%)
History of Respiratory Disease[c]	8 (9.5%)	16 (20.3%)	24 (14.7%)
Hyperlipidaemia[d]	5 (6.0%)	17 (21.5%)	22 (13.5%)
History of Cardiac Disorder[e]	14 (16.7%)	5 (6.3%)	19 (11.7%)
History of Malignancy[f]	7 (8.3%)	6 (7.6%)	13 (8.0%)
Smoker[g]	1 (1.2%)	2 (2.5%)	3 (1.8%)
Median (Q1, Q3) Duration of Symptoms (Days)	13 (11, 17)	11 (8, 14)	13 (10, 16)
Invasive, n (%)	48 (57.1%)	56 (70.9%)	104 (63.8%)
ECMO	0	6 (7.6%)	6 (3.7%)
Invasive Mechanical Ventilation	48 (57.1%)	50 (63.3%)	98 (60.1%)
Median (Q1, Q3) Duration of Invasive Oxygen Support (Days)	5 (3, 8)	2 (1, 5)	4 (2, 7)
Noninvasive, n (%)	35 (41.7%)	23 (29.1%)	58 (35.6%)
NIPPV	12 (14.3%)	4 (5.1%)	16 (9.8%)
High-Flow Oxygen	3 (3.6%)	5 (6.3%)	8 (4.9%)
Low-Flow Oxygen	20 (23.8%)	11 (13.9%)	31 (19.0%)
Room Air	0	3 (3.8%)	3 (1.8%)

a Included the following preferred terms: essential hypertension and hypertension.
b Included the following preferred terms: diabetes mellitus, diabetic neuropathy, type 1 diabetes mellitus, and type 2 diabetes mellitus.
c Included the system organ class Respiratory, Thoracic and Mediastinal Disorders.
d Included the following preferred terms: dyslipidaemia, hypercholesterolaemia, and hyperlipidaemia.
e Included the system organ class Cardiac Disorders.
f Included the system organ class Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps).
g Included the preferred term tobacco user.
The Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to [redacted] 20[redacted], per data entered in electronic case report forms as of 10:00 AM Pacific Daylight Time on [redacted] 20[redacted].
Baseline oxygen support status was defined as the last status on or prior to the first dose date of study drug.
Invasive oxygen support included ECMO and invasive mechanical ventilation.
Noninvasive oxygen support included NIPPV, high-flow oxygen, low-flow oxygen, and room air.
Source: IN-US-540-5755 Interim 1 Summary Report, Tables 2.2 to 2.4 and 3.1.2 to 3.1.4 and Listing 4

3.2. Comparison of Efficacy Results of All Studies

3.2.1. Primary Studies Supporting the Clinical Efficacy of Remdesivir

Summaries of efficacy results from the primary studies supporting efficacy of RDV in participants with COVID-19 are presented below. Detailed efficacy results are presented in the individual CSRs (CO-US-540-5776 Preliminary CSR, Section 9; GS-US-540-5773 Interim [Final Part A] CSR, Section 9; GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Section 9).

3.2.1.1. Study CO-US-540-5776

3.2.1.1.1. Primary Efficacy Endpoint: Time to Recovery

The primary efficacy endpoint was the time to recovery, defined as the elapsed time (in days) from randomization to the earliest day on which a participant was discharged or achieved a clinical status of recovery. Recovery was defined as an improvement from a baseline score of 4, 5, 6, or 7 to a score of 1, 2, or 3, with these lowest 3 categories constituting a clinical status of "recovery" on the 8-point ordinal scale.

Overall, participants in the RDV 10-day group had a statistically significant shorter median time to recovery compared with those in the placebo group, with a median time to recovery of 10 days (95% CI: 9 to 11) in the RDV 10-day group versus 14 days (95% CI: 12 to 17) in the placebo group (RRR 1.31; 95% CI: 1.12 to 1.53; $p < 0.001$) (Table 15). The Kaplan-Meier (KM) curves, representing estimates of cumulative recoveries, diverged on Day 6 and remained separated through Day 27, suggesting a higher proportion of recoveries in the RDV 10-day group versus the placebo group starting from Day 6 up to Day 27 (Figure 2).

Time to Recovery by Baseline Disease Severity

Time to recovery was also analyzed within each baseline disease severity stratum (mild-to-moderate versus severe) (Table 15 and Figure 3).

In participants in the severe disease stratum, the median time to recovery was shorter in the RDV 10-day group compared with the placebo group, with a median time to recovery of 11 days (95% CI: 10 to 13; n = 484) in the RDV 10-day group versus 17 days (95% CI: 14 to 21; n = 466) in the placebo group (RRR 1.34; 95% CI: 1.13 to 1.58). The KM curves for estimates of cumulative recoveries in participants in the severe disease stratum showed separation between the RDV 10-day and placebo groups after approximately Day 6, suggesting a higher proportion of recoveries in the RDV 10-day group versus the placebo group starting from Day 6.

In participants in the mild-to-moderate disease stratum, the median time to recovery was similar in the RDV 10-day group (5 days; 95% CI: 4 to 6; n = 57) and the placebo group (5 days; 95% CI: 4 to 7; n = 55) (RRR 1.16; 95% CI: 0.77 to 1.72).

Table 15. CO-US-540-5776: Outcomes Overall and by Baseline Disease Severity (Intent-to-Treat Population)

	Overall		Mild-to-Moderate Disease Stratum		Severe Disease Stratum	
	RDV 10-Day (N = 541)	**Placebo (N = 521)**	**RDV 10-Day (N = 57)**	**Placebo (N = 55)**	**RDV 10-Day (N = 484)**	**Placebo (N = 466)**
Days to Recovery						
Number of recoveries	351	292	52	46	299	246
Median (95% CI)	10 (9, 11)	14 (12, 17)	5 (4, 6)	5 (4, 7)	11 (10, 13)	17 (14, 21)
Recovery rate ratio (95% CI); p-value[a]	1.31 (1.12, 1.53); p < 0.001		1.16 (0.77, 1.72)		1.34 (1.13, 1.58)	
Mortality						
Hazard ratio (95% CI)[a]	0.73 (0.50, 1.07)		0.35 (0.04, 3.37)		0.75 (0.51, 1.11)	
Number of deaths by 14 days	35	56	1	2	34	54
Kaplan-Meier estimate (95% CI)	8.1% (5.8%, 11.1%)	12.8% (9.9%, 16.3%)	1.8% (0.3%, 12.2%)	6.3% (1.6%, 23.2%)	8.7% (6.3%, 12.0%)	13.4% (10.4%, 17.2%)
Ordinal Scale at Day 15 ± 2 Visit[b], N (%) in Each Category						
Total with Day 15 ordinal score data	453	424	52	46	401	378
1. Not hospitalized, no limitations	97 (21.4)	76 (17.9)	15 (28.8)	12 (26.1)	82 (20.4)	64 (16.9)
2. Not hospitalized, with limitations	175 (38.6)	140 (33.0)	27 (51.9)	25 (54.3)	148 (36.9)	115 (30.4)
3. Hospitalized, no active medical problems	11 (2.4)	6 (1.4)	6 (11.5)	3 (6.5)	5 (1.2)	3 (0.8)
4. Hospitalized, not on oxygen	24 (5.3)	19 (4.5)	1 (1.9)	1 (2.2)	23 (5.7)	18 (4.8)
5. Hospitalized, on oxygen	34 (7.5)	39 (9.2)	1 (1.9)	3 (6.5)	33 (8.2)	36 (9.5)
6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation	16 (3.5)	13 (3.1)	1 (1.9)	0 (0)	15 (3.7)	13 (3.4)
7. Hospitalized, on mechanical ventilation or ECMO	60 (13.3)	74 (17.5)	0 (0)	0 (0)	60 (15.0)	74 (19.6)
8. Death	36 (7.9)	57 (13.4)	1 (1.9)	2 (4.3)	35 (8.7)	55 (14.6)
Odds ratio; p-value[c]	1.46 (1.15, 1.86); p = 0.002		1.13 (0.53, 2.41)		1.50 (1.17, 1.93)	

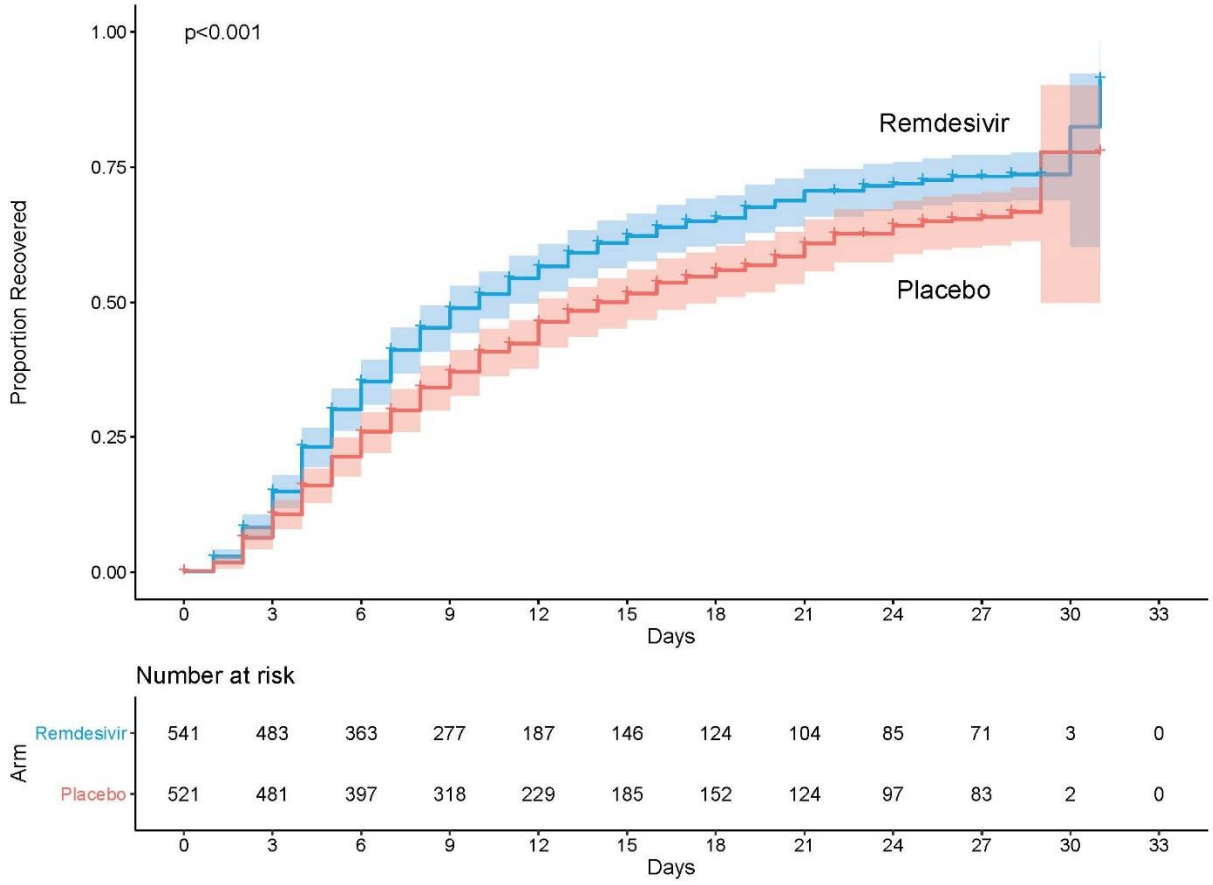
a Recovery rate ratio and hazard ratio calculated from the stratified Cox model for the analysis of the overall study population; an unstratified Cox model was used for the analysis of each baseline disease severity stratum. Recovery rate ratio and hazard ratio p-values calculated using the stratified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

b Ordinal scale at Day 15 visit is the subject's worst ordinal score during the previous day. In the RDV group, 88 subjects did not have ordinal scores for the Day 15 visit at the time of the data freeze (5 mild-to-moderate, 83 severe). In the placebo group, 97 subjects did not have ordinal scores for the Day 15 visit at the time of the data freeze (9 mild-to-moderate, 88 severe). Note, 2 subjects died 15 days postrandomization and are included in the ordinal scale but not in the 14-day mortality estimate.

c Odds ratio and odds ratio p-values calculated using a proportional odds model. Odds ratio values > 1 indicate benefit for RDV. P-value and CIs have not been adjusted for multiple comparisons.

Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Supplemental Table 1

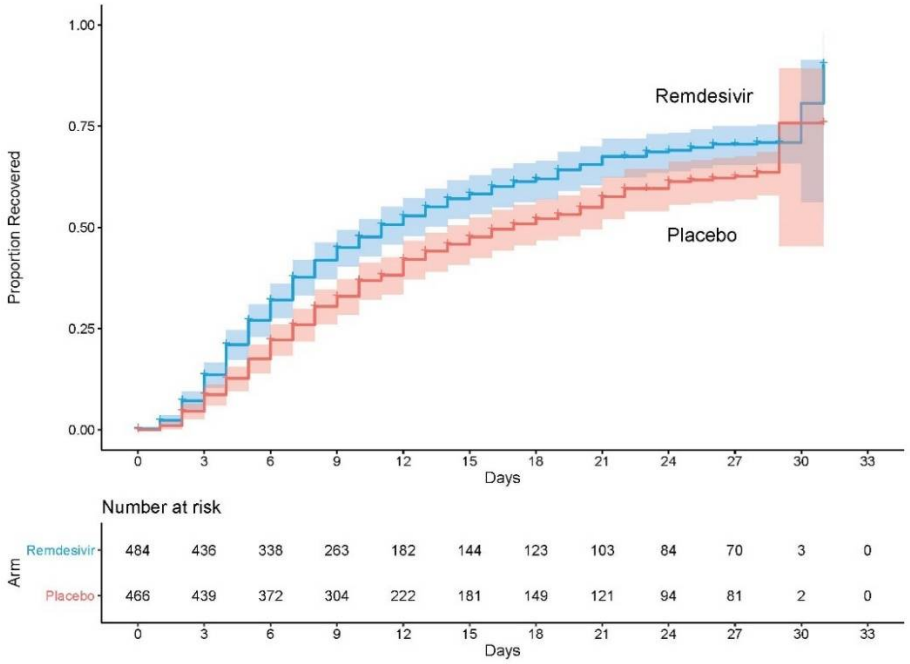
Figure 2. CO-US-540-5776: Kaplan-Meier Estimates of the Cumulative Recoveries Overall (Intent-to-Treat Population)



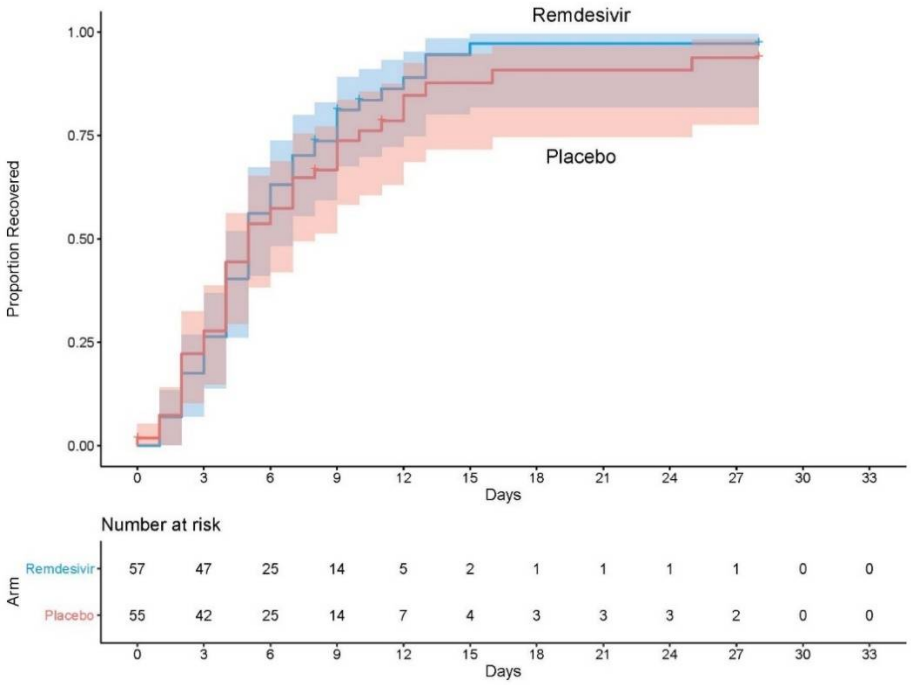
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Figure 2A

Figure 3. CO-US-540-5776: Kaplan-Meier Estimates of the Cumulative Recoveries by Disease Severity (Intent-to-Treat Population)

Severe Disease Stratum



Mild-to-Moderate Disease Stratum



Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Supplemental Figures 2A and 2B

Time to Recovery by Baseline Ordinal Score

Time to recovery was analyzed in subgroups defined by baseline ordinal score (4, 5, 6, or 7) (Table 16 and Figure 4). Shorter median recovery times were consistently observed in participants who had lower ordinal scores at baseline in both the RDV 10-day and placebo groups.

In the subgroup of participants with a baseline ordinal score of 5, a shorter median recovery time was observed in the RDV 10-day group compared with the placebo group (7 days [95% CI: 5 to 7] versus 8 days [95% CI: 7 to 10], respectively; RRR 1.40 [95% CI: 1.12 to 1.74]). In the subgroup of participants with a baseline ordinal score of 6, a numerically shorter median recovery time was also observed in the RDV 10-day group compared with the placebo group. In the subgroup of participants with a baseline ordinal score of 7, the median time to recovery was not estimable in the RDV 10-day group because the follow-up time was not long enough to observe more than 50% recoveries by the time of the 28 April 2020 data cut date.

Table 16. CO-US-540-5776: Outcomes Overall and by Baseline Ordinal Scale Score (Intent-to-Treat Population)

	Overall[a]		Baseline Ordinal Score 4		Baseline Ordinal Score 5		Baseline Ordinal Score 6		Baseline Ordinal Score 7	
	RDV 10-Day (N = 541)	Placebo (N = 521)	RDV 10-Day (N = 74)	Placebo (N = 61)	RDV 10-Day (N = 231)	Placebo (N = 203)	RDV 10-Day (N = 99)	Placebo (N = 101)	RDV 10-Day (N = 129)	Placebo (N = 153)
Days to Recovery										
Number of recoveries	351	292	67	49	189	140	50	46	45	57
Median (95% CI)	10 (9, 11)	14 (12, 17)	5 (4, 6)	5 (4, 7)	7 (5, 7)	8 (7, 10)	14 (LB = 10)[b]	21 (LB = 13)[b]	Not estimable	25 (LB = 21)[b]
Recovery rate ratio (95% CI); p-value[c]	1.31 (1.12, 1.53); p < 0.001		1.34 (0.93, 1.95)		1.40 (1.12, 1.74)		1.24 (0.83, 1.86)		0.84 (0.57, 1.24)	
Mortality										
Hazard ratio (95% CI)	0.73 (0.50, 1.07)		0.29 (0.03, 2.82)		0.34 (0.15, 0.78)		1.03 (0.50, 2.11)		1.05 (0.59, 1.87)	
Number of deaths by 14 days	35	56	1	2	7	20	14	14	13	20
Kaplan-Meier estimate[d] (95% CI)	8.1% (5.8%, 11.1%)	12.8% (9.9%, 16.3%)	1.4% (0.2%, 9.5%)	5.4% (1.4%, 20.0%)	4.2% (2.0%, 8.7%)	11.8% (7.7%, 17.8%)	16.5% (10.0%, 26.6%)	15.7% (9.5%, 25.4%)	11.1% (6.6%, 18.5%)	14.6% (9.6%, 21.9%)
Ordinal Scale at Day 15 ± 2 Visit[e], N (%) in Each Category										
Total with baseline and Day 15 ordinal score data	453	424	66	53	211	174	75	79	101	118
1. Not hospitalized, no limitations	97 (21.4)	76 (17.9)	22 (33.3)	16 (30.2)	54 (25.6)	46 (26.4)	12 (16.0)	7 (8.9)	9 (8.9)	7 (5.9)
2	175 (38.6)	140 (33.0)	32 (48.5)	22 (41.5)	107 (50.7)	75 (43.1)	31 (41.3)	29 (36.7)	5 (5.0)	14 (11.9)
3	11 (2.4)	6 (1.4)	7 (10.6)	4 (7.6)	4 (1.9)	2 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)
4	24 (5.3)	19 (4.5)	1 (1.5)	2 (3.8)	12 (5.7)	8 (4.6)	5 (6.7)	3 (3.8)	6 (5.9)	6 (5.1)
5	34 (7.5)	39 (9.2)	2 (3.0)	5 (9.4)	14 (6.6)	6 (3.4)	1 (1.3)	7 (8.9)	17 (16.8)	21 (17.8)
6	16 (3.5)	13 (3.1)	1 (1.5)	0 (0)	1 (0.5)	3 (1.7)	7 (9.3)	5 (6.3)	7 (6.9)	5 (4.2)
7	60 (13.3)	74 (17.5)	0 (0)	2 (3.8)	12 (5.7)	13 (7.5)	5 (6.7)	14 (17.7)	43 (42.6)	45 (38.1)

	Overall[a]		Baseline Ordinal Score 4		Baseline Ordinal Score 5		Baseline Ordinal Score 6		Baseline Ordinal Score 7	
	RDV 10-Day (N = 541)	**Placebo (N = 521)**	**RDV 10-Day (N = 74)**	**Placebo (N = 61)**	**RDV 10-Day (N = 231)**	**Placebo (N = 203)**	**RDV 10-Day (N = 99)**	**Placebo (N = 101)**	**RDV 10-Day (N = 129)**	**Placebo (N = 153)**
8. Death	36 (7.9)	57 (13.4)	1 (1.5)	2 (3.8)	7 (3.3)	21 (12.1)	14 (18.7)	14 (17.7)	14 (13.9)	20 (16.9)
Odds ratio; p-value[f]	1.46 (1.15, 1.86); p = 0.002		1.47 (0.75, 2.88)		1.27 (0.87, 1.84)		1.53 (0.86, 2.71)		0.98 (0.61, 1.58)	

LB = lower bound

a Overall results are from the primary outcome model stratified by baseline disease stratum ("mild-to-moderate" versus "severe").

b LB = 95% CI lower bound. Upper bound for 95% CI was not estimable.

c Recovery rate ratio and hazard ratio 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 ordinal score subgroup. Recovery rate ratio and hazard ratio p-values calculated using the stratified log-rank test. Recovery rate ratios > 1 indicate benefit for RDV. Hazard ratios < 1 indicate benefit for RDV.

d Kaplan-Meier method was used to estimate mortality by 14 days because not all subjects had full follow-up at the time of analysis. This provides an unbiased estimate for mortality.

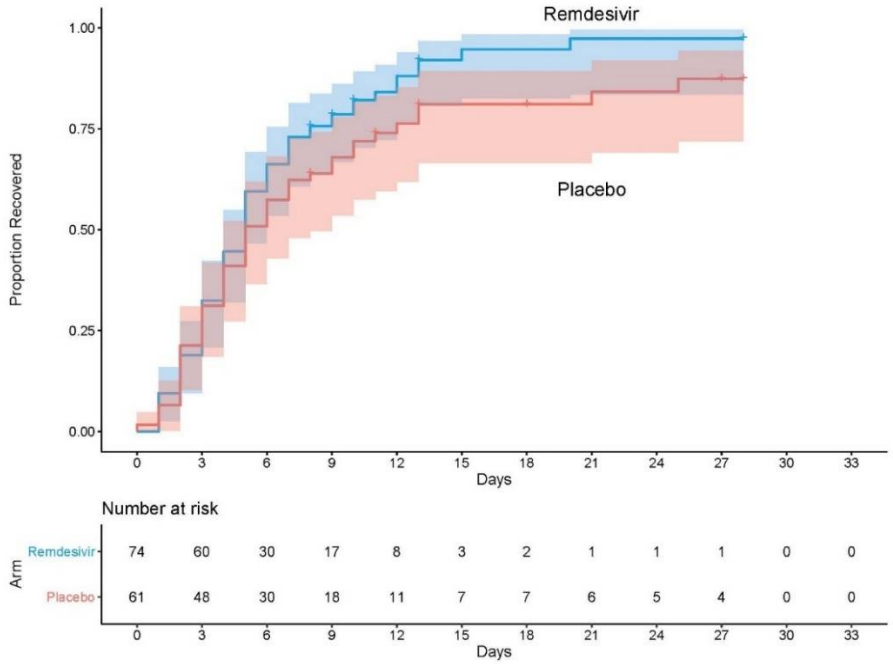
e Ordinal scale at Day 15 visit is the subject's worst ordinal score during the previous day. In the RDV group, 88 subjects did not have ordinal scores for the Day 15 visit at the time of the data freeze (5 mild-to-moderate, 83 severe). In the placebo group, 97 subjects did not have ordinal scores for the Day 15 visit at the time of the data freeze (9 mild-to-moderate, 88 severe). Note, 2 subjects died 15 days postrandomization and are included in the ordinal scale but not in the 14-day mortality estimate.

f Odds ratio and odds ratio p-values calculated using a proportional odds model. Odds ratio values > 1 indicate benefit for RDV. P-value and CIs have not been adjusted for multiple comparisons.

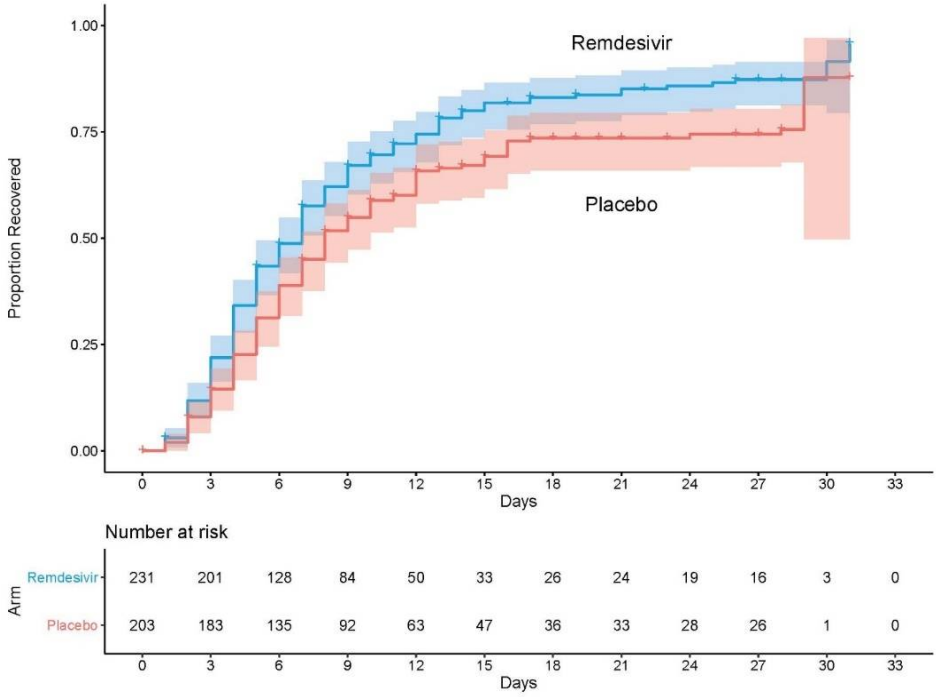
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Table 2

Figure 4. CO-US-540-5776: Kaplan-Meier Estimates of the Cumulative Recoveries by Baseline Ordinal Score (Intent-to-Treat Population)

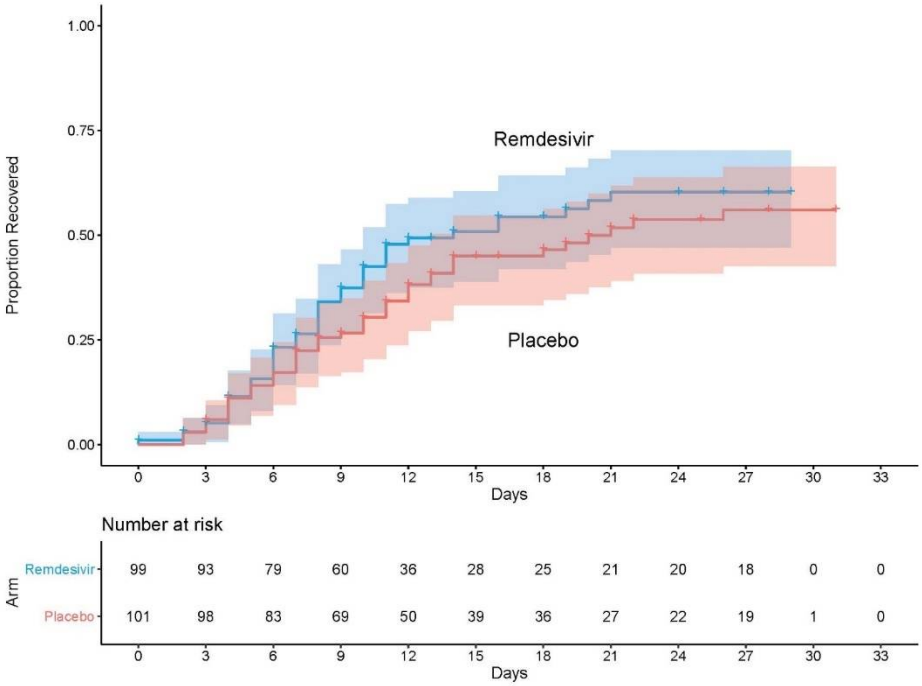
Baseline Ordinal Score 4



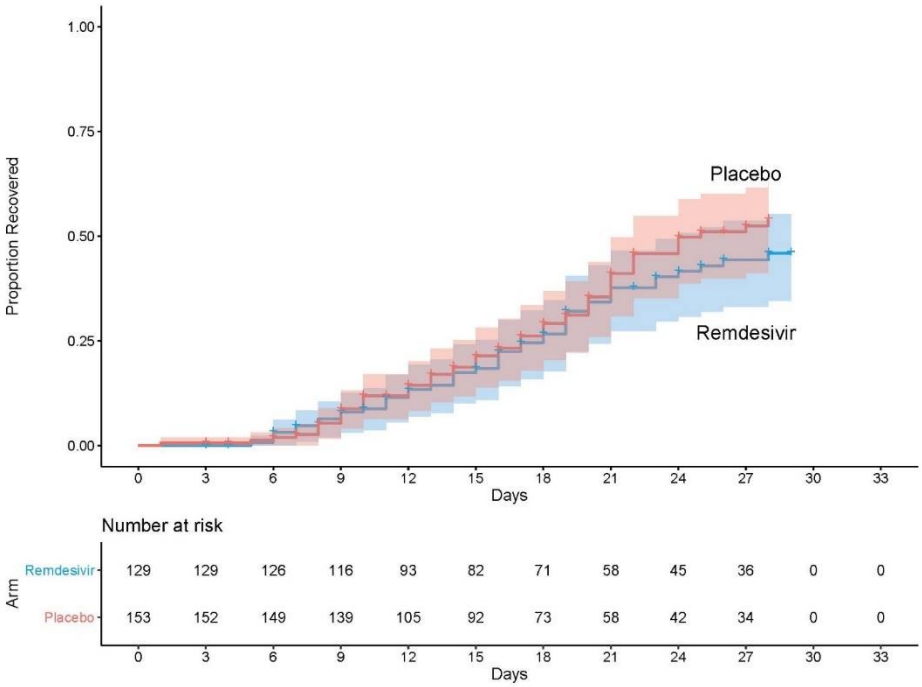
Baseline Ordinal Score 5



Baseline Ordinal Score 6



Baseline Ordinal Score 7



Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Figures 2B to 2E

3.2.1.1.2. Secondary Efficacy Endpoints

3.2.1.1.2.1. Key Secondary Efficacy Endpoint: Clinical Status (8-Point Ordinal Scale) at Day 15

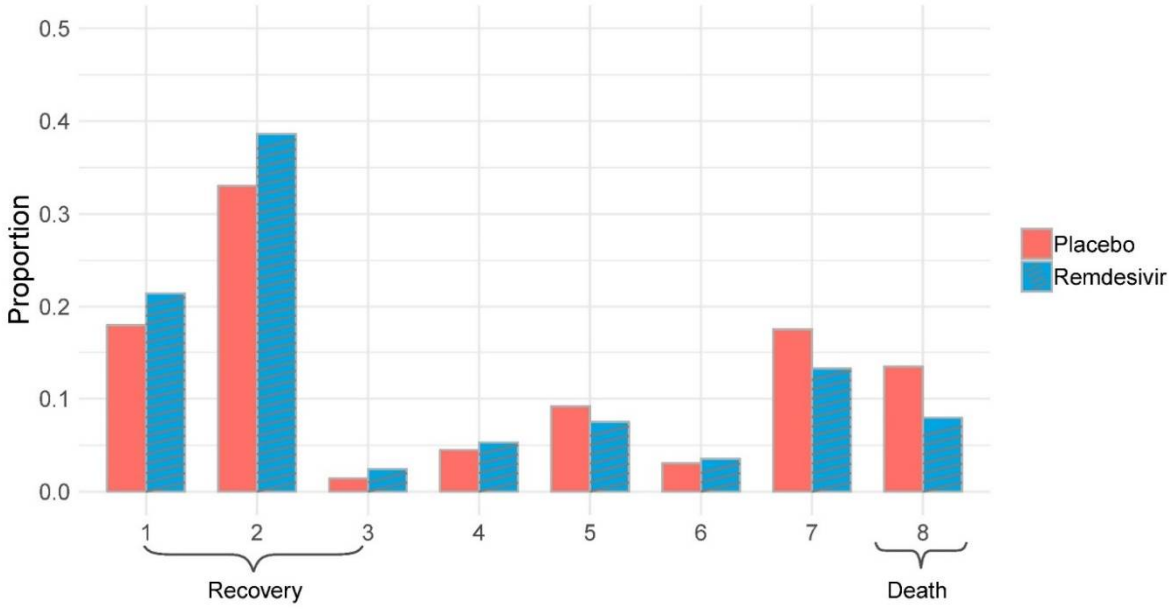
The odds of improvement in the ordinal score at Day 15 were significantly higher in the RDV 10-day group compared with the placebo group, as determined by a proportional odds model (OR for improvement 1.46; 95% CI: 1.15 to 1.86; p = 0.002) (Table 15). In addition, the odds of improvement in the ordinal score were numerically higher in the RDV 10-day group compared with the placebo group in participants in the following strata/subgroups (Table 15 and Table 16):

- Mild-to-moderate disease stratum: 1.13 (95% CI: 0.53 to 2.41) (RDV n = 57; placebo n = 55)
- Severe disease stratum: 1.50 (95% CI: 1.17 to 1.93) (RDV n = 484; placebo n = 466)
- Subgroup with ordinal score of 4: 1.47 (95% CI: 0.75 to 2.88) (RDV n = 74; placebo n = 61)
- Subgroup with ordinal score of 5: 1.27 (95% CI: 0.87 to 1.84) (RDV n = 231; placebo n = 203)
- Subgroup with ordinal score of 6: 1.53 (95% CI: 0.86 to 2.71) (RDV n = 99; placebo n = 101)

In the subgroup of participants with an ordinal score of 7 at baseline, the odds of improvement in the ordinal score were not numerically higher in the RDV 10-day group compared with the placebo group (0.98; 95% CI: 0.61 to 1.58) (RDV n = 129; placebo n = 153).

Higher proportions of Day 15 ordinal scores of 1, 2, and 3 were observed in participants in the RDV 10-day group compared with the placebo group (Figure 5). Lower proportions of Day 15 ordinal scores of 7, indicating poor clinical status and need for invasive mechanical ventilation or ECMO, were observed in participants in the RDV 10-day group compared with the placebo group. Similarly, lower proportions of Day 15 ordinal scores of 8 (death) were observed in the RDV 10-day group compared with the placebo group. However, it should be noted that the proportion of participants in the RDV 10-day group with an ordinal score of 7 at baseline was 23.8% compared with 29.4% in the placebo group (Table 5).

Figure 5. CO-US-540-5776: Histogram of Ordinal Scores on Day 15 by Treatment Group (Intent-to-Treat Population)



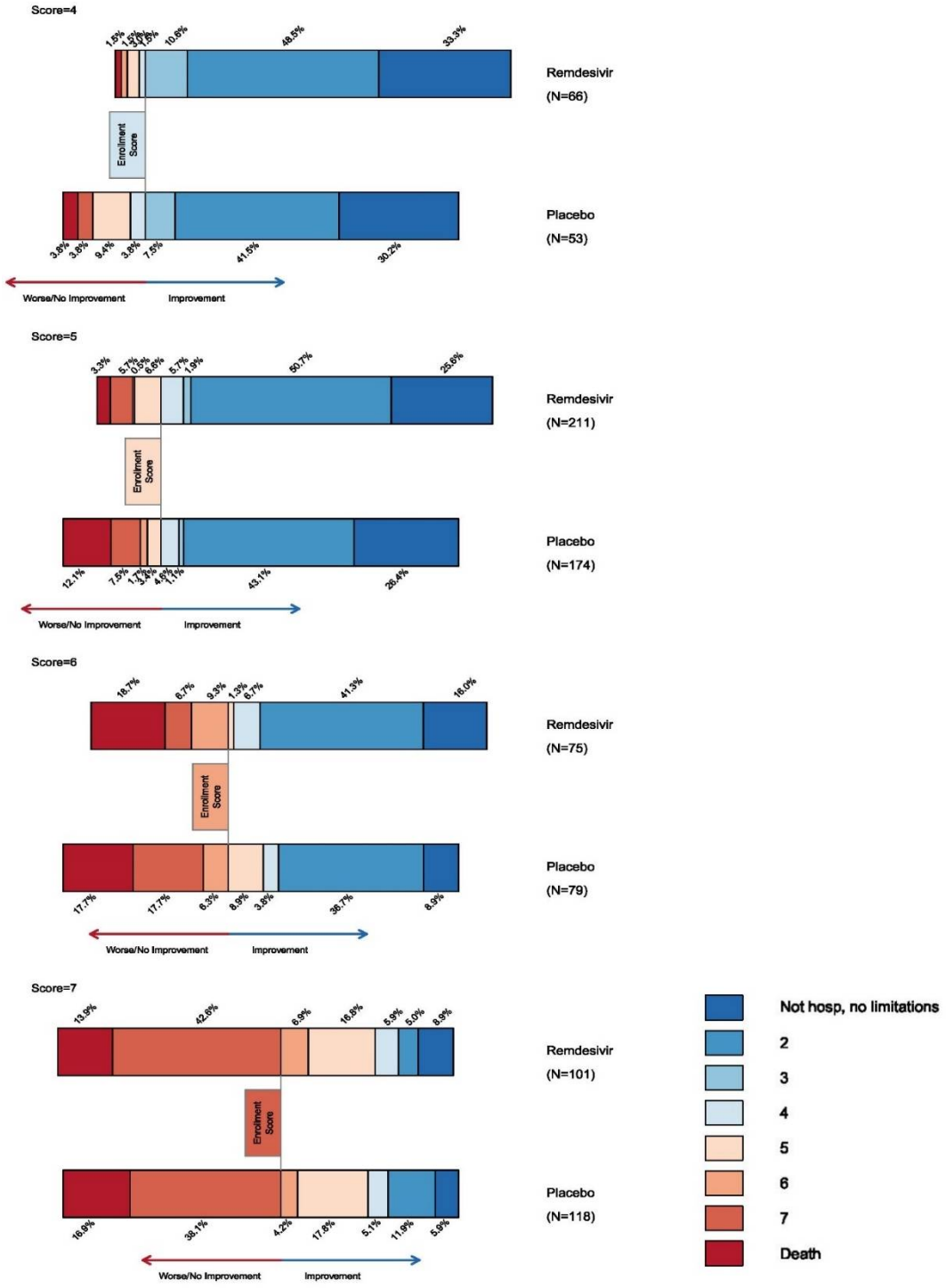
In the above figure, the x-axis indicates the ordinal scores 1 through 8 (1, 2, and 3 as recovery scores and 8 as death), and the y-axis shows the proportion of each of the 8 ordinal scores.
Proportion = proportion of scores at Day 15 on the ordinal scale:
1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities and/or requiring home oxygen
3. Hospitalized, not requiring supplemental oxygen—no longer requiring ongoing medical care
4. Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise)
5. Hospitalized, requiring supplemental oxygen
6. Hospitalized, on noninvasive ventilation or high-flow oxygen devices
7. Hospitalized, on invasive mechanical ventilation or ECMO
8. Death
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Figure 3

Shift bar plots showing changes in clinical status from baseline to Day 15 by baseline ordinal score are presented in Figure 6.

For participants in the subgroups with baseline ordinal scores of 4, 5, or 6, improvements in clinical status at Day 15 were evident in higher proportions in the RDV 10-day group compared with the placebo group. Clinical status improved in the majority of participants in both treatment groups from baseline to Day 15. For participants in the subgroup with a baseline ordinal score of 4, a numerically lower proportion of participants in the RDV 10-day group progressed to requiring oxygen support or to death compared with the placebo group (4 of 66 participants [6.1%] versus 9 of 53 participants [17.0%], respectively, by Day 15) (Table 16).

For participants in the subgroup with a baseline ordinal score of 7, improvements in clinical status at Day 15 were observed in similar proportions in the RDV 10-day and placebo groups. Clinical status did not improve or worsen in the majority of participants in both treatment groups from baseline to Day 15.

Figure 6. CO-US-540-5776: Day 15 Outcomes by Baseline Ordinal Score (Intent-to-Treat Population)



Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Supplemental Figure 1

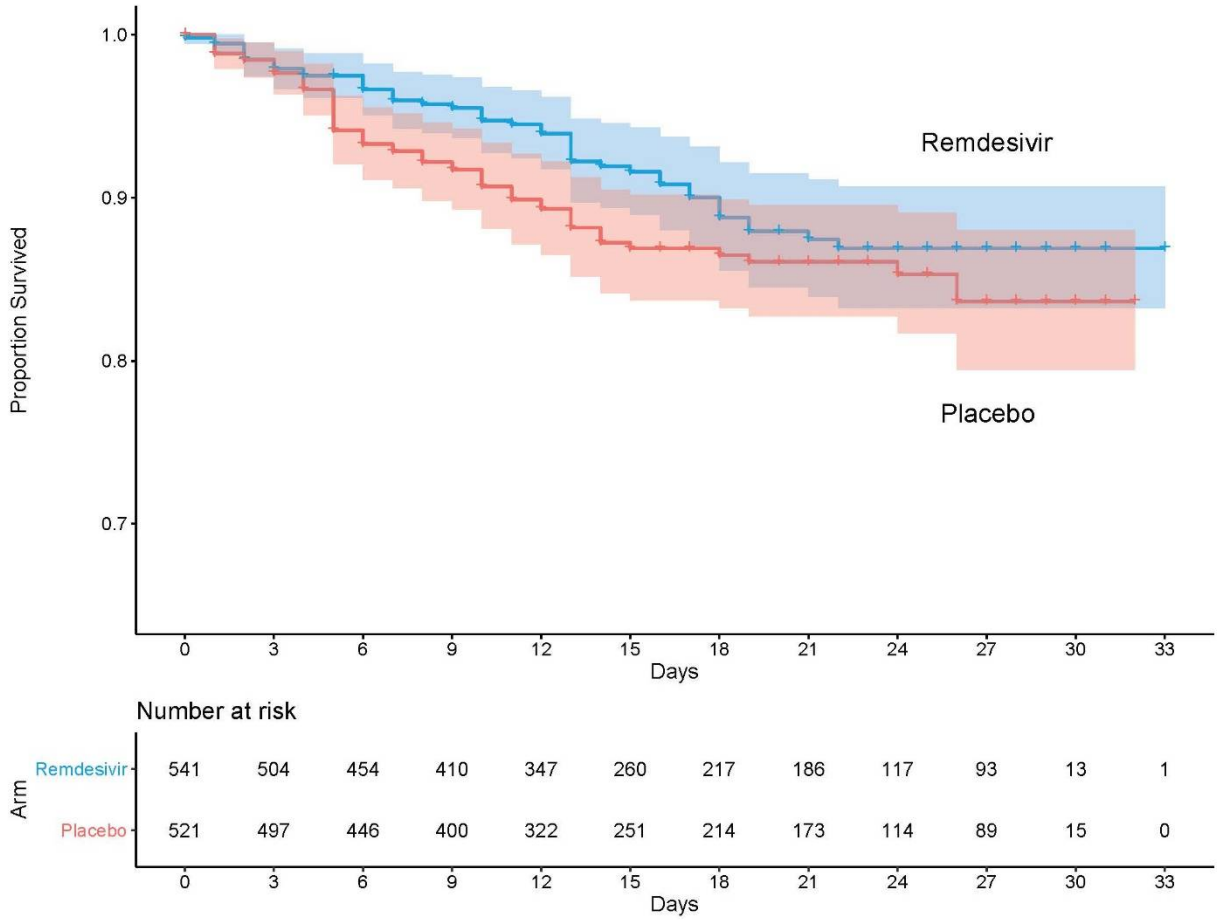
3.2.1.1.2.2. Mortality by Day 14

Overall, the 14-day mortality was numerically lower in the RDV 10-day group (35 of 541 participants) compared with the placebo group (56 of 521 participants) (Table 15). Although the risk of death was 27% lower in the RDV 10-day group compared with the placebo group, the difference was not statistically significant (HR 0.73; 95% CI: 0.50 to 1.07). The KM estimates of 14-day mortality were 8.1% and 12.8% in the RDV 10-day and placebo groups, respectively. The KM survival curves for the RDV 10-day and placebo groups separated early, after approximately 5 days of study treatment, suggesting a lower incidence of mortality in the RDV 10-day group versus the placebo group starting from Day 5 in the overall study population (Figure 7).

In participants in the severe disease stratum at baseline, the 14-day mortality was numerically lower in the RDV 10-day group (34 of 484 participants) compared with the placebo group (54 of 466 participants) (Table 15). A lower risk of death was observed in the RDV 10-day group versus the placebo group, but the difference was not statistically significant (HR 0.75; 95% CI: 0.51 to 1.11). The KM estimates of 14-day mortality were 8.7% and 13.4% in the RDV 10-day and placebo groups, respectively. In participants in the severe disease stratum at baseline, the KM survival curves for the RDV 10-day and placebo groups separated early, after approximately 5 days of study treatment, suggesting a lower incidence of mortality in the RDV 10-day group versus the placebo group starting from Day 5 (Figure 8). In participants in the mild-to-moderate disease stratum at baseline, no meaningful differences in 14-day mortality were observed (RDV 10-day group 1 of 57 participants; placebo group 2 of 55 participants).

In the subgroup of participants with a baseline ordinal score of 5 (hospitalized, on oxygen), a lower risk of death was observed (HR 0.34; 95% CI: 0.15 to 0.78) in the RDV 10-day group (n = 231) versus the placebo group (n = 203) (Table 16). There was clear separation of the KM survival curves after approximately Day 6 of treatment, suggesting a lower incidence of mortality in the RDV 10-day group versus the placebo group starting from approximately Day 6 (CO-US-540-5776 Preliminary CSR, Section 15.1, Supplemental Figure 3C). No other differences were observed in 14-day mortality in the other 3 subgroups defined by baseline ordinal score (4, 6, and 7) (CO-US-540-5776 Preliminary CSR, Section 15.1, Supplemental Figures 3B, 3D, and 3E, respectively).

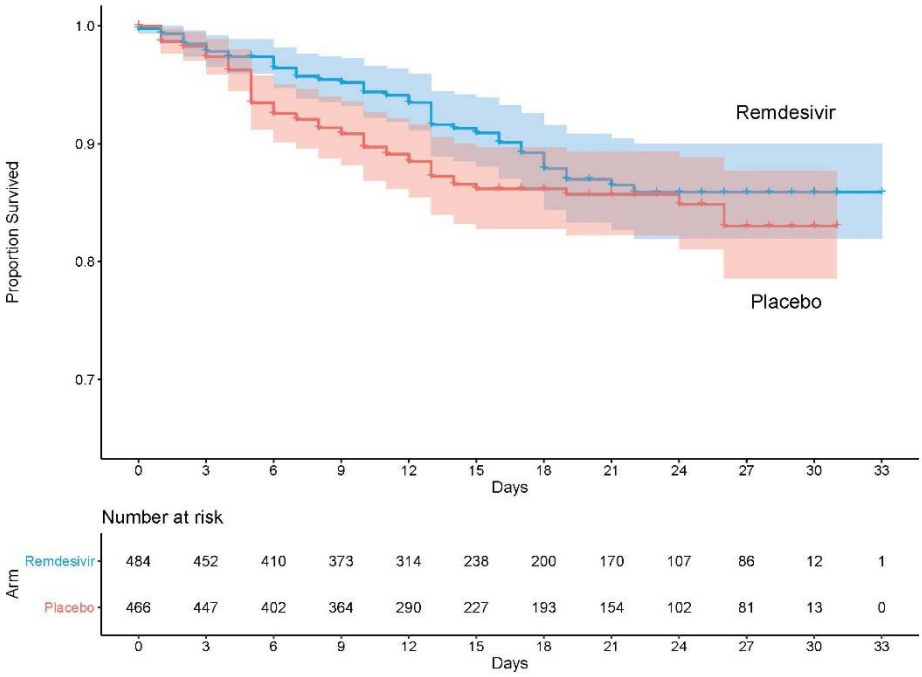
Figure 7. CO-US-540-5776: Kaplan-Meier Estimates of Survival Overall (Intent-to-Treat Population)



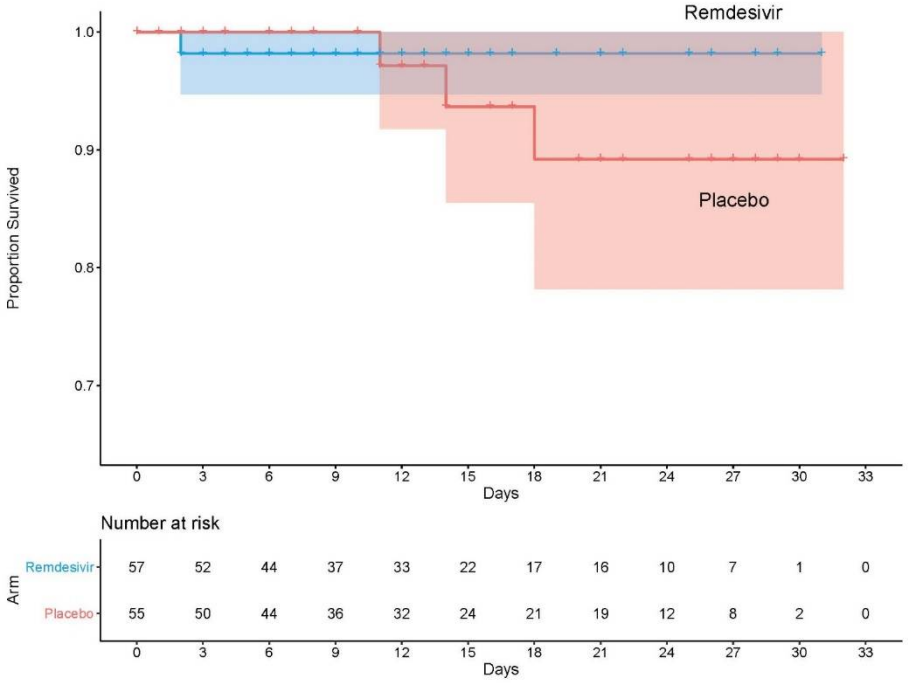
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Supplemental Figure 3A

Figure 8. CO-US-540-5776: Kaplan-Meier Estimates of Survival by Disease Severity (Intent-to-Treat Population)

Severe Disease Stratum



Mild-to-Moderate Disease Stratum



Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Supplemental Figures 4A and 4B

3.2.1.2. Study GS-US-540-5773

3.2.1.2.1. Primary Efficacy Endpoint: Clinical Status (7-Point Ordinal Scale) on Day 14

The primary efficacy endpoint for Study GS-US-540-5773 was clinical status assessed using a 7-point ordinal scale on Day 14 in the FAS.

Primary analysis of the primary efficacy 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 odds of improved clinical status on Day 14 (p = 0.1563) (Table 17).

Because the score test for the proportional odds assumption was statistically significant (p = 0.0040), suggesting that the assumption of proportional odds was not met (ie, the effect of treatment or baseline clinical status was not consistent across the different ordinal scale categories), an alternative analysis was employed (stratified Wilcoxon rank sum test), which demonstrated that there was no statistically significant difference between treatment groups in clinical status on Day 14 (Table 18).

Table 17. GS-US-540-5773: Analysis of Clinical Status (7-Point Ordinal Scale) on Day 14 Using Proportional Odds with Baseline Adjustment (Full Analysis Set)

	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
RDV 10 Days/RDV 5 Days	397	0.0040	−0.29 (0.201)	0.75 (0.507, 1.115)	0.1563
Baseline Clinical Status	—	—	1.32 (0.158)	3.73 (2.734, 5.080)	< 0.0001

SE = standard error
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
Baseline was the last available value recorded on or prior to dosing.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.9.1.1.1

When no adjustment was made for baseline clinical status, differences between the 2 treatment durations on Day 14 were statistically significant (p = 0.0368) (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.9.1.1.2).

Clinical status on the 7-point ordinal scale is presented by study day and treatment group for the FAS in Table 18.

Table 18. GS-US-540-5773: Clinical Status (7-Point Ordinal Scale) by Study Day (Full Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	RDV 10 Days vs RDV 5 Days P-Value
Baseline			
1 - Death	0	0	0.0230
2	4 (2.0%)	9 (4.6%)	
3	49 (24.5%)	59 (29.9%)	
4	113 (56.5%)	108 (54.8%)	
5	34 (17.0%)	21 (10.7%)	
6	0	0	
7 - Not Hospitalized	0	0	
Day 5			
1 - Death	2 (1.0%)	9 (4.6%)	0.1088
2	25 (12.5%)	42 (21.3%)	
3	40 (20.0%)	36 (18.3%)	
4	70 (35.0%)	62 (31.5%)	
5	31 (15.5%)	21 (10.7%)	
6	6 (3.0%)	1 (0.5%)	
7 - Not Hospitalized	26 (13.0%)	26 (13.2%)	
Day 14			
1 - Death	16 (8.0%)	21 (10.7%)	0.1359
2	17 (8.5%)	33 (16.8%)	
3	8 (4.0%)	10 (5.1%)	
4	19 (9.5%)	15 (7.6%)	
5	12 (6.0%)	12 (6.1%)	
6	8 (4.0%)	3 (1.5%)	
7 - Not Hospitalized	120 (60.0%)	103 (52.3%)	
Day 28			
1 - Death	23 (11.5%)	28 (14.2%)	0.1387
2	6 (3.0%)	17 (8.6%)	
3	3 (1.5%)	6 (3.0%)	
4	3 (1.5%)	9 (4.6%)	
5	12 (6.0%)	8 (4.1%)	
6	2 (1.0%)	2 (1.0%)	
7 - Not Hospitalized	151 (75.5%)	127 (64.5%)	

vs = versus
Clinical status: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on noninvasive 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
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
P-values were based on Wilcoxon rank sum test (stratified by baseline clinical status for postbaseline days).
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.9.1.2.1

There were no statistically significant differences in changes from baseline in clinical status on the 7-point ordinal scale between the 2 treatment groups at any postbaseline assessment (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.9.1.9).

Clinical Status on Day 14 by Baseline Oxygen Support Status

Participants on less invasive oxygen support status at baseline tended to be in a higher (better) clinical status category on the 7-point ordinal scale on Day 14 (Table 19).

Table 19. GS-US-540-5773: Clinical Status (7-Point Ordinal Scale) on Day 14 by Baseline Oxygen Support (Full Analysis Set)

	Invasive Mechanical Ventilation		High-Flow Oxygen		Low-Flow Oxygen		Room Air	
	RDV 5 Days (N = 4)	RDV 10 Days (N = 9)	RDV 5 Days (N = 49)	RDV 10 Days (N = 59)	RDV 5 Days (N = 113)	RDV 10 Days (N = 108)	RDV 5 Days (N = 34)	RDV 10 Days (N = 21)
Day 14								
1 - Death	1 (25.0%)	4 (44.4%)	8 (16.3%)	13 (22.0%)	5 (4.4%)	2 (1.9%)	2 (5.9%)	2 (9.5%)
2	2 (50.0%)	4 (44.4%)	6 (12.2%)	19 (32.2%)	9 (8.0%)	9 (8.3%)	0	1 (4.8%)
3	0	0	7 (14.3%)	6 (10.2%)	1 (0.9%)	3 (2.8%)	0	1 (4.8%)
4	1 (25.0%)	0	7 (14.3%)	5 (8.5%)	9 (8.0%)	10 (9.3%)	2 (5.9%)	0
5	0	0	1 (2.0%)	2 (3.4%)	11 (9.7%)	7 (6.5%)	0	3 (14.3%)
6	0	0	1 (2.0%)	0	5 (4.4%)	2 (1.9%)	2 (5.9%)	1 (4.8%)
7 - Not Hospitalized	0	1 (11.1%)	19 (38.8%)	14 (23.7%)	73 (64.6%)	75 (69.4%)	28 (82.4%)	13 (61.9%)

Clinical status: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on noninvasive 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
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment. Baseline was the last available value recorded on or prior to dosing.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.9.1.5

3.2.1.2.2. Other Efficacy Endpoints of Interest

3.2.1.2.2.1. Recovery

The proportions of participants in the FAS with recovery, defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7, are presented by treatment group and study day in Table 20. There were no statistically significant differences between the 2 treatment groups in the proportions of participants with recovery at any time point.

Median (Q1, Q3) time to recovery was shorter in the RDV 5-day group compared with the RDV 10-day group (10 [6, 26] days versus 12 [7, not applicable] days, respectively; p = 0.0249) (GS-US-540-5773 Interim [Final Part A] CSR, Tables 15.9.2.6.1 to 15.9.2.6.3 and Figure 15.9.10).

Table 20. GS-US-540-5773: Proportion of Participants with Recovery (Full Analysis Set)

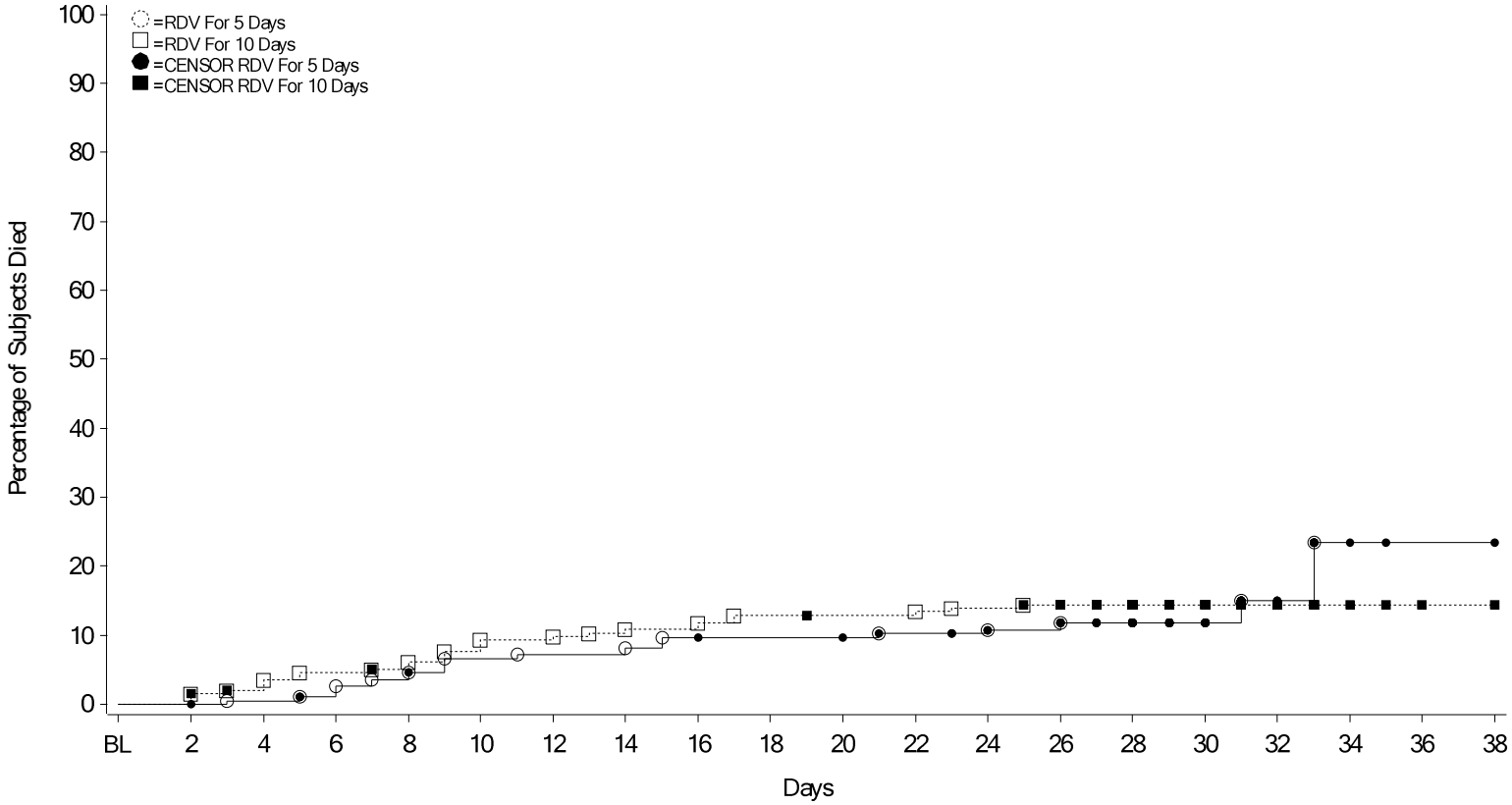
	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	RDV 10 Days vs RDV 5 Days	
			P-Value	Baseline-Adjusted Difference in Percentages (95% CI)
Subjects with Recovery on Day 5				
Recovered	32 (16.0%)	27 (13.7%)	0.9943	0.0% (−7.1% to 7.0%)
95% CI	11.2% to 21.8%	9.2% to 19.3%		
Not Recovered	168 (84.0%)	170 (86.3%)		
Subjects with Recovery on Day 14				
Recovered	128 (64.0%)	106 (53.8%)	0.1912	−5.9% (−15.0% to 3.1%)
95% CI	56.9% to 70.6%	46.6% to 60.9%		
Not Recovered	72 (36.0%)	91 (46.2%)		
Subjects with Recovery on Day 28				
Recovered	153 (76.5%)	129 (65.5%)	0.0792	−7.2% (−15.4% to 0.9%)
95% CI	70.0% to 82.2%	58.4% to 72.1%		
Not Recovered	47 (23.5%)	68 (34.5%)		

vs = versus
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment. Baseline was the last available value recorded on or prior to dosing. Recovery is defined as a baseline score of 2 through 5 improved to 6 or 7 or a baseline score of 6 improved to 7.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson exact method.
P-value comparing the percentages of subjects with recovery was from the Cochran-Mantel-Haenszel test stratified by baseline clinical status. The difference in percentages of subjects with recovery between treatment groups and 95% CI were calculated based on the Mantel-Haenszel percentages adjusted by baseline clinical status.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.9.2.6.4

3.2.1.2.2.2. Mortality

There were no statistically significant differences in time to death between the RDV 5-day and the 10-day groups (Figure 9).

Figure 9. GS-US-540-5773: Kaplan-Meier Estimate of Time to Death – All-Cause Mortality (Full Analysis Set)



	BL	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
○ RDV For 5 Days (n=):	200	199	198	191	186	182	181	179	175	175	174	172	167	158	74	28	10	2	1	
□ RDV For 10 Days (n=):	197	193	188	186	181	175	174	172	170	168	167	166	165	156	74	23	10	3	1	

BL = baseline
Participants who did not die were censored on the day of their last study visit.
Kaplan-Meier curves were not stratified for baseline clinical status.
n represents the numbers of participants remaining at the end of the interval.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Figure 15.9.2

3.2.1.2.2.3. Shift in Oxygen Support Status

There were no notable differences between the treatment groups in shift in oxygen support status from baseline (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.9.2.3.2).

An analysis of oxygen support status from Day 5 to Day 14 was conducted to determine whether participants may have benefitted from receiving more than 5 days of treatment with RDV (Table 21). For participants who were on invasive mechanical ventilation or ECMO on Day 5, those in the RDV 10-day group appeared to have better outcomes than those in the RDV 5-day group. A lower proportion of participants in the RDV 10-day group than the RDV 5-day group died on or before Day 14 (7 of 41 participants [17.1%] versus 10 of 25 participants [40.0%], respectively), and a higher proportion had improvements in oxygen support status on Day 14 (3 participants [7.3%] each improved to high-flow oxygen and low-flow oxygen, and 5 participants [12.2%] were discharged on or before Day 14 in the RDV 10-day group versus 2 participants [8.0%] who improved to low-flow oxygen, 1 participant [4.0%] who improved to room air, and 2 participants [8.0%] who were discharged on or before Day 14 in the RDV 5-day group).

Table 21. GS-US-540-5773: Shift in Oxygen Support Status from Day 5 to Day 14 (Full Analysis Set)

	RDV 5 Days (N = 170)				RDV 10 Days (N = 160)			
	Day 5 Oxygen Support Status				Day 5 Oxygen Support Status			
	Invasive Mechanical Ventilation (N = 25)	High-Flow Oxygen (N = 40)	Low-Flow Oxygen (N = 68)	Room Air (N = 37)	Invasive Mechanical Ventilation (N = 41)	High-Flow Oxygen (N = 35)	Low-Flow Oxygen (N = 62)	Room Air (N = 22)
Oxygen Support Status on Day 14								
Death	10 (40.0%)	4 (10.0%)	0	0	7 (17.1%)	5 (14.7%)	0	0
Invasive Mechanical Ventilation	10 (40.0%)	7 (17.5%)	0	0	23 (56.1%)	9 (26.5%)	0	0
High-Flow Oxygen	0	7 (17.5%)	1 (1.5%)	0	3 (7.3%)	5 (14.7%)	0	0
Low-Flow Oxygen	2 (8.0%)	9 (22.5%)	5 (7.7%)	2 (5.9%)	3 (7.3%)	5 (14.7%)	4 (7.1%)	0
Room Air	1 (4.0%)	2 (5.0%)	5 (7.7%)	5 (14.7%)	0	1 (2.9%)	6 (10.7%)	5 (22.7%)
Discharge	2 (8.0%)	11 (27.5%)	54 (83.1%)	27 (79.4%)	5 (12.2%)	9 (26.5%)	46 (82.1%)	17 (77.3%)
Missing	0	0	3	3	0	1	6	0

Oxygen support status was derived from death, hospital discharge, and the ordinal scale as follows: death for all days on or after the death date; discharge for all days on or after discharged alive date; observed value from the ordinal scale.
Ordinal scale values were mapped as follows: 1 = Death; 2 = Invasive mechanical ventilation; 3 = High-flow oxygen; 4 = Low-flow oxygen; 5 or 6 = Room Air; 7 = Discharge.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table req10636.1

3.2.1.2.2.4. ≥ 2-Point Clinical Improvement

There were no statistically significant differences between the treatment groups in the proportion of participants with a ≥ 2-point improvement from baseline in clinical status on a 7-point ordinal scale at any time point (Table 22).

The median (Q1, Q3) time to a ≥ 2-point clinical improvement was shorter in the RDV 5-day group versus the RDV 10-day group (10 [6, 24] days versus 12 [7, not applicable] days, respectively; p = 0.0298) (GS-US-540-5773 Interim [Final Part A] CSR, Tables 15.9.2.4.1 to 15.9.2.4.3 and Figure 15.9.8).

Table 22. GS-US-540-5773: Proportion of Participants with ≥ 2-Point Improvement (Full Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	RDV 10 Days vs RDV 5 Days	
			P-Value	Baseline-Adjusted Difference in Percentages (95% CI)
Subjects with ≥ 2-Point Improvement on Day 5				
Improved	33 (16.5%)	29 (14.7%)	0.9608	0.2% (−7.1% to 7.5%)
95% CI	11.6% to 22.4%	10.1% to 20.5%		
Not Improved	167 (83.5%)	168 (85.3%)		
Subjects with ≥ 2-Point Improvement on Day 14				
Improved	128 (64.0%)	107 (54.3%)	0.1863	−6.1% (−15.4% to 3.1%)
95% CI	56.9% to 70.6%	47.1% to 61.4%		
Not Improved	72 (36.0%)	90 (45.7%)		
Subjects with ≥ 2-Point Improvement on Day 28				
Improved	155 (77.5%)	132 (67.0%)	0.0916	−7.0% (−15.2% to 1.2%)
95% CI	71.1% to 83.1%	60.0% to 73.5%		
Not Improved	45 (22.5%)	65 (33.0%)		

vs = versus
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment. Baseline was the last available value recorded on or prior to dosing. Clinical improvement is defined as a ≥ 2-point improvement from baseline clinical status or discharged alive. The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson exact method.
P-value comparing the percentages of subjects with improvement was from the Cochran-Mantel-Haenszel test stratified by baseline clinical status. The difference in percentages of subjects with improvement between treatment groups and 95% CI were calculated based on the Mantel-Haenszel percentages adjusted by baseline clinical status.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.9.2.4.4

3.2.1.3. Study GS-US-540-5774

3.2.1.3.1. Primary Efficacy Endpoint: Clinical Status (7-Point Ordinal Scale) on Day 11

The primary efficacy endpoint for Study GS-US-540-5774 was clinical status assessed using a 7-point ordinal scale on Day 11 in the FAS.

Primary analysis of the primary efficacy endpoint demonstrated that treatment with RDV for 5 days resulted in greater odds of improved clinical status on Day 11 compared with treatment with only SOC (p = 0.0174) (Table 23). The score test for the proportional odds assumption was not statistically significant (p = 0.3960), suggesting that the assumption of proportional odds was met. An alternative analysis by Wilcoxon rank sum test further demonstrated a statistically significant difference between treatment groups in clinical status on Day 11 (p = 0.0171) (Table 25).

The comparison of treatment with RDV for 10 days versus treatment with only SOC resulted in similar odds of improved clinical status on Day 11 (p = 0.1826). The score test for the proportional odds assumption was statistically significant (p < 0.0001), suggesting that the assumption of proportional odds was not met (ie, the effect of treatment was not consistent across the different ordinal scale categories). An alternative analysis by Wilcoxon rank sum test demonstrated that there was no statistically significant difference between treatment groups in clinical status on Day 11 (p = 0.1826) (Table 25).

Table 23. GS-US-540-5774: Analysis of Clinical Status (7-Point Ordinal Scale) on Day 11 Using Proportional Odds (Full Analysis Set)

	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
RDV 5 Days/SOC	391	0.3960	0.50 (0.210)	1.65 (1.092, 2.483)	0.0174
RDV 10 Days/SOC	393	< 0.0001	0.27 (0.203)	1.31 (0.880, 1.952)	0.1826

SE = standard error
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.9.1.1.1

Results from the secondary analyses of the primary endpoint with adjustment for baseline clinical status were similar to results from the primary analyses. Odds of improved clinical status on Day 11 were greater in the RDV 5-day group versus the SOC only group (p = 0.0168) and similar between the RDV 10-day and SOC only groups (p = 0.2186) (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.9.1.1.2).

Results from the sensitivity analyses of the primary endpoint excluding participants on oxygen support at baseline were similar to results from the primary analyses. Odds of improved clinical status on Day 11 were greater in the RDV 5-day group versus the SOC only group (p = 0.0483) and similar between the RDV 10-day and SOC only groups (p = 0.5197) (Table 24 and Table 31).

Table 24. GS-US-540-5774: Analysis of Clinical Status (7-Point Ordinal Scale) on Day 11 Using Proportional Odds (Full Analysis Set, Excluding Participants on Oxygen Support at Baseline)

	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
RDV 5 Days/SOC	322	0.8123	0.46 (0.234)	1.59 (1.003, 2.511)	0.0483
RDV 10 Days/SOC	331	< 0.0001	0.14 (0.223)	1.15 (0.746, 1.786)	0.5197

SE = standard error
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
The odds ratio and corresponding 95% CI were from a proportional odds model on Day 11 clinical status with a treatment effect.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table req10643.17

Clinical status on the 7-point ordinal scale is presented by study day and treatment group for the FAS in Table 25.

There was no statistically significant difference between the RDV 5-day and SOC only groups in clinical status on a 7-point ordinal scale at baseline. Postbaseline, there were statistically significant differences between the RDV 5-day and SOC only groups in clinical status on the 7-point ordinal scale on Day 6, following completion of up to 5 days of RDV treatment ($p = 0.0361$), and on Day 8 ($p = 0.0281$), Day 9 ($p = 0.0066$), Day 10 ($p = 0.0210$), and Day 11 ($p = 0.0171$) (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.9.1.2.1). Postbaseline, similar results were observed in clinical status on the 7-point ordinal scale by study day excluding participants on oxygen support at baseline (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Tables 15.9.1.5 and req10643.16).

There was a statistically significant difference between the RDV 10-day and SOC only groups in clinical status on a 7-point ordinal scale at baseline ($p = 0.0337$). There were no statistically significant differences between the RDV 10-day and SOC only groups at any postbaseline assessment.

By Day 11, the percentages of participants with a worsening from baseline in clinical status of ≥ 1 point were as follows: RDV 5-day group 3.1%, 6 participants; RDV 10-day group 6.2%, 12 participants; SOC only group 11.0%, 22 participants and the percentages of deaths reported were as follows: RDV 10-day group 1.0%, 2 participants; SOC only group 2.0%, 4 participants) (Table 25; GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.9.1.8). No deaths were reported in the RDV 5-day group on Day 11.

Table 25. GS-US-540-5774: Clinical Status (7-Point Ordinal Scale) by Study Day (Full Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	RDV 5 Days vs SOC P-Value	RDV 10 Days vs SOC P-Value
Baseline					
1 - Death	0	0	0	0.6285	0.0337
2	0	0	0		
3	2 (1.0%)	1 (0.5%)	2 (1.0%)		
4	29 (15.2%)	23 (11.9%)	36 (18.0%)		
5	160 (83.8%)	163 (84.5%)	160 (80.0%)		
6	0	6 (3.1%)	2 (1.0%)		
7 - Not Hospitalized	0	0	0		
Day 5					
1 - Death	0	1 (0.5%)	1 (0.5%)	0.5667	0.0892
2	0	0	5 (2.5%)		
3	4 (2.1%)	1 (0.5%)	6 (3.0%)		
4	36 (18.8%)	31 (16.1%)	39 (19.5%)		
5	84 (44.0%)	84 (43.5%)	78 (39.0%)		
6	7 (3.7%)	5 (2.6%)	6 (3.0%)		
7 - Not Hospitalized	60 (31.4%)	71 (36.8%)	65 (32.5%)		
Day 7					
1 - Death	0	1 (0.5%)	3 (1.5%)	0.0663	0.5702
2	0	0	5 (2.5%)		
3	4 (2.1%)	1 (0.5%)	5 (2.5%)		
4	21 (11.0%)	18 (9.3%)	21 (10.5%)		
5	52 (27.2%)	77 (39.9%)	65 (32.5%)		
6	9 (4.7%)	7 (3.6%)	7 (3.5%)		
7 - Not Hospitalized	105 (55.0%)	89 (46.1%)	94 (47.0%)		
Day 11					
1 - Death	0	2 (1.0%)	4 (2.0%)	0.0171	0.1826
2	0	1 (0.5%)	4 (2.0%)		
3	5 (2.6%)	0	7 (3.5%)		
4	7 (3.7%)	12 (6.2%)	11 (5.5%)		
5	38 (19.9%)	44 (22.8%)	46 (23.0%)		
6	7 (3.7%)	9 (4.7%)	8 (4.0%)		
7 - Not Hospitalized	134 (70.2%)	125 (64.8%)	120 (60.0%)		

vs = versus
Clinical status: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on noninvasive 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
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
P-value was from the Wilcoxon rank sum test to compare the 5-day dosing and 10-day dosing treatment groups to standard of care.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.9.1.2.1

There was a statistically significant difference in change from baseline in clinical status between the RDV 5-day and SOC only groups on Day 11 (p = 0.0240) (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.9.1.8). There were no statistically significant differences between the RDV 10-day and SOC only groups at any postbaseline assessment.

Clinical Status on Day 11 by Baseline Oxygen Support Status

Most participants across all treatment groups showed an improvement from baseline in oxygen support status on Day 11 (Table 26). This was particularly notable in the RDV 5-day group compared with the SOC only group.

Table 26. GS-US-540-5774: Clinical Status (7-Point Ordinal Scale) on Day 11 by Baseline Oxygen Support (Full Analysis Set)

	High-Flow Oxygen			Low-Flow Oxygen			Room Air		
	RDV 5 Days (N = 2)	RDV 10 Days (N = 1)	SOC (N = 2)	RDV 5 Days (N = 29)	RDV 10 Days (N = 23)	SOC (N = 36)	RDV 5 Days (N = 160)	RDV 10 Days (N = 169)	SOC (N = 162)
Day 11									
1 - Death	0	0	0	0	0	4 (11.1%)	0	2 (1.2%)	0
2	0	0	0	0	0	3 (8.3%)	0	1 (0.6%)	1 (0.6%)
3	2 (100.0%)	0	1 (50.0%)	0	0	2 (5.6%)	3 (1.9%)	0	4 (2.5%)
4	0	1 (100.0%)	0	4 (13.8%)	4 (17.4%)	3 (8.3%)	3 (1.9%)	7 (4.1%)	8 (4.9%)
5	0	0	0	5 (17.2%)	2 (8.7%)	4 (11.1%)	33 (20.6%)	42 (24.9%)	42 (25.9%)
6	0	0	0	0	1 (4.3%)	1 (2.8%)	7 (4.4%)	8 (4.7%)	7 (4.3%)
7 – Not Hospitalized	0	0	1 (50.0%)	20 (69.0%)	16 (69.6%)	19 (52.8%)	114 (71.3%)	109 (64.5%)	100 (61.7%)

Clinical status: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on noninvasive 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.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
Baseline was the last available value recorded on or prior to dosing for RDV groups and electronic case report form record labeled “Day 1 Predose” for SOC.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.9.1.5

3.2.1.3.2. Other Efficacy Endpoints of Interest

3.2.1.3.2.1. Recovery

The proportions of participants in the FAS with recovery, defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7 or an improvement from a baseline score of 6 to a score of 7, are presented by treatment group and study day in Table 27. There was a statistically significant difference between the RDV 5-day and SOC only groups in the proportion of participants with recovery on Day 11 (p = 0.0386), with a higher proportion of participants in the RDV 5-day group than the SOC only group achieving recovery. There were no statistically significant differences between the RDV 5-day and SOC only groups at the earlier time points or between the RDV 10-day and SOC only groups at any time point.

There were no statistically significant differences in the median (Q1, Q3) times to recovery in the RDV 5-day and 10-day groups compared with the SOC only group (6 [5, 10] days and 7 [4, 12] days versus 7 [4, 14] days, respectively) (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Tables 15.9.2.6.1 to 15.9.2.6.3 and Figure 15.9.5).

Table 27. GS-US-540-5774: Proportion of Participants with Recovery (Full Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	RDV 5 Days vs SOC		RDV 10 Days vs SOC	
				P-Value	Difference in Percentages (95% CI)	P-Value	Difference in Percentages (95% CI)
Subjects with Recovery on Day 5							
Recovered	67 (35.1%)	74 (38.3%)	71 (35.5%)	1.0000	−0.4% (−10.0% to 9.1%)	0.6015	2.8% (−6.8% to 12.5%)
95% CI	28.3% to 42.3%	31.5% to 45.6%	28.9% to 42.6%				
Not Recovered	124 (64.9%)	119 (61.7%)	129 (64.5%)				
Subjects with Recovery on Day 7							
Recovered	114 (59.7%)	94 (48.7%)	101 (50.5%)	0.0838	9.2% (−0.8% to 19.0%)	0.7624	−1.8% (−11.7% to 8.2%)
95% CI	52.4% to 66.7%	41.5% to 56.0%	43.4% to 57.6%				
Not Recovered	77 (40.3%)	99 (51.3%)	99 (49.5%)				
Subjects with Recovery on Day 11							
Recovered	141 (73.8%)	132 (68.4%)	128 (64.0%)	0.0386	9.8% (0.3% to 19.0%)	0.3941	4.4% (−5.0% to 13.8%)
95% CI	67.0% to 79.9%	61.3% to 74.9%	56.9% to 70.6%				
Not Recovered	50 (26.2%)	61 (31.6%)	72 (36.0%)				

vs = versus
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized. Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment. Baseline was the last available value recorded on or prior to dosing for RDV groups and electronic case report form record labeled “Day 1 Predose” for SOC.
Recovery is defined as a baseline score of 2 through 5 improved to 6 or 7 or a baseline score of 6 improved to 7.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson exact method.
P-value comparing the percentages of subjects with recovery was from the Fisher exact test. The differences in percentages of subjects with recovery between treatment groups and 95% CI were based on the exact method.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.9.2.6.4

3.2.1.3.2.2. Mortality

There were no statistically significant differences in time to death between either RDV group and the SOC only group (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Figure 15.9.2).

3.2.1.3.2.3. Shift in Oxygen Support Status

Most participants across all treatment groups showed an improvement from baseline in oxygen support status on Day 11 (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.9.2.3.2). This was particularly notable in the RDV 5-day group compared with the SOC only group.

A numerically lower proportion of participants in the RDV groups progressed to requiring oxygen support or to death compared with the SOC only group (15 of 314 participants [4.8%] versus 11 of 148 participants [7.4%], respectively, by Day 11).

3.2.1.3.2.4. ≥ 2-Point Clinical Improvement

There were no statistically significant differences between either RDV group and the SOC only group in the proportion of participants with a ≥ 2-point improvement from baseline in clinical status on a 7-point ordinal scale at any time point (Table 28).

There were no statistically significant differences in the median (Q1, Q3) times to ≥ 2-point clinical improvement in the RDV 5-day and 10-day groups compared with the SOC only group (6 [5,14] days and 8 [4, 14] days versus 8 [5, 17] days, respectively) (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Tables 15.9.2.4.1 to 15.9.2.4.3 and Figure 15.9.3).

Table 28. GS-US-540-5774: Proportion of Participants with ≥ 2-Point Improvement (Full Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	RDV 5 Days vs SOC		RDV 10 Days vs SOC	
				P-Value	Difference in Percentages (95% CI)	P-Value	Difference in Percentages (95% CI)
Subjects with ≥ 2-Point Improvement on Day 5							
Improved	61 (31.9%)	72 (37.3%)	66 (33.0%)	0.8299	−1.1% (−10.4% to 8.3%)	0.3986	4.3% (−5.2% to 13.8%)
95% CI	25.4% to 39.1%	30.5% to 44.5%	26.5% to 40.0%				
Not Improved	130 (68.1%)	121 (62.7%)	134 (67.0%)				
Subjects with ≥ 2-Point Improvement on Day 7							
Improved	106 (55.5%)	92 (47.7%)	94 (47.0%)	0.1056	8.5% (−1.5% to 18.4%)	0.9197	0.7% (−9.3% to 10.6%)
95% CI	48.1% to 62.7%	40.4% to 55.0%	39.9% to 54.2%				
Not Improved	85 (44.5%)	101 (52.3%)	106 (53.0%)				
Subjects with ≥ 2-Point Improvement on Day 11							
Improved	134 (70.2%)	126 (65.3%)	121 (60.5%)	0.0557	9.7% (0.1% to 19.1%)	0.3484	4.8% (−5.0% to 14.4%)
95% CI	63.1% to 76.5%	58.1% to 72.0%	53.4% to 67.3%				
Not Improved	57 (29.8%)	67 (34.7%)	79 (39.5%)				

vs = versus
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized. Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment. Baseline was the last available value recorded on or prior to dosing for RDV groups and electronic case report form record labeled “Day 1 Predose” for SOC. Clinical improvement is defined as a ≥ 2-point improvement from baseline clinical status or discharged alive. The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson exact method.
P-value comparing the percentages of subjects with improvement was from the Fisher exact test. The difference in percentages of subjects with improvement between treatment groups and 95% CI were based on the exact method.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.9.2.4.4

3.2.2. Other Data Supporting the Clinical Efficacy of Remdesivir

3.2.2.1. Study CO-US-540-5758

According to sample size calculations, Study CO-US-540-5758 required a total of 325 events of clinical improvement to provide 80% power if the HR comparing RDV to placebo was 1.4 {Wang 2020}. Because there were no new cases of COVID-19 at the study sites, the study was stopped prematurely with a total of only 148 events of clinical improvement. Because the study was underpowered and utilized a 2:1 randomization, it was unable to demonstrate any statistically significant clinical benefits of RDV (Table 29). The primary endpoint was time to clinical improvement, which was numerically shorter in the RDV group compared with the placebo group.

Table 29. CO-US-540-5758: Clinical Outcomes (Intent-to-Treat Population)

	RDV (N = 158)	Placebo (N = 78)	Difference or Hazard Ratio (95% CI)
Median (IQR) Time to Clinical Improvement (Days)	21.0 (13.0 to 28.0)	23.0 (15.0 to 28.0)	1.23 (0.87, 1.75)[a]
Median (IQR) Duration of Invasive Mechanical Ventilation (Days)[b]	7.0 (4.0 to 16.0)	15.5 (6.0 to 21.0)	−4.0 (−14.0, 2.0)[c]
Day 28 Mortality, n (%)	22 (14)	10 (13)	1.1 (−8.1, 10.3)[c]

a Hazard ratio and 95% CI were estimated by the Cox proportional risk model.
b Number (%) on invasive mechanical ventilation at any time during hospitalization: 11 (7%) for RDV and 10 (13%) for placebo.
c Differences are expressed as rate differences or Hodges-Lehmann estimator and 95% CI.
Clinical improvement was defined as a decline of 2 categories on the modified 7-category ordinal scale of clinical status or hospital discharge.
Source: {Wang 2020}

3.2.2.2. Study IN-US-540-5755

Efficacy data from the compassionate use program are described in detail in the IN-US-540-5755 Interim 1 Summary Report, Section 3.3.

Overall, 30.1% of patients (49 of 163 patients) were discharged over a median (Q1, Q3) of 15 (10, 17) days of follow-up from the first RDV dose (IN-US-540-5755 Interim 1 Summary Report, Tables 4.3.4 and 5.4). In this cohort of patients with > 60% on invasive oxygen support (ECMO or invasive mechanical ventilation) at baseline, the overall mortality was 20.2% (33 patients).

3.3. Comparison of Results in Subpopulations

3.3.1. Primary Studies Supporting the Clinical Efficacy of Remdesivir

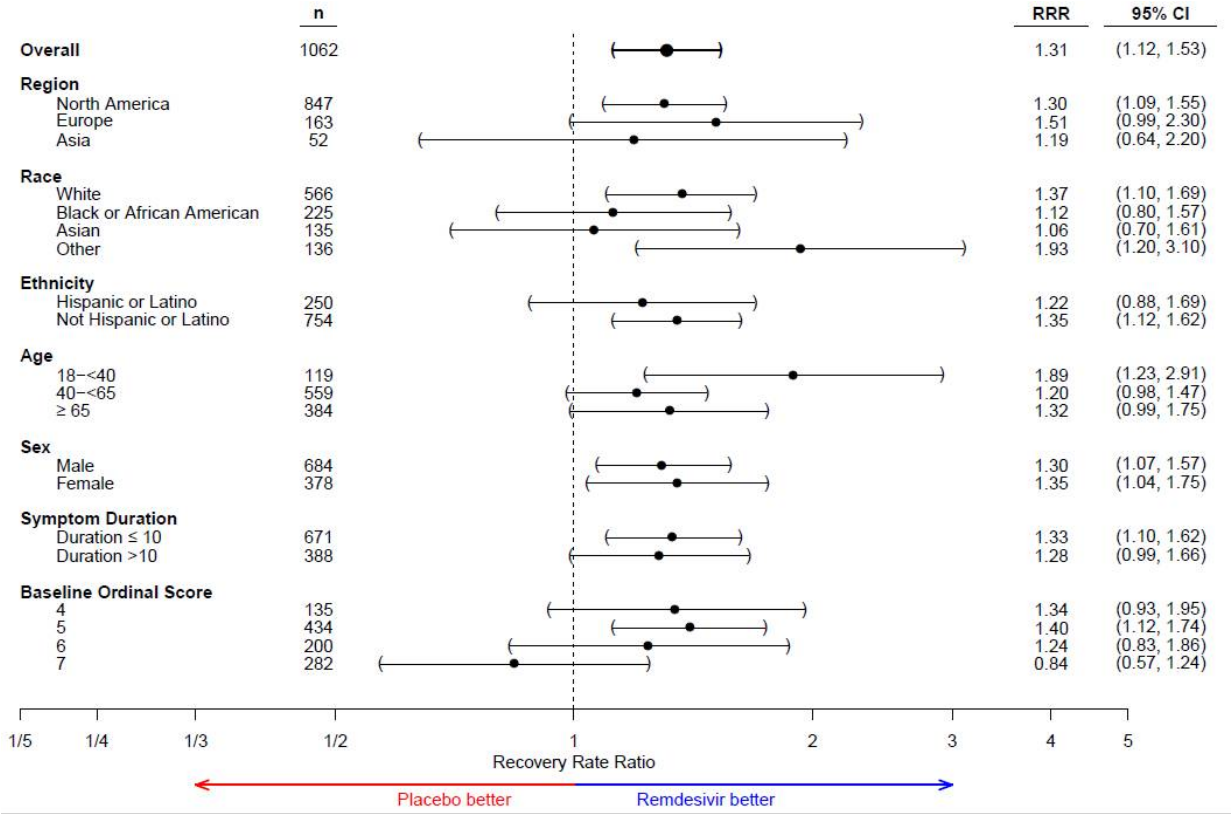
3.3.1.1. Study CO-US-540-5776

Subgroup analyses of the primary efficacy endpoint in Study CO-US-540-5776 were performed to compare RDV 10-day treatment versus placebo in hospitalized adult participants with mild-to-moderate or severe COVID-19. Time to recovery was analyzed for the following subgroups:

- Geographic region: (a) North American sites, (b) Asian sites, and (c) European sites
- Race: (a) white, (b) black/African American, (c) Asian, and (d) other
- Ethnicity: (a) Hispanic or Latino and (b) not Hispanic or Latino
- Age (years): (a) 18 to < 40, (b) 40 to < 65, and (c) ≥ 65
- Sex: (a) female and (b) male
- Duration of symptoms prior to enrollment (days): (a) ≤ 10 and (b) > 10
- Severity of disease (baseline ordinal scale category): (a) 4, (b) 5, (c) 6, and (d) 7

In general, an overall benefit of RDV 10-day treatment over placebo was demonstrated consistently in the majority of the subgroups (Figure 10).

Figure 10. CO-US-540-5776: Forest Plot of Time to Recovery by Subgroup (Intent-to-Treat Population)



Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Figure 4

In addition, time to recovery was also analyzed within each baseline disease severity stratum (Section 3.2.1.1.1). Among participants in the severe disease stratum, the median time to recovery was shorter in the RDV 10-day group compared with the placebo group. Among participants in the mild-to-moderate disease stratum, the median time to recovery was similar between the RDV 10-day and placebo groups.

3.3.1.2. Study GS-US-540-5773

Analysis of Clinical Status on Day 14

In Study GS-US-540-5773, clinical status based on the 7-point ordinal scale is presented by study day and treatment group for subgroups based on sex at birth (male or female), age (< 65 years or ≥ 65 years), baseline oxygen support (invasive mechanical ventilation, high-flow oxygen, low-flow oxygen, or room air), and country (USA, Italy, or ex-Italy) in the GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.9.1.3 to 15.9.1.6 and for subgroups based on race (Asian, black, white, or other) in Table req10636.14. The Italy subgroup tended to have lower (worse) clinical status scores on the 7-point ordinal scale at baseline compared with the USA or ex-Italy subgroups.

Analysis of clinical status on Day 14 based on the 7-point ordinal scale demonstrated that treatment with RDV for 5 days and treatment with RDV for 10 days resulted in similar improvements in clinical status within all the subgroups analyzed (Table 30).

Table 30. GS-US-540-5773: Analysis of Clinical Status (7-Point Ordinal Scale) on Day 14 Using Proportional Odds with Baseline Adjustment by Subgroup (Full Analysis Set)

Subgroup	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
Age Group					
< 65 Years	229	0.0121			
RDV 10 Days/RDV 5 Days			−0.02 (0.283)	0.98 (0.563, 1.705)	0.9412
Baseline Clinical Status			1.14 (0.211)	3.12 (2.061, 4.715)	< 0.0001
≥ 65 Years	168	< 0.0001			
RDV 10 Days/RDV 5 Days			−0.52 (0.297)	0.59 (0.331, 1.060)	0.0776
Baseline Clinical Status			1.53 (0.247)	4.63 (2.857, 7.513)	< 0.0001
Sex					
Male	253	< 0.0001			
RDV 10 Days/RDV 5 Days			−0.18 (0.244)	0.83 (0.516, 1.344)	0.4537
Baseline Clinical Status			1.24 (0.193)	3.46 (2.370, 5.057)	< 0.0001
Female	144	< 0.0001			
RDV 10 Days/RDV 5 Days			−0.48 (0.357)	0.62 (0.308, 1.249)	0.1812
Baseline Clinical Status			1.39 (0.284)	4.00 (2.293, 6.983)	< 0.0001
Country					
USA	229	< 0.0001			
RDV 10 Days/RDV 5 Days			−0.26 (0.298)	0.77 (0.428, 1.379)	0.3771
Baseline Clinical Status			1.40 (0.225)	4.04 (2.600, 6.279)	< 0.0001
Italy	77	< 0.0001			
RDV 10 Days/RDV 5 Days			−0.35 (0.435)	0.70 (0.299, 1.645)	0.4148
Baseline Clinical Status			2.18 (0.531)	8.82 (3.114, 24.957)	< 0.0001
Ex-Italy	320	0.0154			
RDV 10 Days/RDV 5 Days			−0.27 (0.228)	0.77 (0.490, 1.199)	0.2442
Baseline Clinical Status			1.09 (0.177)	2.96 (2.095, 4.191)	< 0.0001

Subgroup	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
Race					
Asian	45	< 0.0001			
RDV 10 Days/RDV 5 Days			−0.15 (0.559)	0.86 (0.288, 2.575)	0.7895
Baseline Clinical Status			0.66 (0.477)	1.94 (0.763, 4.947)	0.1639
Black	44	0.0005			
RDV 10 Days/RDV 5 Days			1.24 (0.877)	3.46 (0.621, 19.284)	0.1567
Baseline Clinical Status			2.51 (0.635)	12.27 (3.536, 42.540)	< 0.0001
White	276	0.0137			
RDV 10 Days/RDV 5 Days			−0.36 (0.239)	0.70 (0.435, 1.112)	0.1291
Baseline Clinical Status			1.25 (0.186)	3.49 (2.425, 5.020)	< 0.0001
Other	32	< 0.0001			
RDV 10 Days/RDV 5 Days			−0.77 (0.805)	0.46 (0.096, 2.250)	0.3409
Baseline Clinical Status			2.40 (0.787)	11.05 (2.360, 51.694)	0.0023

SE = standard error
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment. Baseline was the last available value recorded on or prior to dosing.
The odds ratio and corresponding 95% CI were from a proportional odds model on clinical status at Day 14 with effects for treatment and baseline clinical status.
Other race includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Not Permitted, and Other.
Not Permitted = local regulators did not allow collection of race/ethnicity information. All but 1 value of "Other" are unknown, not specified, etc.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.9.1.7; Table req10636.15

Mortality

Consistent with analyses for the overall study population, there were no statistically significant differences in time to death between the RDV 5-day and 10-day groups in any of the subgroups analyzed (country [USA, Italy, or ex-Italy]; age [< 50 years, ≥ 50 to < 65 years, ≥ 65 to < 75 years, or ≥ 75 years]; and sex at birth [male or female]) (GS-US-540-5773 Interim [Final Part A] CSR, Tables 15.9.2.9.2.1 to 15.9.2.9.2.3, 15.9.2.9.3.1 to 15.9.2.9.3.3, 15.9.2.9.4.1 to 15.9.2.9.4.3, 15.9.2.9.5.1 to 15.9.2.9.5.12, and 15.9.2.9.6.1 to 15.9.2.9.6.6 and Figures 15.9.3 to 15.9.7.2).

3.3.1.3. Study GS-US-540-5774

Analysis of Clinical Status on Day 11

In Study GS-US-540-5774, clinical status based on the 7-point ordinal scale is presented by study day and treatment group for subgroups based on sex at birth (male or female), age (< 65 years or ≥ 65 years), baseline oxygen support (invasive mechanical ventilation, high-flow oxygen, low-flow oxygen, or room air), and country (USA, Italy, or ex-Italy) in the

GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.9.1.3 to 15.9.1.6 and for subgroups based on race (Asian, black, white, or other) in Table req10643.14. A higher proportion of participants in the Italy subgroup were on low-flow oxygen support (ordinal score = 4) compared with participants the USA or ex-Italy subgroups.

Analysis of clinical status based on a 7-point ordinal scale demonstrated that treatment with RDV for 5 days resulted in greater improvements in clinical status on Day 11 compared with treatment with SOC only for the following subgroups: age (< 65 years; p = 0.0487), oxygen support (room air; p = 0.0483), and country (ex-Italy; p = 0.0085) (Table 31).

The comparison of treatment with RDV for 10 days versus treatment with only SOC showed no statistically significant differences in clinical status on Day 11 within any of the subgroups analyzed.

Table 31. GS-US-540-5774: Analysis of Clinical Status (7-Point Ordinal Scale) on Day 11 Using Proportional Odds by Subgroup (Full Analysis Set)

Subgroup	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
RDV 5 Days/SOC					
Age Group					
< 65 Years	284	0.3158	0.52 (0.263)	1.68 (1.003, 2.810)	0.0487
≥ 65 Years	107	< 0.0001	0.50 (0.366)	1.65 (0.805, 3.381)	0.1711
Sex					
Male	239	0.4345	0.46 (0.264)	1.59 (0.948, 2.665)	0.0786
Female	152	< 0.0001	0.55 (0.347)	1.73 (0.874, 3.408)	0.1158
Oxygen Support					
Invasive Mechanical Ventilation	0				
High-Flow Oxygen	4	NE	NE	NE	NE
Low-Flow Oxygen	65	< 0.0001	0.90 (0.511)	2.46 (0.906, 6.708)	0.0774
Room Air	322	0.8123	0.46 (0.234)	1.59 (1.003, 2.511)	0.0483
Country					
USA	161	< 0.0001	0.99 (0.507)	2.69 (0.998, 7.269)	0.0506
Italy	56	0.0870	0.27 (0.496)	1.31 (0.496, 3.468)	0.5852
Ex-Italy	335	0.1158	0.62 (0.235)	1.85 (1.171, 2.939)	0.0085
Race					
Asian	71	0.7022	0.48 (0.454)	1.62 (0.664, 3.933)	0.2898
Black	62	0.6721	2.06 (1.130)	7.81 (0.853, 71.594)	0.0689
White	221	0.3969	0.41 (0.275)	1.51 (0.878, 2.581)	0.1369
Other	37	< 0.0001	0.58 (0.894)	1.79 (0.310, 10.304)	0.5157

Subgroup	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
RDV 10 Days/SOC					
Age Group					
< 65 Years	283	< 0.0001	0.14 (0.249)	1.16 (0.710, 1.882)	0.5606
≥ 65 Years	110	< 0.0001	0.46 (0.361)	1.59 (0.783, 3.220)	0.2004
Sex					
Male	243	< 0.0001	0.37 (0.259)	1.45 (0.876, 2.414)	0.1474
Female	150	< 0.0001	0.11 (0.329)	1.11 (0.583, 2.121)	0.7469
Oxygen Support					
Invasive Mechanical Ventilation	0				
High-Flow Oxygen	3	NE	NE	NE	NE
Low-Flow Oxygen	59	0.4457	0.91 (0.553)	2.48 (0.838, 7.334)	0.1009
Room Air	331	< 0.0001	0.14 (0.223)	1.15 (0.746, 1.786)	0.5197
Country					
USA	184	< 0.0001	−0.06 (0.371)	0.94 (0.455, 1.948)	0.8719
Italy	49	0.0280	−0.18 (0.526)	0.83 (0.297, 2.335)	0.7282
Ex-Italy	344	< 0.0001	0.39 (0.224)	1.47 (0.948, 2.283)	0.0852
Race					
Asian	68	0.8106	−0.49 (0.476)	0.61 (0.241, 1.557)	0.3025
Black	64	< 0.0001	−0.04 (0.647)	0.96 (0.271, 3.419)	0.9518
White	219	< 0.0001	0.48 (0.279)	1.61 (0.932, 2.780)	0.0875
Other	42	< 0.0001	0.50 (0.783)	1.66 (0.357, 7.674)	0.5197

NE = not evaluable due to quasi-complete separation or indistinguishable mean score predicted probabilities; SE = standard error
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
The odds ratio and corresponding 95% CI were from a proportional odds model on Day 11 clinical status with a treatment effect.
Other race includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Not Permitted, and Other.
Not Permitted = local regulators did not allow collection of race/ethnicity information. All but 3 values of "Other" are unknown, not specified, etc.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.9.1.7; Table req10643.15

3.3.2. Other Data Supporting the Clinical Efficacy of Remdesivir

3.3.2.1. Study CO-US-540-5758

In Study CO-US-540-5758, all-cause mortality at Day 28 was also analyzed for subgroups based on duration of symptoms prior to starting study treatment (≤ 10 days or > 10 days) {Wang 2020}. No statistically significant difference in 28-day mortality was observed between the RDV and placebo groups in either subgroup.

3.3.2.2. Study IN-US-540-5755

Efficacy data for patients with confirmed COVID-19 who were treated with RDV in the single-patient compassionate use program (Study IN-US-540-5755) are presented by baseline oxygen support status (invasive or noninvasive) and country subgroup (Italy or outside Italy) in the IN-US-540-5755 Interim 1 Summary Report, Section 3.3.

In addition, clinical outcomes were also analyzed by age (< 50 years, ≥ 50 to < 60 years, ≥ 60 to < 70 years, or ≥ 70 years). Consistent with the current literature, outcomes varied by age; higher percentages of patients < 60 years of age were discharged (42.9% [30 of 70 patients]) compared with patients ≥ 60 years of age (20.4% [19 of 93 patients]) (Table 32) {Guan 2020, Zhou 2020a}. In addition, mortality was higher among older patients, with the lowest incidence of mortality in patients < 50 years of age (9.1% [3 of 33 patients]).

Table 32. IN-US-540-5755: Clinical Outcomes by Age Subgroup – All Patients (Compassionate Use Analysis Set)

	< 50 Years (N = 33)	≥ 50 to < 60 Years (N = 37)	≥ 60 to < 70 Years (N = 41)	≥ 70 Years (N = 52)
Mortality	3 (9.1%)	4 (10.8%)	9 (22.0%)	17 (32.7%)
Discharge	17 (51.5%)	13 (35.1%)	7 (17.1%)	12 (23.1%)

The Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to [redacted] 20[redacted], per data entered in electronic case report forms as of 10:00 AM Pacific Daylight Time on [redacted] 20[redacted].
Source: Adhoc Req 10587, Tables 3.3, 3.6, 3.9, and 3.12

3.3.2.2.1. Exploratory Analysis of Baseline Predictors of Time to Death

Univariate and multivariate analyses were performed to identify predictors of time to death in patients with COVID-19 who were treated with RDV through compassionate use. For this analysis, patients who died during the program (N = 33) were compared with patients who survived (N = 130). Factors evaluated included baseline age, gender, duration of symptoms prior to the first dose of RDV, baseline invasive ventilation (yes/no), and country (Italy versus outside Italy). Factors that remained significant in the final multivariate model ($p < 0.1$) are presented in Table 33.

Table 33. IN-US-540-5755: Analysis of Predictors of Time to Death - All Patients (Compassionate Use Analysis Set)

Baseline Variable	Patients Who Died (N = 33)	Patients Who Survived (N = 130)	Multivariate Hazard Ratio (95% CI)	Multivariate P-Value
Age Categories (Years), n (%)				
< 50	3 (9.1%)	30 (23.1%)	0.34 (0.10 to 1.16)	0.0847
≥ 50 to < 60	4 (12.1%)	33 (25.4%)	0.24 (0.07 to 0.84)	0.0261
≥ 60 to < 70	9 (27.3%)	32 (24.6%)	0.48 (0.20 to 1.13)	0.0918
≥ 70 (Reference)	17 (51.5%)	35 (26.9%)	—	—
Ventilation Status, n (%)				
Invasive Ventilation	27 (81.8%)	77 (59.2%)	3.93 (1.44 to 10.71)	0.0075
Country, n (%)				
Italy	22 (66.7%)	62 (47.7%)	3.46 (1.53 to 7.80)	0.0028

The Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to [redacted]20[redacted], per data entered in electronic case report forms as of 10:00 AM Pacific Daylight Time on [redacted]20[redacted].
A Cox regression model was used for the multivariate analysis. Variables in the final model were selected via a stepwise procedure with entry/stay criteria = 0.35/0.30.
Source: Adhoc Req 10587, Tables 9.1 and 9.2

These results are consistent with findings observed in the ongoing global pandemic as increased age and requiring invasive ventilation are associated with poor clinical outcomes of COVID-19. Time to death was associated with enrollment in Italy, consistent with reports of challenges in that country in accommodating the large influx of severe and critical cases in the health care system at that time point in the pandemic. Gender and duration of symptoms prior to the first dose of RDV were not associated with time to death after considering the other factors.

3.4. Summary of Efficacy Across Studies

The efficacy of RDV for the treatment of COVID-19 was primarily evaluated in 3 pivotal Phase 3 studies in participants with mild-to-moderate to severe COVID-19 (Studies CO-US-540-5776, GS-US-540-5773, and GS-US-540-5774). In addition, supportive efficacy data in individuals with COVID-19 are provided from the investigator-sponsored Phase 3 study in China (Study CO-US-540-5758) and the single-patient compassionate use program (Study IN-US-540-5755). It is important to note that Study IN-US-540-5755 was not designed to evaluate efficacy, and Study CO-US-540-5758 was terminated prematurely due to evolving epidemiology; as such, these data cannot be meaningfully interpreted.

A total of 2029 participants with COVID-19 were randomized and received study treatment or completed the protocol-specified Day 1 visit in the pivotal Phase 3 studies, including a total of 1312 participants who were treated with RDV.

Overall, the demographic and baseline characteristics of the population enrolled in the pivotal studies were largely representative of the hospitalized population with COVID-19 across a spectrum of disease ranging from mild-to-moderate to severe. Both males and females were represented, with ≥ 35% of participants in each study being female. The studies were conducted at sites across 3 continents (Asia, Europe, and North America) and included a racially diverse population, with the proportion of participants who were black or Asian ranging from approximately 12% to 21% and 12% to 19%, respectively.

There were no specified upper limits on age, and the oldest participant enrolled was 98 years of age; over 25% of participants in each study were aged 65 years and older, with higher proportions in Studies CO-US-540-5776 and GS-US-540-5773 (36.2% and 42.3%, respectively). Similarly, there were no specified upper limits on BMI, and a high proportion of participants were obese (BMI ≥ 30 kg/m^2), with a maximum BMI value of 76.9 kg/m^2 across the studies. The mean BMI value in Study CO-US-540-5776 was 30.6 kg/m^2, while the upper 25th percentile values in Studies GS-US-540-5773 and GS-US-540-5774 were 33.5 kg/m^2 and 31.1 kg/m^2, respectively. The study populations had multiple comorbidities, including hypertension (most common), type 2 diabetes mellitus, and cardiac disease.

Clinical Outcomes

Overall, the studies demonstrated that treatment with RDV for up to 10 days was associated with significant improvements in clinical outcomes in participants with moderate to severe COVID-19.

Recovery

Preliminary results from Study CO-US-540-5776 demonstrated that RDV for up to 10 days was more efficacious than placebo in treating hospitalized participants with COVID-19. This benefit was observed for the primary efficacy endpoint of time to recovery for which the study was powered, where a statistically significant shorter median time to recovery was observed in the RDV 10-day group compared with the placebo group (10 days versus 14 days, respectively; RRR 1.31; 95% CI: 1.12 to 1.53; $p < 0.001$). When time to recovery was analyzed within each baseline disease severity stratum, the median time to recovery for participants with severe disease (requiring mechanical ventilation, requiring oxygen, having $SpO_2 \leq 94\%$ on room air, or having tachypnea [respiratory rate ≥ 24 breaths/minute]) was significantly shorter and more pronounced in the RDV 10-day group compared with the placebo group (11 days versus 17 days, respectively). In the subgroup of participants with a baseline ordinal score of 5 (hospitalized, requiring supplemental oxygen), a significantly shorter median recovery time was observed in the RDV 10-day group compared with the placebo group (7 days versus 8 days, respectively). In the subgroup of participants with a baseline ordinal score of 6 (hospitalized, on noninvasive ventilation or high-flow oxygen devices), a numerically shorter median recovery time was also observed in the RDV 10-day group compared with the placebo group (14 days versus 21 days, respectively).

In participants with mild-to-moderate COVID-19 ($SpO_2 > 94\%$ and respiratory rate < 24 breaths/minute without supplemental oxygen) in Study CO-US-540-5776, the median time to recovery was similar in the RDV 10-day and placebo groups (5 days for both groups);

however, a larger sample size in the mild-to-moderate disease stratum would be needed to demonstrate a benefit with RDV for this disease severity population. In the subgroup of participants with a baseline ordinal score of 7 (hospitalized, requiring mechanical ventilation or ECMO), a longer follow-up time would be required to make a meaningful comparison.

In Study GS-US-540-5774, there was a statistically significant difference between the RDV 5-day and SOC only groups in the proportion of participants with recovery on Day 11 ($p = 0.0386$), with a higher proportion of participants in the RDV 5-day group than the SOC only group achieving recovery. There were no statistically significant differences between RDV 5-day and 10-day groups in the proportions of participants with recovery at any time point in Study GS-US-540-5773.

Improvements or Changes in Clinical Status (7- or 8-Point Ordinal Scale)

In Study CO-US-540-5776, the benefit of RDV 10-day treatment over placebo was also observed in the key secondary efficacy endpoint of clinical status (8-point ordinal scale) at Day 15. The odds of improvement in the ordinal score at Day 15 were significantly higher in the RDV 10-day group compared with the placebo group (OR for improvement 1.46; 95% CI: 1.15 to 1.86; $p = 0.002$). Higher proportions of Day 15 ordinal scores of 1, 2, and 3 were observed in participants in the RDV 10-day group compared with the placebo group.

The primary efficacy endpoint for Studies GS-US-540-5773 and GS-US-540-5774 was clinical status assessed using a 7-point ordinal scale on Day 14 (Study GS-US-540-5773) or Day 11 (Study GS-US-540-5774). After adjustment for imbalances in baseline clinical status, Study GS-US-540-5773 showed that a 5-day course of RDV was as effective as a 10-day course for the treatment of participants with severe COVID-19, as demonstrated by the similar odds of improved clinical status on Day 14 ($p = 0.1563$). Among participants who were on invasive mechanical ventilation or ECMO on Day 5, a higher proportion of participants in the RDV 10-day group than the RDV 5-day group had improvements in oxygen support status by Day 14, suggesting that patients on invasive mechanical ventilation on Day 5 may benefit from a longer duration of treatment with RDV.

In participants with moderate COVID-19 in Study GS-US-540-5774, treatment with RDV for 5 days resulted in significantly better odds of improved clinical status on Day 11 compared with treatment with only SOC ($p = 0.0174$). While participants with moderate COVID-19 who received a 10-day course of RDV had outcomes that were numerically superior to those who received only SOC, the differences were not statistically significant ($p = 0.1826$). Similar results were observed in an analysis that excluded participants on oxygen support at baseline; the odds of improved clinical status on Day 11 were greater in the RDV 5-day group compared with the SOC only group ($p = 0.0483$) and similar between the RDV 10-day and SOC only groups ($p = 0.5197$). Given the open-label design of Study GS-US-540-5774 and the requirement for IV administration of RDV, discharge decisions appear to have been influenced by the assigned duration of RDV therapy, with an impact on outcomes. Rates of hospital discharge peaked on the day after the end of dosing in both RDV groups (on Day 6 for the RDV 5-day group and on Day 11 for the RDV 10-day group).

Results from Study GS-US-540-5774 were consistent with observations from Study CO-US-540-5776, which, while underpowered in the mild-to-moderate disease stratum, showed improvements (not statistically significant) in time to recovery and clinical status at Day 15 for the RDV 10-day group compared with the placebo group. In both studies, among participants with moderate disease (baseline ordinal score 4 for Study CO-US-540-5776), a numerically lower proportion of participants who received RDV progressed to requiring oxygen support or to death compared with those who received placebo or only SOC (4 of 66 participants [6.1%] versus 9 of 53 participants [17.0%], respectively, by Day 15 in Study CO-US-540-5776; 15 of 314 participants [4.8%] versus 11 of 148 participants [7.4%], respectively, by Day 11 for Study GS-US-540-5774). As demonstrated in these studies and other viral diseases, treatment in the earlier phase of disease is crucial in preventing disease progression.

Mortality

The efficacy of RDV is further supported by results from analyses of 14-day mortality in Study CO-US-540-5776. Overall, the risk of death was numerically lower in the RDV 10-day group compared with the placebo group (27% lower; HR 0.73; 95% CI: 0.50 to 1.07). In the subgroup of participants with a baseline ordinal score of 5 (hospitalized, requiring supplemental oxygen), a lower risk of death was observed in the RDV 10-day group versus the placebo group (HR 0.34; 95% CI: 0.15 to 0.78).

There were no statistically significant differences in time to death between the RDV 5-day and the 10-day groups in Study GS-US-540-5773 or between either RDV group and the SOC only group in Study GS-US-540-5774. Among participants who were on invasive mechanical ventilation or ECMO on Day 5 in Study GS-US-540-5773, a lower proportion of participants in the RDV 10-day group than the RDV 5-day group died on or before Day 14 (7 of 41 participants [17.1%] versus 10 of 25 participants [40.0%], respectively).

Analyses of Subgroups

Efficacy data from Studies CO-US-540-5776, GS-US-540-5773, and GS-US-540-5774 were analyzed in selected subgroups based on region/country, race/ethnicity, age, sex, and severity of disease (baseline ordinal score or oxygen support status). In addition, the primary efficacy endpoint in Study CO-US-540-5776 was also analyzed by duration of symptoms prior to enrollment.

In Study CO-US-540-5776, an overall benefit of RDV 10-day treatment over placebo was demonstrated consistently in the majority of subgroups analyzed in the preliminary analysis. In Study GS-US-540-5773, analysis of clinical status based on the 7-point ordinal scale demonstrated that treatment with RDV for 5 days and treatment with RDV for 10 days resulted in similar improvements in clinical status on Day 14 in all of the subgroups analyzed.

Conclusions

In summary, RDV has been evaluated in a broad spectrum of hospitalized participants with mild-to-moderate to severe COVID-19, and the conclusions are as follows:

- Remdesivir was associated with significant improvements in clinical outcomes with up to a 10-day course of treatment.
- Remdesivir was associated with statistically and clinically significant reductions in time to recovery and improvements in clinical status, and a trend to improvement in mortality.
- A 5-day course of RDV resulted in statistically and clinically meaningful improvements in participants with moderate to severe COVID-19; however, a 10-day treatment course may yield additional benefit for critically ill patients.

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The proposed clinical regimen for the treatment of patients weighing ≥ 40 kg with COVID-19 is as follows: single RDV 200 mg IV loading dose on Day 1, followed by RDV 100 mg IV, once-daily maintenance doses from Day 2 (for a total treatment duration of either 5 or 10 days).

Selection of this dosing regimen was based on the pharmacokinetic (PK) bridge from animal data to human doses and efficacy using the results of in vivo efficacy studies conducted in SARS-CoV-2- and MERS-CoV-infected rhesus monkeys, and available PK data in healthy rhesus monkeys and Phase 1 studies in healthy participants (m2.7.2, Section 3.5).

Remdesivir showed therapeutic efficacy in SARS-CoV-2-infected rhesus monkeys and prophylactic and therapeutic efficacy in MERS-CoV-infected rhesus monkeys. Administration of RDV 10 mg/kg for the first dose, followed by RDV 5 mg/kg once daily thereafter for 6 days using IV bolus injection initiated 12 hours postinoculation with SARS-CoV-2 resulted in a significant reduction of clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals (Study PC-540-2004).

In MERS-CoV-infected monkeys, prophylactic administration of RDV at 10 or 5 mg/kg once daily for 7 days using IV bolus injection beginning 1 day prior to MERS-CoV inoculation resulted in a significant reduction of clinical scores, clinical signs of respiratory disease, and viral RNA levels compared with vehicle-treated animals. Therapeutic RDV treatment of 5 mg/kg once daily using IV bolus injection initiated 12 hours postinoculation also resulted in reduced clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions (Study PC-399-2038; {De Wit 2020}).

For the treatment of COVID-19, the approach has been to target exposures (plasma and peripheral blood mononuclear cells [PBMCs]) associated with efficacy at 10 and 5 mg/kg in the SARS-CoV-2- and MERS-CoV-infected rhesus monkeys. Using allometric scaling, the proposed clinical once-daily maintenance dose of 100 mg provides systemic exposure of RDV in plasma and GS-443902 (active triphosphate) in PBMCs similar with that observed in rhesus monkeys at the 5-mg/kg IV dose of RDV (Studies AD-399-2030 and GS-US-399-5505).

To target efficacy observed at the 10-mg/kg loading dose in infected rhesus monkeys requires a loading dose of 200 mg in humans. Pharmacokinetics of a single dose of 200-mg RDV in healthy participants is similar to the expected exposure in rhesus monkeys at 10 mg/kg (Study AD-399-2002).

High intracellular trough concentrations of GS-443902 have been observed in human PBMCs following a single RDV 200-mg dose or multiple IV doses of RDV 100 mg (Study GS-US-399-5505). These concentrations are approximately 1000-fold above the in vitro EC_{50} against SARS-CoV-2 (clinical isolate; EC_{50} = 0.0099 µM) and SARS-CoV in primary human airway epithelial cells (EC_{50} = 0.0066 µM) (Study PC-540-2003). These concentrations are also comparable with those observed in rhesus monkeys receiving RDV 5-mg/kg doses for 7 days and the doses associated with efficacy in SARS-CoV-2- and MERS-CoV-infected rhesus monkey models.

Dose selection of RDV in pediatric patients weighing ≥ 40 kg was informed by a physiologically based PK model developed to characterize the PK of RDV and the primary circulating nucleoside metabolite, GS-441524, in adults. Simulations indicated that use of the adult dosage regimen in pediatric participants ≥ 40 kg is predicted to maintain RDV and GS-441524 exposures generally within the expected adult steady-state exposure range following the adult dosage regimen. These simulations did not account for possible diminished liver or kidney function due to SARS-CoV-2 infection because the impact of infection on the PK of RDV and GS-441524 is currently unknown.

The proposed clinical dosing regimen is confirmed by clinical safety and efficacy data in participants with moderate to severe COVID-19 (Studies CO-US-540-5776, GS-US-540-5773, GS-US-540-5774, and CO-US-540-5758) and adult patients with COVID-19 who participated in the single-patient compassionate use program (Study IN-US-540-5755), as well as clinical safety data from a large safety database of individuals who have received RDV to date.

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

No data are available at this time.

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7. APPENDIX

7.1. Tabular Summary of Studies Relevant for Efficacy

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication	CO-US-540-5776 (ACTT-1)	To evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19	Phase 3, multicenter, adaptive, randomized, double-blind, placebo-controlled study	Single loading dose of IV RDV 200 mg on Day 1, followed by QD maintenance doses of IV RDV 100 mg for the duration of the hospitalization for up to 10 days	Up to 10 days	Randomized: 1062 Completed: 774	Hospitalized adults with COVID-19	Study ongoing; Preliminary CSR
Uncontrolled Clinical Studies	GS-US-540-5773	To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14	Phase 3, randomized study	Part A • Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Part B • Mechanically Ventilated Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected	Part A: • Treatment Group 1: 5 days • Treatment Group 2: 10 days Part B • Mechanically Ventilated Treatment Group: 10 days • Extension Treatment Group: either 5 or 10 days	Randomized: 401 Completed: 332	Adults with confirmed severe COVID-19	Study ongoing; Interim (Final Part A) CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	GS-US-540-5774	To evaluate the efficacy of 2 RDV regimens compared with SOC, with respect to clinical status assessed by a 7-point ordinal scale on Day 11	Phase 3, open-label, randomized, multicenter study	Part A • Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Treatment Group 3: continued SOC therapy Part B • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected	Up to 10 days	Randomized: 596 Completed: 228	Adults with confirmed moderate COVID-19	Study ongoing; Interim 1 (Part A Day 11) CSR
Uncontrolled Clinical Studies	CO-US-540-5758	To assess time to clinical improvement up to Day 28, defined as time from randomization to the point of a decline of 2 levels on a 6-point ordinal scale of clinical status	Phase 3, randomized, double-blind, placebo-controlled, multicenter study	IV RDV 200 mg or placebo on Day 1, followed by IV RDV 100 mg or placebo on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10	10 days	Enrolled: 237 ITT Population: 236	Adults admitted to hospital with RT-PCR-confirmed SARS-CoV-2 infection and radiologically confirmed pneumonia	Study completed; {Wang 2020}

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Compassionate Use Data	IN-US-540-5755	To provide RDV for single-patient compassionate use for the treatment of COVID-19	Single-patient compassionate use	Single loading dose of IV RDV 200 mg on Day 1 followed by QD maintenance doses of IV RDV 100 mg for up to 9 days	Up to 10 days	163	Patients with PCR-confirmed COVID-19 who were hospitalized with substantial clinical symptoms where the benefits of treatment with an investigational agent outweighed the risks	Study ongoing; Interim 1 Summary Report

ACTT = Adaptive COVID-19 Treatment Trial; COVID-19 = coronavirus disease 2019; CSR = clinical study report; ITT = intent-to-treat; IV = intravenous; PCR = polymerase chain reaction; QD = once daily; RDV = remdesivir (GS-5734™); RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care
Completed = number of subjects who completed the study.

7.2. Additional Efficacy Analysis

Additional outputs presenting data from analyses that were not prespecified in the statistical analysis plans for Studies GS-US-540-5773 and GS-US-540-5774 or the Statistical Analysis Specification for Study IN-US-540-5755 are included in this submission.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.4—SUMMARY OF CLINICAL SAFETY

REMDESIVIR
(GS-5734™)

Gilead Sciences

[redacted] 2020

CONFIDENTIAL AND PROPRIETARY INFORMATION

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTT	Adaptive COVID-19 Treatment Trial
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CoV	coronavirus
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CSR	clinical study report
DAIDS	Division of AIDS
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
EVD	Ebola virus disease
FDA	Food and Drug Administration
Gilead	Gilead Sciences
IRR	infusion-related reaction
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MH	Mantel-Haenszel
NA	not applicable
NIAID	National Institute of Allergy and Infectious Diseases
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
SAE	serious adverse event
SARS	severe acute respiratory syndrome
SMQ	Standardized MedDRA Query
SOC	standard of care
ULN	upper limit of normal

US	United States
WBC	white blood cell
WHO	World Health Organization

1. EXPOSURE TO THE DRUG

1.1. Background

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei province, China {Huang 2020}. Sequencing analyses from respiratory tract samples of patients identified a novel coronavirus (CoV), which was named severe acute respiratory syndrome (SARS)-CoV-2 {Zhou 2020b}. Cases of the novel infectious disease caused by the SARS-CoV-2 virus, coronavirus disease 2019 (COVID-19), rapidly increased throughout the world. The situation is a major global health emergency, as evident by the International Health Regulations Emergency Committee of the World Health Organization declaration on 30 January 2020 that the SARS-CoV-2 outbreak constitutes a Public Health Emergency of International Concern {World Health Organization (WHO) 2020b}. On 11 March 2020, the World Health Organization declared COVID-19 a pandemic {World Health Organization (WHO) 2020c}. As of 26 June 2020, a total of 9,473,214 confirmed cases and 484,249 associated deaths were reported worldwide, including 2,414,870 cases and 124,325 deaths in the United States (US) and 2,619,753 cases and 195,535 deaths in Europe {Centers for Disease Control and Prevention (CDC) 2020, World Health Organization (WHO) 2020a}.

Remdesivir (RDV, GS-5734™) is a novel antiviral treatment developed by Gilead Sciences (Gilead) that has been evaluated for the treatment of COVID-19. Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad-spectrum activity against members of the CoVs (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (eg, Ebola virus, Marburg virus), and paramyxoviruses (eg, respiratory syncytial virus, Nipah virus, Hendra virus).

Remdesivir exhibits potent in vitro and in vivo antiviral activity against SARS-CoV-2. Remdesivir showed potent in vitro activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells (half-maximal effective concentration [EC_{50}] = 0.0099 μM) and also potently inhibited a recombinant chimeric virus expressing the polymerase (nsp12) gene of SARS-CoV-2 in a backbone of SARS-CoV in Huh7 cells (EC_{50} = 0.0035 μM). In SARS-CoV-2-infected rhesus monkeys, administration of RDV (10 mg/kg for the first dose, followed by 5 mg/kg once daily thereafter) using intravenous (IV) bolus injection initiated 12 hours postinoculation of SARS-CoV-2 resulted in a significant reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and viral RNA levels compared with vehicle-treated animals.

On 01 May 2020, based on early data from clinical studies, the US Food and Drug Administration issued an emergency use authorization for RDV for the treatment of COVID-19 in patients with severe disease, on the basis that RDV may be effective in treating COVID-19 and given the available information supporting the benefit-risk profile of RDV for use in this population {U. S. Food and Drug Administration (FDA) 2020}.

Remdesivir has demonstrated safety and efficacy for the treatment of COVID-19 through clinical evaluation at the proposed dosing regimen, as described in this dossier. Remdesivir was first approved by the Japanese Pharmaceuticals and Medical Devices Agency on 07 May 2020 for the treatment of patients with severe COVID-19 and has since been approved in a number of additional territories globally.

1.2. Overall Safety Evaluation Plan and Narratives of Safety Studies

A comprehensive nonclinical pharmacology and virology, pharmacokinetics (PK), and toxicology program provide support to the clinical evaluation of RDV for the treatment of COVID-19.

Table 1 presents the clinical studies providing safety data to support the proposed RDV indication for the treatment of COVID-19. The main focus of this Summary of Clinical Safety is the primary safety data from 3 pivotal Phase 3 studies (CO-US-540-5776, GS-US-540-5773, and GS-US-540-5774) with supportive data from an investigator-sponsored Phase 3 study in China (CO-US-540-5758) and a compassionate use program (IN-US-540-5755). Additional safety data are provided from a study in participants with Ebola virus disease (EVD) (CO-US-399-5366) and 4 Phase 1 studies in healthy participants.

Due to differences in study design, treatment durations, and the patient populations studied, safety data are presented by each individual study.

1.2.1. Sources of Data Supporting the Clinical Safety of Remdesivir

Safety data are provided from the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Phase 3 study comparing RDV versus placebo in hospitalized participants with COVID-19 (CO-US-540-5776 [ACTT-1]), from Part A (Day 28) of the Gilead-sponsored Phase 3 study comparing 2 RDV regimens (5 days versus 10 days) in participants with severe COVID-19 (GS-US-540-5773), and from Part A (Day 11) of the Gilead-sponsored Phase 3 study evaluating 2 RDV regimens (5 days and 10 days) versus standard of care (SOC) in participants with moderate COVID-19 (GS-US-540-5774).

Additional safety data from individuals with COVID-19 are provided from an investigator-sponsored Phase 3 study in China (CO-US-540-5758) and the compassionate use program (IN-US-540-5755). Data are also provided from the Phase 2/3 study (CO-US-399-5366 [PALM]) evaluating various investigational treatments including RDV for treatment of EVD {Mulangu 2019}and 4 completed Phase 1 studies in healthy participants (GS-US-399-1812, GS-US-399-4231, GS-US-399-1954, and GS-US-399-5505).

Information on study design and populations for these studies is provided in Table 1.

Furthermore, a safety review conducted to assess 2 safety signals of infusion-related reactions (IRRs) and hypersensitivity events is also included in the date presented in this module.

Table 1. Overview of Primary Studies Providing Safety Data for Remdesivir

Study	Study Design	Treatment Regimens	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
Studies/Programs in Individuals with COVID-19					
CO-US-540-5776 (ACTT-1) {Beigel 2020}	Phase 3, adaptive, randomized, double-blind, placebo-controlled, multicenter study to evaluate available investigational treatments for COVID-19 including RDV (sponsored by NIAID)	• Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg QD for a total of up to 10 days • Treatment Group 2: continued SOC therapy together with placebo to match	RDV: N = 531 Placebo: N = 517	Adult participants hospitalized with COVID-19 Efficacy and safety data through 28 April 2020	m2.7.3, Section 2.1.1 CO-US-540-5776 Preliminary CSR
GS-US-540-5773 {Goldman 2020}	Phase 3, randomized, open-label, multicenter study conducted in 2 parts: Part A, a randomized, open-label, multicenter part; Part B, a 2-group, multicenter study	• Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10	RDV 5-day: N = 200 RDV 10-day: N = 197	Participants with severe COVID-19 who were hospitalized; participants in Part A were not to be mechanically ventilated at screening Efficacy and safety data through Day 14 of Part A Final efficacy and safety data for Part A	m2.7.3, Section 2.1.2 GS-US-540-5773 Interim (Final Part A) CSR

Study	Study Design	Treatment Regimens	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
GS-US-540-5774	Phase 3, randomized, open-label, multicenter study conducted in 2 parts: Part A, a randomized, open-label, multicenter part; Part B, a 2-treatment-group, multicenter study	• Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Treatment Group 3: continued SOC therapy	RDV 5-day: N = 191 RDV 10-day: N = 193 SOC: N = 200	Participants with moderate COVID-19 who were hospitalized Efficacy and safety data through Day 14 of Part A	m2.7.3, Section 2.1.3 GS-US-540-5774 Interim 1 (Part A Day 11) CSR
CO-US-540-5758	Phase 3, randomized, double-blind, placebo-controlled, Phase 3 study in China to evaluate the efficacy and safety of RDV in hospitalized adult patients with severe COVID-19 (sponsored by investigator)	• Single loading dose of IV RDV 200 mg or placebo on Day 1 followed by QD maintenance doses of IV RDV 100 mg or placebo for 9 days	RDV: N = 155 Placebo: N = 78;	Hospitalized patients with severe COVID-19 Available efficacy and safety data as of the data cutoff date, as study was stopped prematurely because of the control of the outbreak in Wuhan and on the basis of the termination criteria specified in the protocol	m2.7.3, Section 2.2.1 {Wang 2020}

Study	Study Design	Treatment Regimens	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
IN-US-540-5755[b]	Single patient compassionate use	Single loading dose of IV RDV 200 mg on Day 1 followed by QD maintenance doses of IV RDV 100 mg for up to 9 days	RDV = N = 163[c]	Patients with PCR confirmed COVID-19 who were hospitalized with substantial clinical symptoms where the benefits of treatment with an experimental agent outweighed the risks. Efficacy and safety data from 163 patients through [redacted]20[redacted]	m2.7.3, Section 2.2.2 IN-US-540-5755 Interim 1 Summary Report
Study in Participants with Ebola Virus Disease					
CO-US-399-5366 (PALM)	Phase 2/3, open-label, randomized, parallel-group study to assess the safety and efficacy of investigational treatments, including RDV (RDV arm completed)	Continued SOC therapy together with RDV IV loading dose on Day 1 (200 mg in adults and adjusted for body weight in pediatric patients), followed by a daily IV maintenance dose (100 mg in adults) starting on Day 2 and continuing for 9 to 13 days, depending on viral load	N = 175, all RDV	Adult and pediatric participants with Ebola virus disease. Serious adverse event data from 175 patients treated with RDV	m2.7.4, Section 1.2.2.1 {Mulangu 2019}

Study	Study Design	Treatment Regimens	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
Healthy Participants					
GS-US-399-1812	Phase 1, blinded, randomized, placebo-controlled, first-in-human, single-ascending dose study	• Cohort 1: RDV 3 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 2: RDV 10 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 3: RDV 30 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 4: RDV 75 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 5: RDV 150 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 6: RDV 225 mg solution formulation or placebo over 2 hours as an IV infusion • Cohort 7: RDV 75 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 8: RDV 150 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 9: RDV 75 mg or placebo lyophilized formulation over 30 minutes as an IV infusion	RDV: 78	Healthy adult participants PK and safety data	m2.7.2, Section 2.2.1 GS-US-399-1812 Final CSR

Study	Study Design	Treatment Regimens	Number of Participants[a] by Treatment Regimen	Participant Population and Data Presented	Location of Study Narrative and Report
GS-US-399-1954	Phase 1, blinded, randomized, placebo-controlled multiple dose study	• Cohort 1: RDV 150 mg or placebo administered IV over 1 hour, QD, for 7 days • Cohort 2: RDV 150 mg or placebo administered IV over 1 hour, QD, for 14 days	RDV: 16	Healthy adult participants PK and safety data	m2.7.2, Section 2.2.2 GS-US-399-1954 Final CSR
GS-US-399-4231	Phase 1, single-center, open-label, mass balance study	• Single dose of RDV 150 mg containing a mixture of both unlabeled and radiolabeled [14C]-RDV administered via IV infusion over 0.5 hour on the morning of Day 1	RDV: 8	Healthy adult male participants PK and safety data	m2.7.2, Section 2.2.3 GS-US-399-4231 Final CSR
GS-US-399-5505	Phase 1, blinded, randomized, placebo-controlled, multiple dose study	• Cohort 1: RDV 200 mg or placebo administered IV, QD for the first day, followed by 100 mg RDV or placebo administered IV, QD, for 4 days • Cohort 2: RDV 200 mg or placebo administered IV, QD for the first day, followed by 100 mg RDV or placebo administered IV, QD, for 9 days • Cohort 3: RDV 200 mg or placebo administered IV, QD for the first day, followed by 100 mg RDV or placebo administered IV, QD, for up to 13 days. Cohort 3 was not enrolled.	RDV: 29	Healthy adult participants PK and safety data	m2.7.2, Section 2.2.4 GS-US-399-5505 Final CSR

a Participants who received at least 1 dose of study treatment.
b As of [redacted] 20[redacted], IN-US-540-5755 shifted from an investigator-sponsored single-patient compassionate use program to a Gilead-sponsored expanded access program (GS-US-540-5821; NCT04323761/2020-001453-49) to accelerate the emergency use of RDV for severely ill adult patients. The single-patient compassionate use program (IN-US-540-5755) is currently accepting pediatric patients < 18 years of age and pregnant women with confirmed COVID-19.
c Participants who received at least 1 dose of RDV on or prior to [redacted] 20[redacted], per data entered in electronic case report forms as of [redacted] 20[redacted].

1.2.2. Narratives of Safety Studies

The study narrative for CO-US-399-5366 (PALM Study) is presented below. Study narratives for studies CO-US-540-5776, GS-US-540-5773, GS-US-540-5774, and CO-US-540-5758, and the compassionate use program (IN-US-540-5755), are presented in m2.7.3. Study narratives, including safety data, for the 4 Phase 1 clinical pharmacology studies (Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505) are presented in m2.7.2.

1.2.2.1. CO-US-399-5366 (PALM Study)

Location:	{Mulangu 2019}
Title:	A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. Mulangu S, Dodd LE, Davey RT Jr., Tshiani Mbaya O, Proschan M, Mukadi D, et al. N Engl J Med 2019; 381(24):2293-303
Primary Objective(s):	To study the safety and efficacy of intravenous (IV) investigational treatments in patients with Ebola virus disease (EVD).
Study Design and Subject Population:	This was an open-label, 1:1:1:1 randomized, parallel, interventional Phase 2/3 study designed to assess the safety and efficacy of IV investigational treatments in patients with EVD: ZMapp™, a triple monoclonal antibody; REGN-EB3 ([redacted]), a coformulated mixture of 3 human immunoglobulin G1 monoclonal antibodies; mAb114, a single monoclonal antibody; and RDV. The primary endpoint was death at 28 days. Patients in the remdesivir (RDV, GS-5734™) group received an IV loading dose on Day 1 (200 mg in adults and adjusted for body weight in pediatric patients), followed by a daily maintenance dose (100 mg in adults) starting on Day 2 and continuing for 9 to 13 days, depending on viral load. A total of 175 patients were randomized to receive RDV. All enrolled patients received standard care, which consisted of administration of IV fluids, daily clinical laboratory testing, correction of hypoglycemia and electrolyte imbalances, and administration of broad-spectrum antibiotic agents and antimalarial agents. A total of 681 patients with EVD were enrolled and randomized at [redacted] to receive treatment. The majority of patients were ≥ 18 years of age (74.4%); 12.8% were 6 to 17 years of age, and 12.8% were 5 years of age or younger, of whom 0.7% were neonates (≤ 7 days old). A total of 55.6% patients were female, of whom 6.1% were pregnant at the time of EVD diagnosis. During the course of the study, the data and safety monitoring board recommended that patients be assigned only to the MAb114 and REGN-EB3 groups for the remainder of the trial; the recommendation was based on the results of an interim analysis that showed superiority of these groups to ZMapp and RDV with respect to mortality.
Summary of Results and Conclusions:	One of 9 serious adverse events reported for patients receiving RDV was considered related to RDV. This SAE of hypotension, which occurred during administration of the loading dose, led to fatal cardiac arrest. The independent pharmacovigilance committee noted that the death could not be readily distinguished from underlying fulminant EVD.

1.3. Overall Extent of Exposure

The safety profile of RDV presented in this summary is based on data from 1936 individuals who received at least 1 dose of IV RDV, including 1630 with COVID-19; 175 with EVD; and 131 healthy participants in the Phase 1 studies (Table 2).

Table 2. Summary of the Extent of Exposure to Intravenously Administered Remdesivir

Study ID	Number Who Received RDV	Dose Regimen of IV RDV
Studies in Participants with COVID-19		
CO-US-540-5776 {Beigel 2020}	531 hospitalized participants with COVID-19	200 mg on Day 1 100 mg/day for up to 9 days (up to 10 days total)
GS-US-540-5773 {Goldman 2020}	397 hospitalized participants with severe COVID-19	200 mg on Day 1 100 mg/day for 4 or 9 days (5 or 10 days total)
GS-US-540-5774	384 hospitalized participants with moderate COVID-19	200 mg on Day 1 100 mg/day for 4 or 9 days (5 or 10 days total)
CO-US-540-5758 {Wang 2020}	155 hospitalized participants with COVID-19	200 mg on Day 1 100 mg/day for up to 9 days (up to 10 days total)
IN-US-540-5755	163 hospitalized patients with COVID-19	200 mg on Day 1 100 mg/day for up to 9 days (up to 10 days total)
Study in Participants with Ebola Virus		
CO-US-399-5366 (PALM) {Mulangu 2019}	175 participants with EVD	200 mg on Day 1 100 mg/day for 9 to 13 days (10 to 14 days total)
Studies in Healthy Participants		
GS-US-399-1812	78 healthy participants	3 to 225 mg – single dose
GS-US-399-1954	16 healthy participants	150 mg/day for up to 14 days
GS-US-399-5505	29 healthy participants	200 mg on Day 1 100 mg/day for 4 or 9 days (5 or 10 days total)
GS-US-399-4231	8 healthy participants	150 mg – single dose

1.4. Demographic and Other Characteristics of Study Population

1.4.1. Demographic and Other Characteristics in Individuals with COVID-19

1.4.1.1. Study CO-US-540-5776

The baseline demographics and clinical characteristics for Study CO-US-540-5776 are described in m2.7.3, Section 3.1.1.1.3.

1.4.1.2. Study GS-US-540-5773

The baseline demographics and clinical characteristics for Study GS-US-540-5773 are described in m2.7.3, Section 3.1.1.2.3.

1.4.1.3. Study GS-US-540-5774

The baseline demographics and clinical characteristics for Study GS-US-540-5773 are described in m2.7.3, Section 3.1.1.3.3.

1.4.1.4. Study CO-US-540-5758

The baseline demographics and clinical characteristics for Study CO-US-540-5758 are described in m2.7.3, Section 3.1.2.1.2.

1.4.1.5. Compassionate Use Program (IN-US-540-5755)

The baseline demographics and clinical characteristics for the compassionate use program (IN-US-540-5755) are described in m2.7.3, Section 3.1.2.2.2.

1.4.2. Demographic and Other Characteristics in Participants with Ebola Virus Disease

The mean age of participants with EVD receiving RDV in Study CO-US-399-5366 (PALM) of EVD was 29.6 ± 17.2 years of age, and the majority of participants (56%) were female {Mulangu 2019}.

1.4.3. Demographic and Other Characteristics in Healthy Participants

All participants in the Phase 1 studies were healthy adults between 19 and 55 years of age, and the majority of participants (> 58%) were male. Full details are provided in the individual clinical study reports (CSRs): GS-US-399-1812 Final CSR, Section 8.3, GS-US-399-1954 Final CSR, Section 8.3, GS-US-399-5505 Final CSR, Section 8.3, GS-US-399-4231 Final CSR, Section 8.3.

2. ADVERSE EVENTS

An overall summary of adverse events (AEs) by study is presented in this section. All AEs presented in this summary were treatment emergent and are referred to as AEs throughout this document. Additionally, the relationship of AEs to study treatments and severity of AEs was investigator assigned.

Full details of AEs are provided in the individual CSRs, summary reports or publications (CO-US-540-5776 Preliminary CSR, Section 11.2 through 11.5, GS-US-540-5773 Interim [Final Part A] CSR, Section 11.2 through 11.5, GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Section 11.2 through 11.5, CO-US-540-5758 {Wang 2020}, IN-US-540-5755 Interim 1 Summary Report, Section 3.4, CO-US-399-5366 {Mulangu 2019}, GS-US-399-1812 Final CSR, Section 11.2 through 11.5; GS-US-399-1954 Final CSR, Section 11.2 through 11.5, GS-US-399-4231 Final CSR, Section 11.2 through 11.5; GS-US-399-5505 Final CSR, Section 11.2 through 11.5).

2.1. Adverse Events in Individuals with COVID-19

2.1.1. Study CO-US-540-5776

Remdesivir was well tolerated as demonstrated by the similarity in incidence between the RDV 10-day and placebo groups in nonserious Grade 3 or 4 AEs and serious adverse events (SAEs). The majority of AEs were generally consistent with the underlying manifestations of COVID-19.

2.1.1.1. Grade 3 or 4 Nonserious Adverse Events

Nonserious Grade 3 or 4 AEs were reported in 159 participants (29.9%) in the RDV 10-day group and 170 participants (32.9%) in the placebo group (Table 3). The 3 most commonly reported Grade 3 or 4 AEs in each treatment group were as follows:

- RDV 10-day group — pyrexia (5.1%, 27 of 531 participants), decreased hemoglobin (4.5%, 24 participants), and decreased glomerular filtration rate (4.3%, 23 participants).
- Placebo group — anemia (5.4%, 28 of 517 participants), aspartate aminotransferase (AST) increased (4.3%, 22 participants), and decreased hemoglobin and decreased lymphocyte count (each 4.1%, 21 participants).
- The incidence and types of common AEs were generally similar between the 2 treatment groups.

Table 3. CO-US-540-5776: Nonserious Grade 3 or 4 Adverse Events Occurring in ≥ 5 Subjects in Any Preferred Term by Treatment Group (Treated Population)

MedDRA System Organ Class	Preferred Term	RDV 10-day (N = 531) No. (%)	Placebo (N = 517) No. (%)
Any System Organ Class	Any Preferred Term	159 (29.9)	170 (32.9)
Blood and lymphatic system disorders	Anaemia[a]	20 (3.8)	28 (5.4)
	Lymphopenia[b]	1 (0.2)	11 (2.1)
Cardiac disorders	Atrial fibrillation	3 (0.6)	8 (1.5)
General disorders and administration site conditions	Pyrexia	27 (5.1)	18 (3.5)
Infections and infestations	Pneumonia	7 (1.3)	4 (0.8)
	Septic shock	3 (0.6)	2 (0.4)
Investigations	Haemoglobin decreased[a]	24 (4.5)	21 (4.1)
	Glomerular filtration rate decreased[c]	23 (4.3)	19 (3.7)
	Aspartate aminotransferase increased[d]	15 (2.8)	22 (4.3)
	Lymphocyte count decreased[b]	14 (2.6)	21 (4.1)
	Blood glucose increased[e]	14 (2.6)	7 (1.4)
	Alanine aminotransferase increased[d]	9 (1.7)	12 (2.3)
	Blood bilirubin increased	7 (1.3)	9 (1.7)
	Blood creatinine increased[c]	9 (1.7)	6 (1.2)
	Prothrombin time prolonged	8 (1.5)	3 (0.6)
	Transaminases increased[d]	3 (0.6)	8 (1.5)
	Blood albumin decreased	6 (1.1)	3 (0.6)
	Creatinine renal clearance decreased[c]	3 (0.6)	4 (0.8)
Metabolism and nutrition disorders	Hyperglycaemia[e]	12 (2.3)	12 (2.3)
	Acidosis	5 (0.9)	4 (0.8)
	Hypoalbuminaemia	4 (0.8)	5 (1.0)
	Alkalosis	4 (0.8)	2 (0.4)
Psychiatric disorders	Delirium	4 (0.8)	4 (0.8)

MedDRA System Organ Class	Preferred Term	RDV 10-day (N = 531) No. (%)	Placebo (N = 517) No. (%)
Renal and urinary disorders	Acute kidney injury[c]	15 (2.8)	18 (3.5)
Respiratory, thoracic and mediastinal disorders	Hypoxia[f]	7 (1.3)	6 (1.2)
	Dyspnoea[f]	6 (1.1)	3 (0.6)
	Respiratory distress[f]	3 (0.6)	5 (1.0)
Vascular disorders	Hypotension	11 (2.1)	8 (1.5)
	Hypertension	13 (2.4)	4 (0.8)
	Deep vein thrombosis	6 (1.1)	9 (1.7)

Bacteraemia has been redacted from the table as it occurred in only 1 treatment group.
a The combined number of subjects with either anaemia and/or haemoglobin decreased are 43 for RDV and 48 for placebo.
b The combined number of subjects with either lymphopenia and/or lymphocyte count decreased are 15 for RDV and 32 for placebo.
c The combined number of subjects with either glomerular filtration rate decreased, acute kidney injury, blood creatinine increased and/or creatinine renal clearance decreased are 43 for RDV and 42 for placebo.
d The combined number of subjects with either transaminases increased, aspartate aminotransferase increased and/or alanine aminotransferase increased are 23 for RDV and 37 for placebo.
e The combined number of subjects with either hyperglycaemia and/or blood glucose increased are 26 for RDV and 19 for placebo.
f The combined number of subjects with either hypoxia, dyspnoea, and/or respiratory distress are 16 for RDV and 14 for placebo.
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Table 4

2.1.1.2. Deaths

Mortality was evaluated as a secondary efficacy endpoint. Overall, the number of participants who died by 14 days was numerically lower in the RDV 10-day group (35 of 541 participants) than in the placebo group (56 of 521 participants). The Kaplan-Meier estimates of 14-day mortality were 8.1% and 12.8% in the RDV 10-day and placebo groups, respectively.

2.1.1.3. Other Serious Adverse Events

Serious adverse events were reported in 21.1% (112 of 531 participants) in the RDV 10-day group and 26.9% (139 of 517 participants) in the placebo group (Table 4).

The 3 most commonly reported SAEs in each treatment group were as follows:

- RDV 10-day group — respiratory failure (5.1%, 27 of 531 participants), respiratory distress (1.7%, 9 participants), and acute respiratory failure and cardiac arrest (each 1.3%, 7 participants).

- Placebo group — respiratory failure (9.1%, 47 of 517 participants), acute respiratory failure (2.9%, 15 participants), and respiratory distress (2.3%, 12 participants).

Table 4. CO-US-540-5776: Serious Adverse Events Occurring in ≥ 5 Participants in Any Preferred Term by Treatment Group (Treated Population)

MedDRA System Organ Class	Preferred Term	RDV 10-day (N = 531) No. (%)	Placebo (N = 517) No. (%)
Any System Organ Class	Any Preferred Term	112 (21.1)	139 (26.9)
Cardiac disorders	Cardiac arrest	7 (1.3)	4 (0.8)
	Atrial fibrillation	4 (0.8)	1 (0.2)
General disorders and administration site conditions	Multiple organ dysfunction syndrome	5 (0.9)	1 (0.2)
Infections and infestations	Septic shock	4 (0.8)	9 (1.7)
Renal and urinary disorders	Acute kidney injury[a]	5 (0.9)	9 (1.7)
	Renal impairment	1 (0.2)	6 (1.2)
Respiratory, thoracic and mediastinal disorders	Respiratory failure	27 (5.1)	47 (9.1)
	Acute respiratory failure	7 (1.3)	15 (2.9)
	Respiratory distress[b]	9 (1.7)	12 (2.3)
	Pneumothorax	4 (0.8)	3 (0.6)
	Hypoxia[b]	3 (0.6)	4 (0.8)
	Pulmonary embolism	3 (0.6)	3 (0.6)
	Acute respiratory distress syndrome	4 (0.8)	1 (0.2)
Surgical and medical procedures	Endotracheal intubation	6 (1.1)	9 (1.7)
	Mechanical ventilation	1 (0.2)	5 (1.0)
Vascular disorders	Hypotension	4 (0.8)	8 (1.5)
	Shock	4 (0.8)	3 (0.6)

a The combined number of subjects with either glomerular filtration rate decreased or acute kidney injury are 8 for RDV and 10 for placebo.
b The combined number of subjects with either hypoxia or respiratory distress are 12 for RDV and 16 for placebo.
Source: CO-US-540-5776 Preliminary CSR, Section 15.1, Table 3

2.1.2. Study GS-US-540-5773

Remdesivir was generally well tolerated in both the 5-day and 10-day treatment groups. The incidence and types of AEs were generally similar between the 2 treatment groups and were generally consistent with the manifestations of COVID-19. Serious adverse events and deaths that occurred during the study were generally consistent with underlying manifestations of COVID-19. Serious adverse events, Grade 4 AEs, and AEs leading to premature discontinuation of study treatment occurred in significantly higher proportions of participants in the RDV 10-day group than the RDV 5-day group which was likely attributable to an imbalance in baseline disease severity.

2.1.2.1. Overall Summary of AEs

Comparisons for the proportions of participants with overall AEs were adjusted for baseline clinical status. Similar percentages of participants in the RDV 5-day and RDV 10-day groups had AEs during the study (71.5%, 143 of 200 participants and 75.1%, 148 of 197 participants, respectively) (Table 5).

Serious adverse events were reported in 21.5% (43 participants) and 34.5% (68 participants) in the RDV 5-day and RDV 10-day groups, respectively. The difference in percentages between the groups was statistically significant (p = 0.0136). Serious adverse events considered related to study treatment were reported in 1.5% (3 participants) and 2.0% (4 participants) in the RDV 5-day and RDV 10-day groups, respectively. A similar percentage of participants in each treatment group died (RDV 5-day group 12.5%, 25 participants; RDV 10-day group 14.2%, 28 participants).

Grade 3 or higher AEs were reported in 31.5% (63 participants) and 42.6%, (84 participants) in the RDV 5-day and RDV 10-day groups, respectively. Grade 3 or higher AEs considered related to study treatment were reported in a similar percentage of participants in each group (4.0%, 8 participants and 5.1%, 10 participants in the RDV 5-day and RDV 10-day groups, respectively).

Adverse events considered related to study treatment were reported in a similar percentage of participants in each treatment group (RDV 5-day group 16.5%, 33 participants; RDV 10-day group 20.3%, 40 participants).

Adverse events that led to premature discontinuation of study treatment were reported in a lower percentage of participants in the RDV 5-day group (4.5%, 9 participants) compared with the RDV 10-day group (11.2%, 22 participants); the difference between treatment groups was statistically significant (p = 0.0289).

Through Day 5, Grade 3 or higher AEs and SAEs were reported in lower percentages of participants in the RDV 5-day group than the RDV 10-day group, when both groups had received the same treatment regimen. The percentages of participants with overall AEs occurring on or after Day 6 were generally similar between the groups when categorized by oxygen support status at Day 5 (GS-US-540-5773 Interim [Final Part A] CSR, Table req10636.2). On Days 6 through 10, the only significant difference between groups was in the percentage of participants with study treatment-related AEs (1.5%, 3 participants vs 8.0%, 15 participants in the RDV 5-day vs 10-day groups, respectively).

The percentages of participants with overall AEs occurring on or after Day 6 were generally similar between the groups when categorized by oxygen support status at Day 5, when both groups had received the same treatment regimen (GS-US-540-5773 Interim [Final Part A] CSR, Table req10636.3).

Table 5. GS-US-540-5773: Overall Summary of Adverse Events (Safety Analysis Set)

			RDV 10 Days vs RDV 5 Days	
	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	p-value	Baseline-Adjusted Difference in Percentages (95% CI)
Subjects Experiencing Any Treatment-Emergent AE	143 (71.5%)	148 (75.1%)	0.7678	1.3% (−7.4% to 10.0%)
95% CI	64.7% to 77.6%	68.5% to 81.0%		
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent AE	63 (31.5%)	84 (42.6%)	0.0880	7.8% (−1.3% to 16.9%)
95% CI	25.1% to 38.4%	35.6% to 49.9%		
Subjects Experiencing Any Treatment-Emergent Study Drug-Related AE	33 (16.5%)	40 (20.3%)	0.2437	4.6% (−3.3% to 12.5%)
95% CI	11.6% to 22.4%	14.9% to 26.6%		
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Study	8 (4.0%)	10 (5.1%)	0.6427	1.0% (−3.7% to 5.6%)
95% CI	1.7% to 7.7%	2.5% to 9.1%		
Subjects Experiencing Any Treatment-Emergent SAE	43 (21.5%)	68 (34.5%)	0.0136	10.5% (2.1% to 19.0%)
95% CI	16.0% to 27.8%	27.9% to 41.6%		
Subjects Experiencing Any Treatment-Emergent Study Drug-Related SAE	3 (1.5%)	4 (2.0%)	0.7265	0.5% (−2.8% to 3.8%)
95% CI	0.3% to 4.3%	0.6% to 5.1%		
Subjects Experiencing Any Treatment-Emergent AE Leading to Premature	9 (4.5%)	22 (11.2%)	0.0289	5.9% (0.4% to 11.3%)
95% CI	2.1% to 8.4%	7.1% to 16.4%		
Subjects who had Treatment-Emergent Death	25 (12.5%)	28 (14.2%)	0.9548	−0.2% (−6.7% to 6.3%)
95% CI	8.3% to 17.9%	9.7% to 19.9%		

Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson Exact method.
P-value comparing the percentages was from CMH test stratified by baseline clinical status. The difference in percentages between treatment groups and 95% CI were calculated based on the MH percentages adjusted by baseline clinical status.
Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.11.2.1.1.1

2.1.2.2. Common Adverse Events

The 3 most commonly reported AEs in each treatment group were as follows (Table 6):

- RDV 5-day group — nausea (10.0%, 20 of 200 participants), constipation (6.5%, 13 participants), and acute respiratory failure (6.0%, 12 participants)
- RDV 10-day group — acute respiratory failure (10.7%, 21 of 197 participants), nausea (8.6%, 17 participants), and acute kidney injury (8.1%, 16 participants)

The incidence and types of common AEs reported were generally similar between the 2 treatment groups, with the exception of a lower incidence of acute kidney injury in the RDV 5-day group compared with the RDV 10-day group (RDV 5-day group 2.0%, 4 participants; RDV 10-day group 8.1%, 16 participants).

Table 6. GS-US-540-5773: Adverse Events by Preferred Term Reported for ≥ 5% of Participants in Either Treatment Group (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)
Number of Subjects Experiencing Any Treatment-Emergent AE	143 (71.5%)	148 (75.1%)	291 (73.3%)
Number of Subjects Experiencing Any Treatment-Emergent AE by Preferred Term			
Nausea	20 (10.0%)	17 (8.6%)	37 (9.3%)
Acute respiratory failure	12 (6.0%)	21 (10.7%)	33 (8.3%)
Constipation	13 (6.5%)	13 (6.6%)	26 (6.5%)
Alanine aminotransferase increased	10 (5.0%)	15 (7.6%)	25 (6.3%)
Respiratory failure	8 (4.0%)	15 (7.6%)	23 (5.8%)
Hypokalaemia	10 (5.0%)	12 (6.1%)	22 (5.5%)
Aspartate aminotransferase increased	8 (4.0%)	13 (6.6%)	21 (5.3%)
Hypotension	9 (4.5%)	12 (6.1%)	21 (5.3%)
Insomnia	10 (5.0%)	11 (5.6%)	21 (5.3%)
Acute kidney injury	4 (2.0%)	16 (8.1%)	20 (5.0%)
Corona virus infection	9 (4.5%)	10 (5.1%)	19 (4.8%)
Diarrhoea	10 (5.0%)	9 (4.6%)	19 (4.8%)

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.11.2.1.3

2.1.2.3. Adverse Events by Severity

Grade 3 or higher AEs were reported in 31.5% (63 of 200 participants) and 42.6%, (84 of 197 participants) in the RDV 5-day and RDV 10-day groups, respectively (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.11.2.2.2.3).

Grade 3 AEs were reported in similar percentages of participants in each group (RDV 5-day group 11.5%, 23 participants; RDV 10-day group 9.6%, 19 participants), whereas Grade 4 AEs were reported in a lower percentage of participants in the RDV 5-day group (8.0%, 16 participants) than the RDV 10-day group (18.8%, 37 participants) (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.11.2.2.2.3).

The 3 most commonly reported individual Grade 3 or higher AEs in each treatment group were as follows (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.11.2.2.2.4):

- RDV 5-day group — acute respiratory failure (5.5%, 11 participants), and respiratory failure and corona virus infection (each 4.0%, 8 participants)

- RDV 10-day group — acute respiratory failure (10.2%, 20 participants), respiratory failure (7.6%, 15 participants), and corona virus infection and acute kidney injury (each 5.1%, 10 participants)

Grade 3 or higher study treatment–related AEs were reported in similar percentages of participants in the RDV 5-day group (4.0%, 8 participants) and RDV 10-day group (5.1%, 10 participants) (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.11.2.3.2.4). With the exception of hypertriglyceridemia in 1 participant in the RDV 5-day group, all Grade 3 or higher study treatment–related AEs were hepatic AEs and are presented in Section 2.4.1.1.2.1.

2.1.2.4. Adverse Events by Relationship to Study Treatment

Adverse events considered related to study treatment were reported in a similar percentage of participants in each treatment group (RDV 5-day group 16.5%, 33 of 200 participants; RDV 10-day group 20.3%, 40 of 197 participants) (Table 5).

The 3 most commonly reported AEs considered related to study treatment in each treatment group were as follows (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.11.2.3.1.2):

- RDV 5-day group — nausea (4.5%, 9 participants), and transaminases increased and AST increased (each 2.5%, 5 participants)

- RDV 10-day group — alanine aminotransferase (ALT) increased (7.1%, 14 participants), AST increased (5.6%, 11 participants), and nausea (2.5%, 5 participants)

Serious AEs considered related to study treatment are presented in Section 2.1.2.6.

2.1.2.5. Deaths

A similar percentage of deaths was reported in each treatment group (RDV 5-day group 12.5%, 25 of 200 participants; RDV 10-day group 14.2%, 28 of 197 participants) (Table 5 and GS-US-540-5773 Interim [Final Part A] CSR, Listing 16.2.7.4).

2.1.2.6. Serious Adverse Events

Serious adverse events were reported in 21.5% (43 of 200 participants) in the RDV 5-day group and 34.5% (68 of 197 participants) in the RDV 10-day group (Table 5). The difference in percentages between the groups was statistically significant (p = 0.0136).

The 3 most commonly reported SAEs in each treatment group were as follows (Table 7):

- RDV 5-day group — acute respiratory failure (5.0%, 10 participants), corona virus infection (4.0%, 8 participants), and respiratory failure (3.0%, 6 participants)
- RDV 10-day group — acute respiratory failure (9.1%, 18 participants), and corona virus infection and respiratory failure (each 5.1%, 10 participants)

Table 7. GS-US-540-5773: Serious Adverse Events by Preferred Term for ≥ 1% of Participants in Either Treatment Group (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)
Number of Subjects Experiencing Any Treatment-Emergent SAE	43 (21.5%)	68 (34.5%)	111 (28.0%)
Number of Subjects Experiencing Any Treatment-Emergent SAE by Preferred Term			
Acute respiratory failure	10 (5.0%)	18 (9.1%)	28 (7.1%)
Corona virus infection	8 (4.0%)	10 (5.1%)	18 (4.5%)
Respiratory failure	6 (3.0%)	10 (5.1%)	16 (4.0%)
Respiratory distress	3 (1.5%)	5 (2.5%)	8 (2.0%)
Septic shock	2 (1.0%)	5 (2.5%)	7 (1.8%)
Hypoxia	2 (1.0%)	4 (2.0%)	6 (1.5%)
Multiple organ dysfunction syndrome	2 (1.0%)	4 (2.0%)	6 (1.5%)
Pneumothorax	2 (1.0%)	4 (2.0%)	6 (1.5%)
Acute kidney injury	2 (1.0%)	3 (1.5%)	5 (1.3%)
Acute respiratory distress syndrome	1 (0.5%)	4 (2.0%)	5 (1.3%)
Dyspnoea	4 (2.0%)	1 (0.5%)	5 (1.3%)
Pneumonia viral	3 (1.5%)	2 (1.0%)	5 (1.3%)
Pulmonary embolism	1 (0.5%)	4 (2.0%)	5 (1.3%)
Transaminases increased	3 (1.5%)	2 (1.0%)	5 (1.3%)
Hypotension	1 (0.5%)	3 (1.5%)	4 (1.0%)
Sepsis	2 (1.0%)	1 (0.5%)	3 (0.8%)
Cardiac arrest	0	2 (1.0%)	2 (0.5%)
Pneumonia	2 (1.0%)	0	2 (0.5%)

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.11.4.5

Serious adverse events considered related to study treatment were reported in 1.5% (3 participants) and 2.0% (4 participants) in the RDV 5-day and RDV 10-day groups, respectively (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.11.4.9); all events were hepatic SAEs and are presented in Section 2.4.1.1.2.1.

2.1.2.7. Discontinuations Due to Adverse Events

Adverse events that led to premature discontinuation of study treatment were reported in a lower percentage of participants in the RDV 5-day group (4.5%, 9 of 200 participants) than the RDV 10 day group (11.2%, 22 of 197 participants) (Table 5). The difference between treatment groups was statistically significant (p = 0.0289).

The most common AE that led to premature study treatment discontinuation was transaminase increased in the RDV 5-day group (1.5%, 3 participants) and acute kidney injury in the RDV 10-day group (2.5%, 5 participants) (Table 8). All other AEs reported by ≥ 1% of participants that led to premature study treatment discontinuation were hepatic events and are presented in Section 2.4.1.1.2.1.

Table 8. GS-US-540-5773: Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term for ≥ 1% of Participants in Either Treatment Group (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)
Number of Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	9 (4.5%)	22 (11.2%)	31 (7.8%)
Number of Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation by System Organ Class And Preferred Term			
Hepatobiliary disorders	0	2 (1.0%)	2 (0.5%)
Hypertransaminasaemia	0	2 (1.0%)	2 (0.5%)
Investigations	6 (3.0%)	8 (4.1%)	14 (3.5%)
Transaminases increased	3 (1.5%)	1 (0.5%)	4 (1.0%)
Alanine aminotransferase increased	0	3 (1.5%)	3 (0.8%)
Liver function test increased	1 (0.5%)	2 (1.0%)	3 (0.8%)
Aspartate aminotransferase increased	0	2 (1.0%)	2 (0.5%)
Renal and urinary disorders	0	6 (3.0%)	6 (1.5%)
Acute kidney injury	0	5 (2.5%)	5 (1.3%)

Adverse events were coded using MedDRA 22.1.
System organ classes are presented alphabetically and preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.11.5.1

2.1.3. Study GS-US-540-5774

Remdesivir was generally well tolerated in both the 5-day and 10-day treatment groups. The incidence and types of common AEs were generally similar between treatment groups and were generally consistent with the underlying manifestations of COVID-19. The overall safety profile of RDV was similar to SOC.

2.1.3.1. Overall Summary of AEs

Numerically higher percentages of participants in the RDV 5-day and RDV 10-day groups had AEs during the study compared with the SOC only group (RDV 5-day group 50.8%, 97 of 191 participants; RDV 10-day group 54.9%, 106 of 193 participants; and SOC only group 45.0%, 90 of 200 participants) (Table 9).

Serious adverse events were reported in lower percentages of participants in the RDV 5-day group (4.2%, 8 participants) and RDV 10-day group (3.6%, 7 participants) compared with the SOC only group (9.0%, 18 participants). The difference in percentages between the RDV 10-day group and the SOC only group was statistically significant (p = 0.0376). The only SAE considered related to study treatment was in 1 participant (0.5%, decreased heart rate; Listing 16.2.7.5) in the RDV 5-day group. A similar percentage of participants in each treatment group died (RDV 5-day group 1.0%, 2 participants; RDV 10-day group 1.0%, 2 participants; SOC only group 2.0%, 4 participants).

Grade 3 or higher AEs were reported in a similar percentage of participants in each treatment group (RDV 5-day group 10.5%, 20 participants; RDV 10-day group 10.9%, 21 participants; SOC only group 12.0%, 24 participants). The percentages of participants with any Grade 3 or higher AE considered related to the study treatment were 3.1% (6 participants) in the RDV 5-day group and 2.6% (5 participants) in the RDV 10-day group.

Adverse events considered related to study treatment were reported in a higher percentage of participants in the RDV 5-day group (18.8%, 36 participants) compared with the RDV 10-day group (12.4%, 24 participants).

Adverse events that led to discontinuation of study treatment were reported in 2.1% (4 participants) in the RDV 5-day group and 3.6% (7 participants) in the RDV 10-day group.

Adverse events considered related to study treatment and AEs leading to discontinuation of study treatment were only applicable to the RDV treatment groups.

Table 9. GS-US-540-5774: Overall Summary of Adverse Events (Safety Analysis Set)

				RDV 5 Days vs. SOC Only		RDV 10 Days vs. SOC Only	
	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC Only (N = 200)	p-value	Difference in Percentages (95% CI)	p-value	Difference in Percentages (95% CI)
Subjects Experiencing Any Treatment-Emergent AE	97 (50.8%)	106 (54.9%)	90 (45.0%)	0.2665	5.8% (-4.2% to 15.7%)	0.0554	9.9% (-0.1% to 19.7%)
95% CI	43.5% to 58.1%	47.6% to 62.1%	38.0% to 52.2%				
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent AE	20 (10.5%)	21 (10.9%)	24 (12.0%)	0.7492	-1.5% (-8.1% to 5.1%)	0.7536	-1.1% (-7.6% to 5.5%)
95% CI	6.5% to 15.7%	6.9% to 16.2%	7.8% to 17.3%				
Subjects Experiencing Any Treatment-Emergent Study Drug-Related AE	36 (18.8%)	24 (12.4%)	NA	NA	NA	NA	NA
95% CI	13.6% to 25.1%	8.1% to 17.9%	NA				
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Study Drug-Related AE	6 (3.1%)	5 (2.6%)	NA	NA	NA	NA	NA
95% CI	1.2% to 6.7%	0.8% to 5.9%	NA				
Subjects Experiencing Any Treatment-Emergent SAE	8 (4.2%)	7 (3.6%)	18 (9.0%)	0.0679	-4.8% (-10.1% to 0.2%)	0.0376	-5.4% (-10.6% to -0.5%)
95% CI	1.8% to 8.1%	1.5% to 7.3%	5.4% to 13.9%				
Subjects Experiencing Any Treatment-Emergent Study Drug-Related SAE	1 (0.5%)	0	NA	NA	NA	NA	NA
95% CI	0.0% to 2.9%	0.0% to 1.9%	NA				
Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	4 (2.1%)	7 (3.6%)	NA	NA	NA	NA	NA
95% CI	0.6% to 5.3%	1.5% to 7.3%	NA				
Subjects who had Treatment-Emergent Death	2 (1.0%)	2 (1.0%)	4 (2.0%)	0.6856	-1.0% (-4.1% to 2.0%)	0.6854	-1.0% (-4.2% to 1.9%)
95% CI	0.1% to 3.7%	0.1% to 3.7%	0.5% to 5.0%				

Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson Exact method.
The differences in percentages between treatment groups and 95% CI were calculated based on exact method.
P-value was from the Fisher exact test to compare each RDV group and the SOC group.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.11.2.1.1.1

2.1.3.2. Common Adverse Events

The 3 most commonly reported AEs by treatment group were as follows (Table 10):

- RDV 5-day group — nausea (9.9%, 19 of 191 participants), and diarrhea and headache (each 5.2%, 10 participants)
- RDV 10-day group — nausea (9.3%, 18 of 193 participants), hypokalemia (6.7%, 13 participants), and diarrhea and headache (each 5.2%, 10 participants)
- SOC only group — diarrhea (7.0%, 14 of 200 participants), constipation (4.5%, 9 participants), and pyrexia and insomnia (each 3.5%, 7 participants)

The incidence and types of common AEs were generally similar between the treatment groups, with the exception of a higher incidence of nausea in the RDV 5-day group and RDV 10-day group compared with the SOC only group (RDV 5-day group 9.9%, 19 participants; RDV 10-day group 9.3%, 18 participants; SOC only group 3.0%, 6 participants).

Table 10. GS-US-540-5774: Adverse Events by Preferred Term Reported for ≥ 2% of Participants in Any Treatment Group (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC Only (N = 200)
Number of Subjects Experiencing Any Treatment-Emergent AE	97 (50.8%)	106 (54.9%)	90 (45.0%)
Number of Subjects Experiencing Any Treatment-Emergent AE by Preferred Term			
Nausea	19 (9.9%)	18 (9.3%)	6 (3.0%)
Diarrhoea	10 (5.2%)	10 (5.2%)	14 (7.0%)
Hypokalaemia	9 (4.7%)	13 (6.7%)	4 (2.0%)
Headache	10 (5.2%)	10 (5.2%)	5 (2.5%)
Constipation	8 (4.2%)	5 (2.6%)	9 (4.5%)
Alanine aminotransferase increased	8 (4.2%)	6 (3.1%)	5 (2.5%)
Phlebitis	7 (3.7%)	7 (3.6%)	5 (2.5%)
Pyrexia	2 (1.0%)	8 (4.1%)	7 (3.5%)
Rash	7 (3.7%)	4 (2.1%)	6 (3.0%)
Insomnia	7 (3.7%)	2 (1.0%)	7 (3.5%)
Aspartate aminotransferase increased	5 (2.6%)	5 (2.6%)	5 (2.5%)
Hypotension	6 (3.1%)	6 (3.1%)	1 (0.5%)
Vomiting	5 (2.6%)	5 (2.6%)	3 (1.5%)
Hypertransaminasaemia	3 (1.6%)	6 (3.1%)	3 (1.5%)
Hypocalcemia	6 (3.1%)	6 (3.1%)	0
Anaemia	3 (1.6%)	3 (1.6%)	4 (2.0%)
Dyspnoea	4 (2.1%)	5 (2.6%)	1 (0.5%)
Cough	2 (1.0%)	1 (0.5%)	5 (2.5%)
Acute respiratory failure	1 (0.5%)	1 (0.5%)	5 (2.5%)
Transaminases increased	3 (1.6%)	4 (2.1%)	0
Chest pain	1 (0.5%)	4 (2.1%)	1 (0.5%)

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.11.2.1.3

2.1.3.3. Adverse Events by Severity

The majority of AEs reported in this study were Grade 1 or 2 in severity (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.2.2.1). Grade 1 AEs were reported in higher percentages of participants in the RDV 5-day group (26.2%, 50 of 191 participants) and RDV 10-day group (24.4%, 47 of 193 participants) than the SOC only group (17.5%, 35 of 200 participants).

Grade 3 or higher AEs reported in each treatment group were as follows: RDV 5-day group 10.5%, 20 participants; RDV 10-day group 10.9%, 21 participants; and SOC only group 12.0%, 24 participants (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.2.2.2.3). Grade 3 AEs were reported in each treatment group as follows: RDV 5-day group 8.9%, 17 participants; RDV 10-day group 8.8%, 17 participants; and SOC only group 6.5%, 13 participants. Grade 4 AEs were reported in each treatment group as follows: RDV 5-day group 0.5%, 1 participant; RDV 10-day group 1.0%, 2 participants; and SOC only group 3.5%, 7 participants.

Grade 3 or higher individual AEs reported in at least 2 participants in each treatment group were as follows (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.2.2.2.4):

- RDV 5-day group — increased ALT, hypotension, and increased AST (each 1.0%, 2 of 191 participants)
- RDV 10-day group — hypotension (2.1%, 4 of 193 participants) and increased ALT, dyspnea, and increased transaminases (each 1.0%, 2 participants)
- SOC only group — acute respiratory failure (2.5%, 5 of 200 participants), anemia (1.5%, 3 participants), and acute kidney injury, increased ALT, cardiac arrest, respiratory distress, and respiratory failure (each 1.0%, 2 participants)

Grade 3 or higher AEs of hypotension occurred in the RDV treatment groups but not the SOC only group. Of these 4 of 6 occurred after RDV dosing was completed.

The percentages of participants with Grade 3 or higher study treatment-related AEs were 3.1%, 6 participants in the RDV 5-day group and 2.6%, 5 participants in the RDV 10-day group (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.2.3.2.3).

2.1.3.4. Adverse Events by Relationship to Study Treatment

Adverse events considered related to study treatment were reported in 18.8% (36 of 191 participants) in the RDV 5-day group and 12.4% (24 of 193 participants) in the RDV 10-day group (Table 9). Adverse events considered related to study treatment were not applicable to the SOC group.

The 3 most commonly reported AEs considered related to study treatment in each treatment group were as follows (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.2.3.1.2):

- RDV 5-day group — nausea (6.8%, 13 of 191 participants), increased ALT (3.7%, 7 participants), and increased AST and rash (each 2.6%, 5 participants)

- RDV 10-day group — nausea (3.6%, 7 of 193 participants), hypertransaminasemia (2.1%, 4 participants), and increased ALT, increased AST, diarrhea, headache, and vomiting (each 1.6%, 3 participants)

Serious adverse events considered related to study treatment are presented in Section 2.1.3.6.

2.1.3.5. Deaths

A similar percentage of deaths was reported in each treatment group (RDV 5-day group 1.0%, 2 of 191 participants; RDV 10-day group 1.0%, 2 of 193 participants; SOC only group 2.0%, 4 of 200 participants) (Table 9 and GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Listing 16.2.7.4).

2.1.3.6. Serious Adverse Events

Serious adverse events were reported in lower percentages of participants in the RDV treatment groups (RDV 5-day group 4.2%, 8 of 191 participants; RDV 10-day group 3.6%, 7 of 193 participants) than the SOC only group (9.0%, 18 of 200 participants; Table 11). The difference in percentages between the RDV 10-day group and SOC only group was statistically significant (p = 0.0376) (Table 9).

Table 11. GS-US-540-5774: Serious Adverse Events by Preferred Term for ≥ 1% of Participants in Any Treatment Group (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC Only (N = 200)
Number of Subjects Experiencing Any Treatment-Emergent SAE	8 (4.2%)	7 (3.6%)	18 (9.0%)
Number of Subjects Experiencing Any Treatment-Emergent SAE by Preferred Term			
Acute respiratory failure	0	0	5 (2.5%)
Respiratory distress	0	1 (0.5%)	2 (1.0%)
Respiratory failure	1 (0.5%)	0	2 (1.0%)
Cardiac arrest	0	0	2 (1.0%)

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.11.4.5

Only 1 SAE of decreased heart rate in a participant in the RDV 5-day group (0.5%) was considered related to study treatment; this SAE led to premature discontinuation of study treatment and resolved the same day (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.4.9 and Listing 16.2.7.7). No other SAE led to discontinuation of study treatment.

2.1.3.7. Discontinuations Due to Adverse Events

Study treatment discontinuation was recorded only for the RDV treatment groups. Adverse events leading to study treatment discontinuation were reported in a similar percentage of participants in each RDV group (RDV 5-day group 2.1%, 4 of 191 participants; RDV 10-day group 3.6%, 7 of 193 participants; Table 12).

Adverse events that led to premature discontinuation in more than 1 participant in each RDV treatment group were as follows: RDV 5-day group: rash 2 participants (1.0%); RDV 10-day group: increased ALT 3 participants (1.6%) and increased AST 2 participants (1.0%).

Table 12. GS-US-540-5774: Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)
Number of Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	4 (2.1%)	7 (3.6%)
Number of Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation by System Organ Class And Preferred Term		
Hepatobiliary disorders	0	1 (0.5%)
Hypertransaminasaemia	0	1 (0.5%)
Investigations	2 (1.0%)	5 (2.6%)
Alanine aminotransferase increased	1 (0.5%)	3 (1.6%)
Aspartate aminotransferase increased	0	2 (1.0%)
Blood alkaline phosphatase increased	0	1 (0.5%)
Blood bilirubin increased	0	1 (0.5%)
Heart rate decreased	1 (0.5%)	0
Transaminases increased	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.5%)
Acute respiratory failure	0	1 (0.5%)
Skin and subcutaneous tissue disorders	2 (1.0%)	0
Rash	2 (1.0%)	0

Adverse events were coded using MedDRA 22.1.
System organ classes are presented alphabetically and preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.11.5.1

2.1.4. Study CO-US-540-5758

Remdesivir was well tolerated as demonstrated by the similar incidence of AEs and SAEs between the RDV-10 day and placebo groups. The majority of AEs were generally consistent with the underlying manifestations of COVID-19.

Adverse events were reported in 66% (102 of 155 participants) of the RDV group and 64% (50 of 78 participants) of the placebo group {Wang 2020}. Grade 3 or 4 AEs were reported in 8% (13 participants) of the RDV group and 14% (11 participants) of the placebo group. The most common Grade 3 or 4 AEs (reported in > 1% of participants in either treatment group) were thrombocytopenia (RDV, 3%; placebo, 4%) and anemia (RDV, 1%; placebo, 3%).

Serious AEs were reported in 18% (28 participants) of the RDV group and 26% (20 participants) of the placebo group. The most common SAEs (reported in > 1% of participants in either treatment group) were respiratory failure or acute respiratory distress syndrome (RDV, 10%; placebo, 5%), cardiopulmonary failure (RDV, 5%; placebo, 9%), and multiple organ dysfunction syndrome (RDV, 1%; placebo, 3%).

More participants in the RDV group than the placebo group discontinued study treatment due to AEs (RDV, 12%; placebo 5%). The most common AEs leading to study treatment discontinuation (reported in > 1% of participants in either treatment group) were secondary infection (RDV, 3%; placebo, 9%), respiratory failure or acute respiratory distress syndrome (RDV, 5%; placebo, 1%), and cardiopulmonary failure (RDV, 2%; placebo, 1%). [Note the error carried over from {Wang 2020}: the percentage of placebo-treated participants who discontinued study treatment due to secondary infection (9%) is higher than the total percentage of placebo-treated participants who discontinued study treatment due to AE (5%).]

All deaths during the observation period were judged by the site investigators to be unrelated to study treatment.

2.1.5. Compassionate Use Program (IN-US-540-5755)

Patients treated with RDV through the compassionate use program (IN-US-540-5755) were of high medical acuity in the midst of a global pandemic of COVID-19. As such, data such as severity and relatedness of AEs to RDV were inconsistently reported by sites, limiting the interpretability of collected data.

Overall, AEs were reported in 50.3% of the 163 patients treated with RDV through [redacted] 20[redacted]. The most common AEs (> 4% overall) were respiratory failure (6.7%), transaminases increased (4.9%), acute kidney injury (4.9%), hypotension (4.9%), and diarrhea (4.3%). Fewer patients on noninvasive baseline oxygen support had AEs than did patients on invasive baseline oxygen support (41.4% vs 55.8%). The following AEs were reported in higher percentages of patients on invasive baseline oxygen support than patients on noninvasive baseline oxygen support (> 4% difference between groups): respiratory failure (9.6% vs 1.7%), CoV infection (5.8% vs 1.7%), acute kidney injury (6.7% vs 1.7%), renal impairment (4.8% vs 0), hypotension (6.7% vs 1.7%), and multiple organ dysfunction syndrome (4.8% vs 0), consistent with the increased severity of illness in these patients (IN-US-540-5755 Interim 1 Summary Report, Table 9 and Table 10). The incidence and types of AEs were generally consistent with the underlying manifestations of COVID-19.

Serious AEs were reported in 23.3% of patients. Fewer patients on noninvasive baseline oxygen support had SAEs than did patients on invasive baseline oxygen support (15.5% vs 27.9%). The only SAE occurring in > 5% of all patients was respiratory failure, which occurred in 10 patients (6.1%) overall and was more common among patients on invasive baseline oxygen support (8.7%) than patients on noninvasive baseline oxygen support (1.7%) (IN-US-540-5755 Interim 1 Summary Report, Table 11). Serious adverse events and deaths that occurred in this program were generally consistent with the underlying manifestations of COVID-19.

Overall, 13 patients (8.0%) discontinued RDV due to AEs and 33 patients (20.2%) died. Most discontinuations due to AEs were associated with renal dysfunction (4 patients) or due to hepatic AEs (5 patients). Note, the protocol specified that RDV was to be permanently discontinued if a patient had ALT ≥ 5 times the upper limit of normal (ULN) or creatinine clearance (CrCl) < 30 mL/min. Two patients discontinued due to multiple organ failure, 1 patient due to systolic dysfunction, and 1 patient due to respiratory distress (IN-US-540-5755 Interim 1 Summary Report, Listing 8).

2.2. Adverse Events in Participants with Ebola Virus Disease

2.2.1. Study CO-US-399-5366

In Study CO-US-399-5366 (PALM), 175 participants with EVD were treated with IV RDV (200 mg on Day 1; 100 mg/day beginning on Day 2 for 9 to 13 days). A total of 9 SAEs judged by the site investigator as not related to underlying EVD were reported for participants receiving RDV. Of these, an event of hypotension, which occurred during administration of the loading dose and led to fatal cardiac arrest, was considered related to RDV. The independent pharmacovigilance committee noted that the death could not be readily distinguished from underlying fulminant EVD {Mulangu 2019}.

2.3. Adverse Events in Healthy Participants

The most commonly reported AEs (in ≥ 5 healthy participants who received RDV across the 4 Phase 1 studies) were infusion-site phlebitis, constipation, headache, ecchymosis, nausea, and pain in extremity. All AEs were Grade 1 or 2 in severity. Treatment-related AEs were infrequently reported and primarily consisted of infusion-site phlebitis, headache, rash or pruritus, and gastrointestinal adverse effects. No Grade 3 or 4 AEs, hepatic AEs, SAEs, or deaths were reported. Two participants discontinued RDV due to AEs of nausea (and additionally paresthesia in 1 of the participants).

2.3.1. Study GS-US-399-1812

In Study GS-US-399-1812, a total of 17 of 78 participants (21.8%) who received RDV and 2 of 18 participants (11.1%) who received placebo had at least 1 AE.

Among the participants who received RDV solution formulation in Cohorts 1 to 6, 4 of the 8 (50.0%) in Cohort 1 (3 mg), 3 of the 8 (37.5%) in Cohort 2 (10 mg), 1 of the 8 (12.5%) in Cohort 3 (30 mg), 1 of the 8 (12.5%) in Cohort 4 (75 mg), 1 of the 8 (12.5%) in Cohort 5 (150 mg), and 3 of the 8 (37.5%) in Cohort 6 (225 mg) had at least 1 AE. There was no dose-proportional increase in the proportions of participants with AEs across Cohorts 1 to 6.

Among the participants who received RDV lyophilized formulation in Cohorts 7 to 9, 1 of the 10 (10.0%) in Cohort 7 (75 mg infused over 2 hours) and 3 of the 10 (30.0%) in Cohort 9 (75 mg infused over 30 minutes) had at least 1 AE.

No AE was reported for > 1 participant within an individual dose group. Constipation was the only AE reported for > 1 participant overall in the study, occurring in 3 of 78 participants (3.8%) who received RDV (1 participant each in the 3, 30, and 225 mg groups).

No Grade 3 or 4 AEs, SAEs, AEs leading to study treatment or study discontinuation, pregnancies, or deaths were reported during the study.

Two participants had an AE considered by the investigator to be related to study treatment, both of whom received RDV solution formulation. One participant in Cohort 2 (10 mg solution formulation) had dizziness, and 1 participant in Cohort 6 (225 mg solution formulation) had generalized pruritus. Both AEs started on Day 1 and resolved on the same day. No action was taken with study treatment and both participants completed the study.

Five participants had an AE considered by the investigator to be related to study procedure, 4 of whom received RDV solution formulation (infusion site extravasation [3 mg dose], medical device site dermatitis [3 mg dose], ecchymosis [10 mg dose], and presyncope [75 mg dose]) and 1 of whom received RDV lyophilized formulation (medical device site irritation [75 mg dose over 30 minutes]). For all participants, no action was taken with study treatment and the participants completed the study. All events resolved within 3 days, with the exception of ecchymosis, which started on Day 2 and resolved on Day 28.

2.3.2. Study GS-US-399-1954

In Study GS-US-399-1954, a total of 9 of 16 participants (56.3%) who received RDV and 4 of 8 participants (50.0%) who received placebo had at least 1 AE. Among the participants who received RDV, 6 of the 8 (75.0%) in Cohort 1 and 3 of the 8 (37.5%) in Cohort 2 had AEs.

The only AEs reported for > 1 participant were constipation, dyspepsia, and pain in extremity in participants who had received RDV (each 3 participants [18.8%]).

One participant in Cohort 1 received RDV and discontinued study treatment due to the AE of nausea considered related to study treatment. No Grade 3 or 4 AEs, SAEs, pregnancies, or deaths were reported during the study.

Three participants had AEs considered related to RDV. One participant in Cohort 1 had study treatment-related related headache, nausea, vomiting, and tremor (left leg and hand) on Day 3. The tremor resolved on the same day, and the other 3 AEs resolved between Days 4 and 7. The participant discontinued study treatment after dosing on Day 4 (due to the AE nausea). Additional study treatment-related AEs occurred after study treatment discontinuation (decreased appetite, starting on Day 5, resolved on Day 7; and constipation, starting on Day 8, resolved on Day 9). The participant also had elevated ALT and AST. In Cohort 2, 2 participants who received RDV had study treatment-related dyspepsia starting on Day 4, which resolved on Day 19 in 1 participant and Day 20 in the other.

One participant who received placebo in Cohort 2 experienced Grade 1 diarrhea that was considered related to study treatment by the investigator. The diarrhea started on Day 7 and resolved on Day 12.

Nine participants had an ≥ 1 AE that was considered by the investigator to be related to study procedure, 6 of whom received RDV (pain in extremity [3 participants], infusion site extravasation, infusion site hemorrhage, infusion site pain, contact dermatitis, pruritis, and ecchymosis [1 participant each]) and 3 of whom received placebo (contact dermatitis, pruritis, and dermatitis, and iron deficiency anemia [1 participant each]). All study procedure-related AEs resolved, and time to resolution ranged from < 1 day to 52 days.

2.3.3. Study GS-US-399-4231

In Study GS-US-399-4231, a total of 7 of 8 participants (87.5%) experienced AEs. Diarrhea, erythema, and rhinorrhea were reported in 2 participants each. No other AEs were reported in more than 1 participant.

No Grade 3 or 4 AEs, SAEs, deaths, or AEs leading to premature discontinuation of study treatment were reported.

Headache and rash pruritic (1 participant each) were the only AEs considered related to study treatment by the investigator. Four participants experienced AEs related to study procedures: erythema, peripheral swelling, and contusion (all in 1 participant), and erythema, sneezing, and contact dermatitis (1 participant each).

2.3.4. Study GS-US-399-5505

In Study GS-US-399-5505, across Cohorts 1 and 2, a total of 24 of 29 participants who received RDV and 2 of 7 participants who received placebo had at least 1 AE (Cohort 1: 7 of 9 participants [77.8%] and 0 of 2 participants (0%), respectively; Cohort 2: 17 of 20 participants (85.0%) and 2 of 5 participants (40.0%), respectively).

The most frequently reported AEs included infusion site phlebitis (all in the RDV treatment group of Cohort 2, 8 of 20 participants [40.0%]), nausea (all in RDV treatment groups, Cohort 1: 2 of 9 participants [22.2%]; Cohort 2: 2 of 20 participants [10.0%]), and headache (Cohort 1: 2 of 9 participants [22.2%] in the RDV treatment group, 0 of 2 participants [0%] in the placebo group; Cohort 2: 1 of 20 participants [5.0%] in the RDV treatment group, 1 of 5 participants [20.0%] in the placebo group).

All of the AEs were Grade 1 and 2 in severity, with the majority reported as Grade 1. No Grade 3 or 4 AEs, SAEs, deaths, or pregnancies were reported during the study.

All of the AEs considered related to the study treatment were in the RDV treatment group. The most frequently reported treatment-related AEs reported among the 9 participants in Cohort 1 and 20 participants in Cohort 2 were as follows: infusion site phlebitis (Cohort 1: 0 participants; Cohort 2: 8 participants [40.0%]); nausea (Cohort 1: 2 participants [22.2%]; Cohort 2: 1 participant [5.0%]); headache (Cohort 1: 2 participants [22.2%]; Cohort 2: 1 participant

[5.0%]); and abnormal dreams (Cohort 1: 2 participants [22.2%]; Cohort 2: 1 participant 5.0%]). The 8 participants with infusion site phlebitis were in Cohort 2b only and were a majority subset of a total of 13 participants who experienced infusion site reaction AEs (Cohort 1: 1 of 9 participants [11.1%] in the RDV treatment group, 0 of 2 participants [0%] in the placebo group; Cohort 2: 11 of 20 participants [55.0%] in the RDV treatment group, 1 of 5 participants [20.0%] in the placebo group). A total of 16 infusion site reaction AEs was reported; the majority were Grade 1 and reported in Cohort 2. Fifteen infusion site reaction AEs were deemed related to the study procedures; among these, 8 were also deemed related to RDV.

Adverse events of nausea and paresthesia, both Grade 1, led to the discontinuation of study treatment in 1 participant in the RDV treatment group of Cohort 1. This participant also prematurely discontinued from the study because of AEs of Grade 1 nausea, myalgia, headache, paresthesia, hyperhidrosis, and Grade 2 hypotension.

2.4. Other Adverse Events of Interest

Hepatic safety is described in Section 2.4.1, renal safety in Section 2.4.2 and IRRs in Section 2.4.3.

2.4.1. Hepatic Safety

Increased transaminases are common in patients with COVID-19. Abnormal ALT and AST levels and slightly elevated bilirubin levels have been reported in 16% to 53% of reported cases in China {Chen 2020a, Huang 2020, Shi 2020, Wu 2020, Yang 2020}.

Grade 1 and 2 transient increases in transaminases were observed in the multiple-dose Phase 1 studies in healthy participants (Section 2.4.1.2).

For Studies GS-US-540-5773 and GS-US-540-5774, preferred terms (PTs) for defining hepatic AEs were identified from a Medical Dictionary for Regulatory Activities (MedDRA) search term listing (GS-US-540-5773 Interim [Final Part A] CSR, Appendix 16.1.9 and GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Appendix 16.1.9). In Study GS-US-540-5773, the incidence of hepatic AEs and Grade 3 or 4 laboratory abnormalities were comparable between the RDV 5-day and RDV 10-day treatment groups. In Study GS-US-540-5774, the incidence of hepatic AEs and Grade 3 or 4 laboratory abnormalities was similar across RDV and SOC treatment groups. The incidence of hepatic AEs was similar between RDV-treated participants and placebo-treated participants in Studies CO-US-540-5776 and CO-US-540-5758.

2.4.1.1. Hepatic Safety in Individuals with COVID-19

2.4.1.1.1. Study CO-US-540-5776

The combined numbers of participants with 1 or more hepatic-related nonserious Grade 3 or 4 AEs (either transaminases increased, AST increased, and/or ALT increased) were 23 (4.3%) in the RDV 10-day group and 37 (7.2%) in the placebo group (Table 3). No hepatic-related SAEs (either transaminases increased, AST increased, and/or ALT increased) occurred in ≥ 5 participants (Table 4).

2.4.1.1.2. Study GS-US-540-5773

2.4.1.1.2.1. Hepatic Adverse Events

Hepatic AEs were reported in 13.5% (27 of 200 participants) in the RDV 5-day group and 18.8% (37 of 197 participants) in the RDV 10-day group (Table 13).

Table 13. GS-US-540-5773: Overall Summary of Hepatic Adverse Events (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)
Subjects Experiencing Any Treatment-Emergent Hepatic AE	27 (13.5%)	37 (18.8%)
95% CI	9.1% to 19.0%	13.6% to 24.9%
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Hepatic AE	10 (5.0%)	15 (7.6%)
95% CI	2.4% to 9.0%	4.3% to 12.2%
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Hepatic AE	16 (8.0%)	26 (13.2%)
95% CI	4.6% to 12.7%	8.8% to 18.7%
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Study Drug-Related Hepatic AE	7 (3.5%)	10 (5.1%)
95% CI	1.4% to 7.1%	2.5% to 9.1%
Subjects Experiencing Any Treatment-Emergent Hepatic SAE	4 (2.0%)	5 (2.5%)
95% CI	0.5% to 5.0%	0.8% to 5.8%
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Hepatic SAE	3 (1.5%)	4 (2.0%)
95% CI	0.3% to 4.3%	0.6% to 5.1%
Subjects Experiencing Any Treatment-Emergent Hepatic AE Leading to Premature Study Drug Discontinuation	5 (2.5%)	9 (4.6%)
95% CI	0.8% to 5.7%	2.1% to 8.5%

Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson Exact method.
Hepatic events include preferred terms from MedDRA 22.1 search term list 'Acute and non-infectious liver events'.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table req10636.4

The overall pattern and types of hepatic AEs were similar in the 2 treatment groups (Table 14). The 3 most commonly reported hepatic AEs in the RDV 5-day and RDV 10-day groups were ALT increased (5.0%, 10 participants vs 7.6%, 15 participants), AST increased (4.0%, 8 participants vs 6.6%, 13 participants), and transaminases increased (each 3.0%, 6 participants).

Table 14. GS-US-540-5773: Hepatic Adverse Events by Preferred Term (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N=397)
Number of Subjects Experiencing Any Treatment-Emergent Hepatic AE	27 (13.5%)	37 (18.8%)	64 (16.1%)
Number of Subjects Experiencing Any Treatment-Emergent Hepatic AE by Preferred Term			
Alanine aminotransferase increased	10 (5.0%)	15 (7.6%)	25 (6.3%)
Aspartate aminotransferase increased	8 (4.0%)	13 (6.6%)	21 (5.3%)
Transaminases increased	6 (3.0%)	6 (3.0%)	12 (3.0%)
Hepatic enzyme increased	3 (1.5%)	2 (1.0%)	5 (1.3%)
Hypertransaminasaemia	1 (0.5%)	4 (2.0%)	5 (1.3%)
Liver function test increased	2 (1.0%)	3 (1.5%)	5 (1.3%)
Hepatitis	1 (0.5%)	2 (1.0%)	3 (0.8%)
Blood bilirubin increased	1 (0.5%)	1 (0.5%)	2 (0.5%)
Hepatic failure	1 (0.5%)	0	1 (0.3%)
International normalised ratio increased	0	1 (0.5%)	1 (0.3%)

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Hepatic events include preferred terms from MedDRA 22.1 search term list 'Acute and non-infectious liver events'.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table req10636.5

The combined numbers of participants in each treatment group with 1 or more transaminase-related AEs (using the PTs ALT increased, AST increased, hepatic enzymes increased, hypertransaminasemia, liver function test increased, and transaminases increased) were 24 (12.0%) in the RDV 5-day group and 33 (16.8%) in the RDV 10-day group (GS-US-540-5773 Interim [Final Part A] CSR, Table req10636.6).

Hepatic SAEs were reported in 2.0% (4 participants) in the RDV 5-day group and 2.5% (5 participants) in the RDV 10-day group (Table 13). Serious hepatic AEs considered related to study treatment were transaminases increased (1.5%, 3 participants in the RDV 5-day group and 1.0%, 2 participants in the RDV 10-day group), and hypertransaminasemia and hepatic enzyme increased (no participant in the RDV 5-day group and 0.5%, 1 participant each in the RDV 10-day group) (GS-US-540-5773 Interim [Final Part A] CSR, Tables 15.11.4.9 and req10636.5, and Listing req10636.1).

Grade 3 or higher hepatic AEs were reported in 5.0% (10 participants) in the RDV 5-day group and 7.6% (15 participants) in the RDV 10-day group (Table 13). Of the Grade 3 or higher study treatment–related hepatic AEs (reported in 3.5%, 7 participants and 5.1%, 10 participants in the RDV 5-day and RDV 10-day groups, respectively), the most common were transaminases increased, reported in 1.5% (3 participants) each in the RDV 5-day and RDV 10-day groups, and ALT increased, reported in no participants in the RDV 5-day group versus 2.5% (5 participants) in the RDV 10-day group (GS-US-540-5773 Interim [Final Part A] CSR Tables 15.11.2.3.2.4 and req10636.5). Other Grade 3 or higher study treatment–related AEs were AST increased, hepatic enzyme increased, liver function test increased, and hypertransaminasemia.

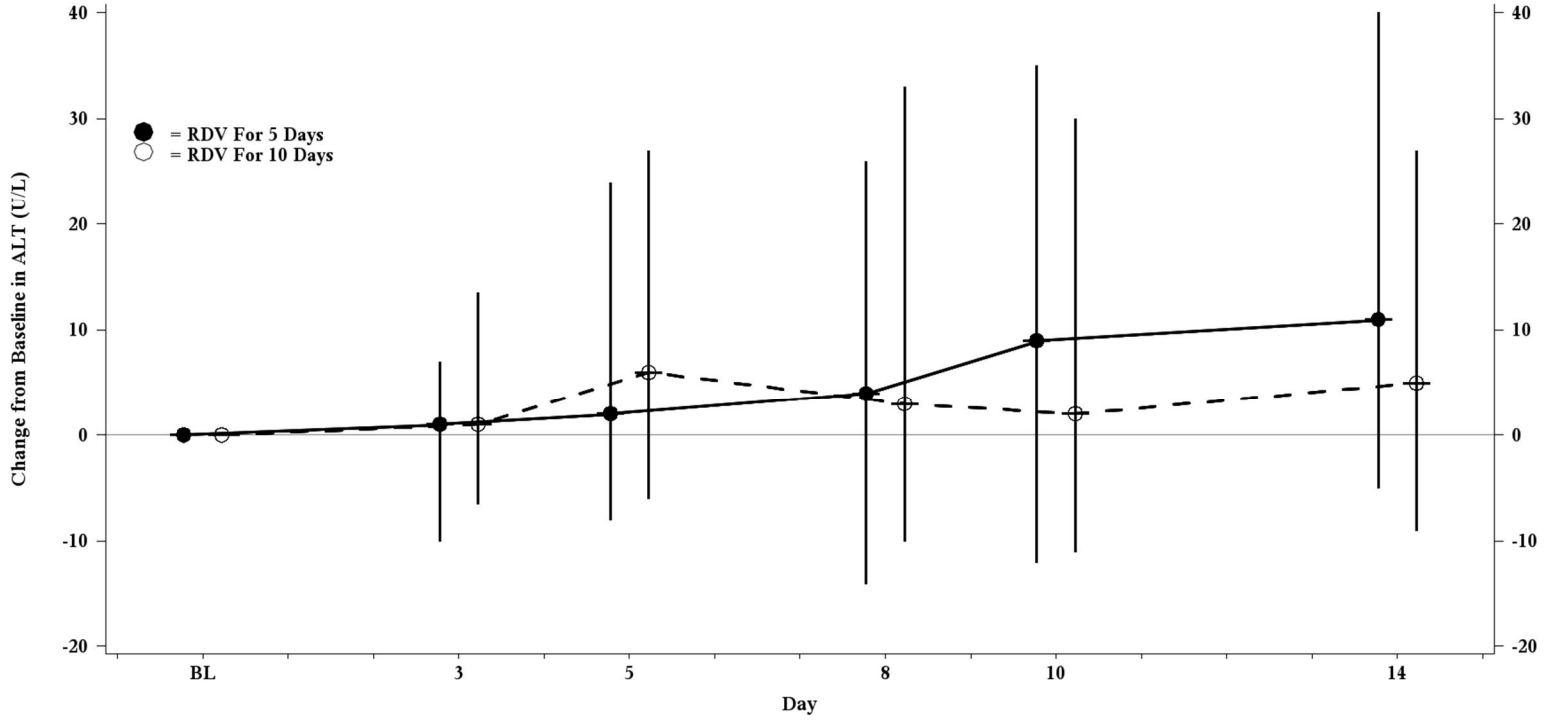
Hepatic AEs leading to study treatment discontinuation were reported in 2.5% (5 participants) and 4.6%, (9 participants) in the RDV 5-day and RDV 10-day groups, respectively, with the most common being transaminases increased (1.5%, 3 participants and 0.5%, 1 participant, respectively) (Table 8, Table 13, and GS-US-540-5773 Interim [Final Part A] CSR, Listing req10636.1). Other hepatic AEs that led to study treatment discontinuation were ALT increased (no participant and 1.5%, 3 participants in the RDV 5-day and RDV 10-day groups, respectively) and liver function test increased (0.5%, 1 participant and 1.0%, 2 participants in the RDV 5-day and RDV 10-day groups, respectively). Hypertransaminasemia and AST increased that led to study treatment discontinuation were each reported in no participant in the RDV 5-day group and 1.0% (2 participants) in the RDV 10-day group.

Nonserious AEs of hepatitis were reported in 3 participants (1 in the RDV 5-day group and 2 in the RDV 10-day group) (GS-US-540-5773 Interim [Final Part A] CSR, Table req10636.5 and Listing req10636.1). Grade 3 hepatitis was reported in 1 participant in the RDV 5-day group on Day 11, 6 days after study treatment completion; the event was ongoing and considered not related to study treatment. Grade 2 hepatitis was reported in 2 participants in the RDV 10-day group, as follows: 1 on Day 5 that was ongoing through the end of the study and considered not related to study treatment, and 1 with an onset and resolution on Day 2 that was considered related to study treatment. No action was taken with study treatment in either participant. An SAE of Grade 4 hepatic failure was reported in 1 participant in the RDV 5-day group on Day 20, 15 days after study treatment completion. The participant had SAEs of acute respiratory failure and acute kidney failure at the time of the event and died as a result of pulmonary embolism on Day 26 (GS-US-540-5773 Interim [Final Part A] CSR, Listing 16.2.7.4). The hepatic failure was considered not related to study treatment.

2.4.1.1.2.2. Liver-related Laboratory Abnormalities

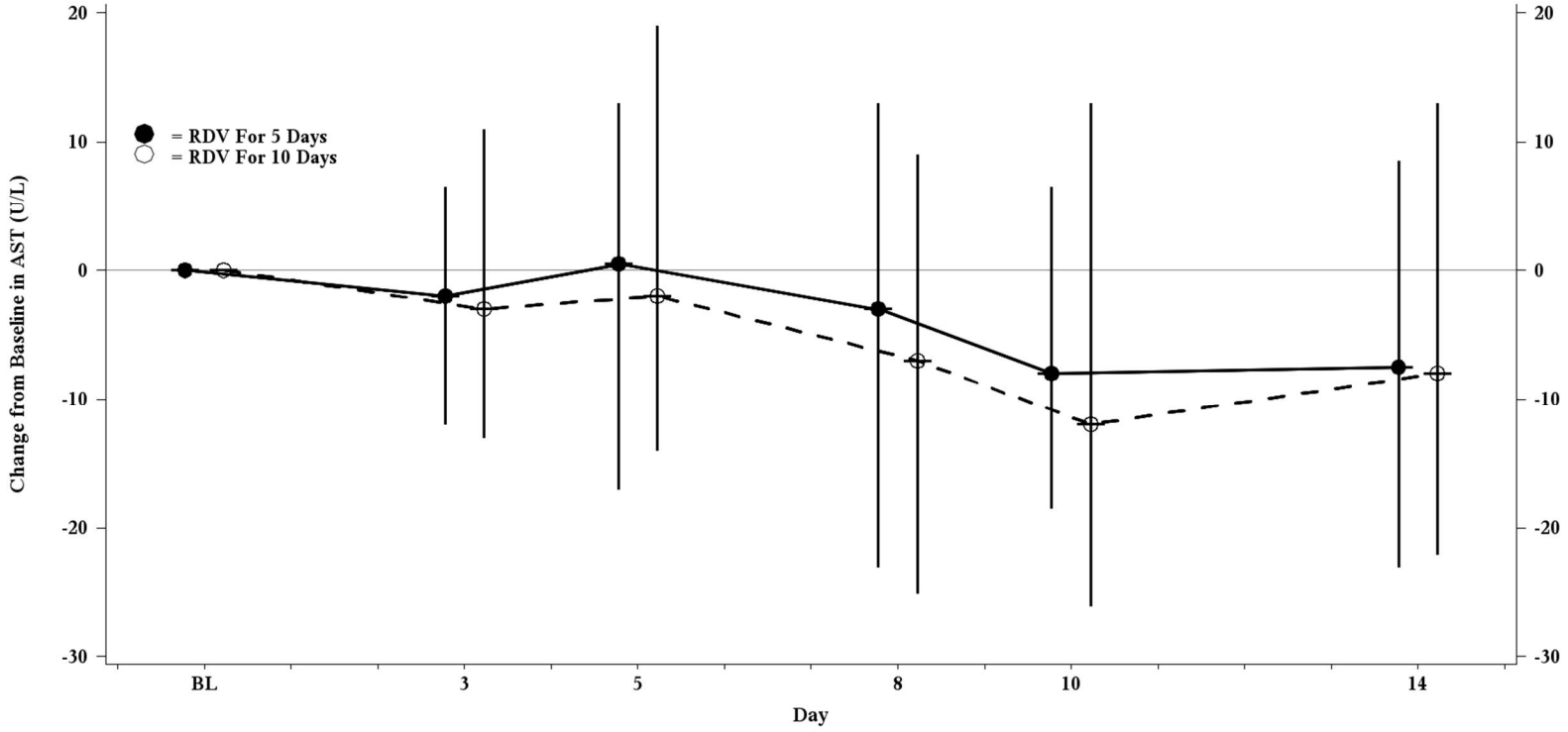
Changes in ALT, AST, and total bilirubin during the study are presented in GS-US-540-5773 Interim [Final Part A] CSR, Tables 15.11.6.1.5, 15.11.6.1.6, and 15.11.6.1.7, respectively. Median ALT increased and median AST decreased in both treatment groups during the study (Figure 1 and Figure 2). There were no significant differences between the RDV 5-day and RDV 10-day groups in ALT or AST at any time point.

Figure 1. **GS-US-540-5773: Median (Q1, Q3) Change from Baseline in ALT (U/L) by Study Day (Safety Analysis Set)**



BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5773 Interim (Final Part A) CSR, Figure 15.11.6.3.1

Figure 2. **GS-US-540-5773: Median (Q1, Q3) Change from Baseline in AST (U/L) by Study Day (Safety Analysis Set)**



BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5773 Interim (Final Part A) CSR, Figure 15.11.6.3.2

A summary of all Grade 3 or higher laboratory abnormalities is provided in Table 20. Grade 3 or 4 increased ALT, Grade 3 or 4 increased AST, and Grade 3 or 4 total bilirubin were each reported in similar percentages of participants in the RDV 5-day and RDV 10-day groups.

A listing of participants with ALT or AST > 3 × ULN or total bilirubin 1 × ULN is provided in GS-US-540-5773 Interim (Final Part A) CSR, Listing 16.2.8.8.

2.4.1.1.3. Study GS-US-540-5774

2.4.1.1.3.1. Hepatic Adverse Events

Hepatic AEs were reported in 7.9% (15 of 191 participants) in the RDV 5-day group, 9.8%, (19 of 193 participants) in the RDV 10-day group, and 5.5% (11 of 200 participants) in the SOC only group (Table 15). Hepatic AEs considered related to study treatment were reported for a similar number of participants in the RDV 5-day and RDV 10-day treatment groups.

Table 15. GS-US-540-5774: Overall Summary of Hepatic Adverse Events (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC Only (N = 200)
Subjects Experiencing Any Treatment-Emergent Hepatic AE	15 (7.9%)	19 (9.8%)	11 (5.5%)
95% CI	4.5% to 12.6%	6.0% to 14.9%	2.8% to 9.6%
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Hepatic AE	4 (2.1%)	7 (3.6%)	2 (1.0%)
95% CI	0.6% to 5.3%	1.5% to 7.3%	0.1% to 3.6%
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Hepatic AE	9 (4.7%)	11 (5.7%)	NA
95% CI	2.2% to 8.8%	2.9% to 10.0%	NA
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Study Drug-Related Hepatic AE	3 (1.6%)	4 (2.1%)	NA
95% CI	0.3% to 4.5%	0.6% to 5.2%	NA
Subjects Experiencing Any Treatment-Emergent Hepatic SAE	0	1 (0.5%)	0
95% CI	0.0% to 1.9%	0.0% to 2.9%	0.0% to 1.8%
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Hepatic SAE	0	0	NA
95% CI	0.0% to 1.9%	0.0% to 1.9%	NA
Subjects Experiencing Any Treatment-Emergent Hepatic AE Leading to Premature Study Drug Discontinuation	1 (0.5%)	6 (3.1%)	NA
95% CI	0.0% to 2.9%	1.1% to 6.6%	NA

Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson Exact method.
Hepatic events include preferred terms from MedDRA 22.1 search term list 'Acute and non-infectious liver events'.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table req10643.2

The overall pattern and types of hepatic AEs were generally similar between the treatment groups (Table 16). The 3 most commonly reported hepatic AEs in each treatment group were as follows:

- RDV 5-day group — increased ALT (4.2%, 8 participants), increased AST (2.6%, 5 participants), and hypertransaminasemia and increased transaminases (each 1.6%, 3 participants)
- RDV 10-day group — increased ALT and hypertransaminasemia (each 3.1%, 6 participants), and increased AST (2.6%, 5 participants)
- SOC only group — increased ALT and increased AST (each 2.5%, 5 participants), and hypertransaminasemia (1.5%, 3 participants)

Table 16. GS-US-540-5774: Hepatic Adverse Events by Preferred Term (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC Only (N = 200)
Number of Subjects Experiencing Any Treatment-Emergent Hepatic AE	15 (7.9%)	19 (9.8%)	11 (5.5%)
Number of Subjects Experiencing Any Treatment-Emergent Hepatic AE by Preferred Term			
Alanine aminotransferase increased	8 (4.2%)	6 (3.1%)	5 (2.5%)
Aspartate aminotransferase increased	5 (2.6%)	5 (2.6%)	5 (2.5%)
Hypertransaminasaemia	3 (1.6%)	6 (3.1%)	3 (1.5%)
Transaminases increased	3 (1.6%)	4 (2.1%)	0
Cholestasis	1 (0.5%)	1 (0.5%)	1 (0.5%)
Blood bilirubin increased	1 (0.5%)	1 (0.5%)	0
Liver function test increased	1 (0.5%)	0	1 (0.5%)
Blood alkaline phosphatase increased	0	1 (0.5%)	0
Gamma-glutamyltransferase increased	0	1 (0.5%)	0

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Hepatic events include preferred terms from MedDRA 22.1 search term list 'Acute and non-infectious liver events'.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table req10643.3

The combined numbers of participants in each treatment group with 1 or more transaminase-related AEs (using the PTs ALT increased, AST increased, hepatic enzymes increased, hypertransaminasemia, liver function test increased, and transaminases increased) were 15 (7.9%) in the RDV 5-day group, 17 (8.8%) in the RDV 10-day group, and 10 (5.0%) in the SOC only group (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table req10643.1).

The only hepatic SAE was in 1 participant in the RDV 10-day group who had a Grade 3 hepatic SAE of increased ALT considered unrelated to study treatment with Day 8 onset and resolution by Day 10 (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.4.1, Listing 16.2.7.5).

Grade 3 or higher study treatment–related hepatic AEs were reported in 1.6%, 3 participants in the RDV 5-day group and 2.1%, 4 participants in the RDV 10-day group. Grade 3 or higher study treatment-related increased ALT was reported in 1.0%, 2 participants in the RDV 5-day group versus 0.5%, 1 participant in the RDV 10-day group, and Grade 3 or higher study treatment-related increased AST was reported in 1.0%, 2 participants in the RDV 5-day group versus no participant in the RDV 10-day group (Table 15 and GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.2.3.2).

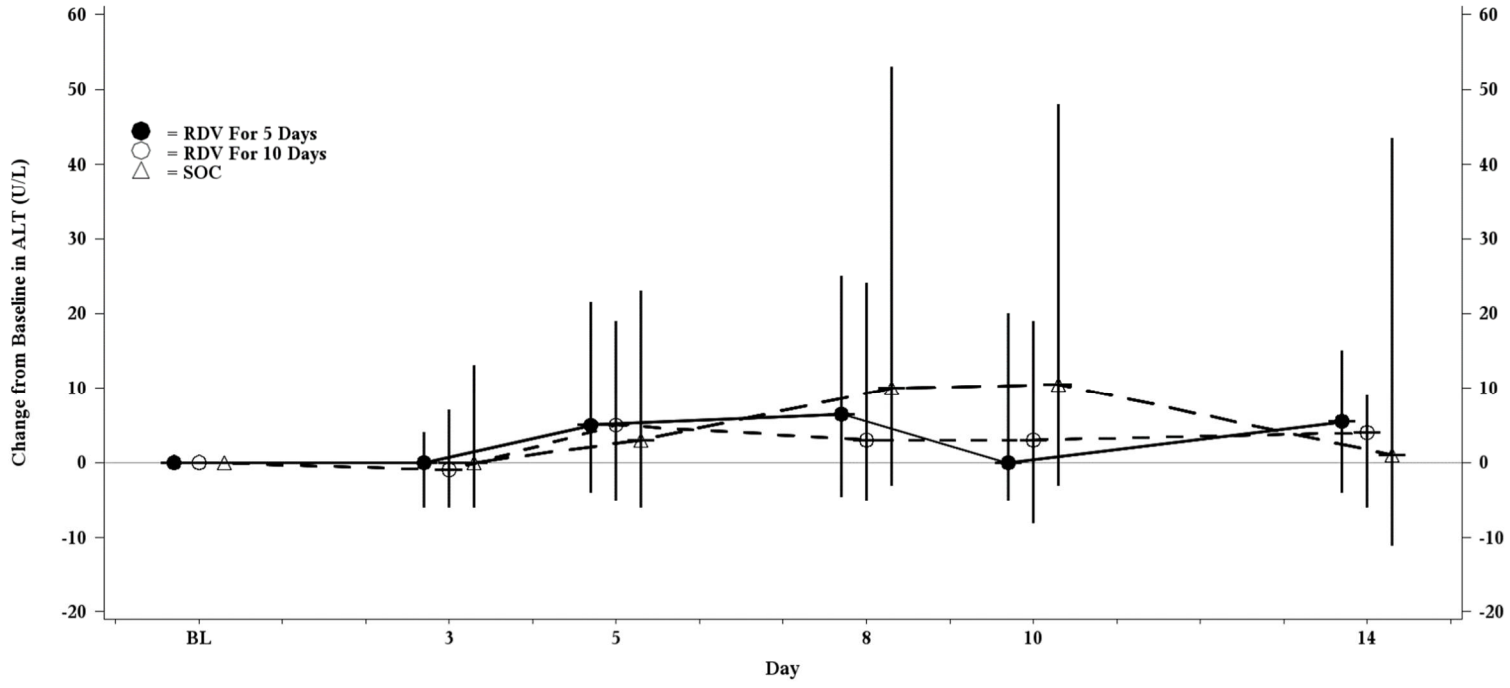
Hepatic AEs leading to study treatment discontinuation were reported in 3.1% (6 participants) in the RDV 10-day group and 0.5% (1 participant) in the RDV 5-day group (Table 15, Table 12, and GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Listing req10643.1). Hepatic AEs that led to study treatment discontinuation in the RDV treatment groups were as follows:

- RDV 5-day group: increased ALT (0.5%, 1 participant)
- RDV 10-day group: increased ALT (1.6%, 3 participants), increased AST (1.0%, 2 participants), and increased blood alkaline phosphatase, increased blood bilirubin, hypertransaminasemia, and increased transaminases (each 0.5%, 1 participant)

2.4.1.1.3.2. Liver-related Laboratory Abnormalities

Changes in ALT, AST, and total bilirubin during the study are presented in GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.11.6.1.5, 15.11.6.1.6, and 15.11.6.1.7, respectively. Median ALT increased and median AST decreased in all treatment groups during the study (Figure 3 and Figure 4). The only statistically significant differences between treatment groups in median change from baseline in ALT were at Day 10 ($p = 0.0183$ for the RDV 5-day group vs SOC only group and $p = 0.0465$ for the RDV 10-day group vs SOC only group). The differences were not clinically relevant. There were no statistically significant differences in median changes from baseline in AST between the RDV 5-day group or RDV 10-day group and the SOC only group at any timepoint. The only statistically significant differences between treatment groups in median change from baseline in total bilirubin were at Day 3 ($p = 0.0041$ for the RDV 5-day group vs SOC only group and $p = 0.0018$ for the RDV 10-day group vs SOC only group). The differences were not clinically relevant.

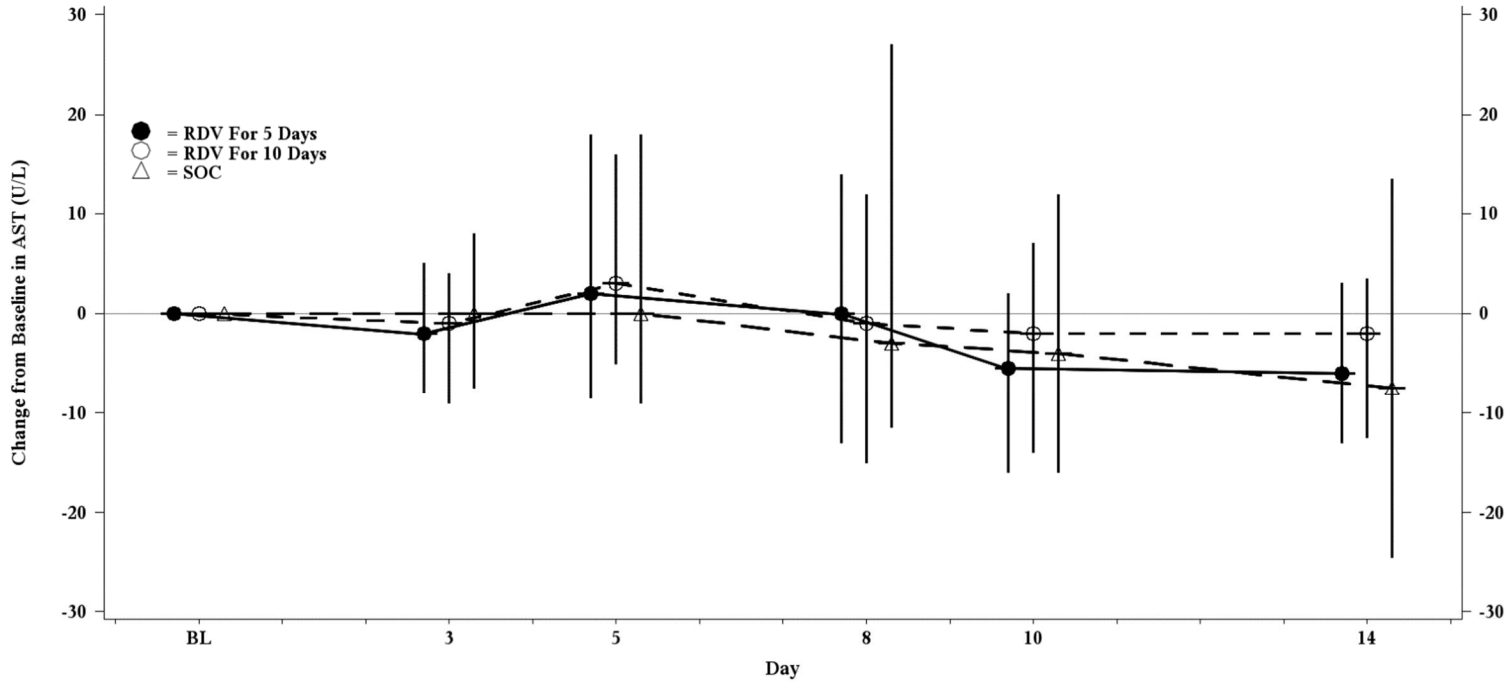
Figure 3. GS-US-540-5774: Median (Q1, Q3) Change from Baseline in ALT (U/L) by Study Day (Safety Analysis Set)



RDV For 5 Days (n=):	191	172	152	76	54	38
RDV For 10 Days (n=):	193	169	141	93	81	41
SOC (n=):	200	170	131	83	66	44

BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Figure 15.11.6.3.1

Figure 4. GS-US-540-5774: Median (Q1, Q3) Change from Baseline in AST (U/L) by Study Day (Safety Analysis Set)



RDV For 5 Days (n=):	186	163	144	74	52	39
RDV For 10 Days (n=):	187	161	132	86	73	36
SOC (n=):	193	160	126	80	65	44

BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Figure 15.11.6.3.22

A summary of all Grade 3 or higher laboratory abnormalities is provided in Table 21. Grade 3 or 4 increased ALT and Grade 3 or 4 increased AST were each reported in lower percentages of participants in the RDV 5-day and RDV 10-day groups than the SOC only group.

Fewer participants in the RDV treatment groups had Grade 4 liver-related laboratory abnormalities compared with the SOC only group. Grade 4 liver-related laboratory abnormalities were reported as follows:

RDV 5-day group: increased AST (0.6%, 1 participant)

RDV 10-day group: hyperbilirubinemia (0.6%, 1 participant)

SOC only group: increased AST (2.7%, 5 participants), increased ALT (1.6%, 3 participants), hyperbilirubinemia (0.6%, 1 participant)

A listing of participants with ALT or AST > 3 × ULN or total bilirubin > 1 × ULN is provided in GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Listing 16.2.8.8.

2.4.1.1.4. Study CO-US-540-5758

The incidence of hepatic AEs was similar between RDV-treated participants and placebo-treated participants in Study CO-US-540-5758 (Table 17). Few Grade 3 or 4 hepatic AEs were reported in either treatment group. No participant experienced a hepatic SAE. In the RDV group, 2 (1%) participants discontinued study treatment due to increased ALT and 1 (1%) participant discontinued study treatment due to increased total bilirubin—it is not clear from the publication whether this was 2 or 3 unique individuals.

Table 17. CO-US-540-5758: Hepatic Adverse Events Reported in ≥ 2% of Participants in Any Treatment Group by Treatment Group (Safety Population)

	RDV (N = 155)		Placebo (N = 78)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Increased total bilirubin	15 (10%)	1 (1%)	7 (9%)	0
Aspartate aminotransferase increased	7 (5%)	0	9 (12%)	0

Events shown are from Gilead's MedDRA search term list for acute and noninfectious liver events.
Source: {Wang 2020}

2.4.1.1.5. Compassionate Use Program (IN-US-540-5755)

A total of 12.3% patients (20/163 patients) in the compassionate use program (IN-US-540-5755) had hepatic AEs. For 19 of the 20 patients the reported AEs were elevated liver function tests. Five patients discontinued RDV due to hepatic AEs: 4 patients due to AEs of elevated liver function tests (per protocol guidance that RDV should be permanently discontinued patients with ALT > 5 times the ULN) and 1 patient due to worsening hepatitis. Two patients had a hepatic AE considered to be serious (1 patient due to increased ALT and 1 patient with hepatitis); neither were deemed related to RDV (IN-US-540-5755 Interim 1 Summary Report, Section 3.4.1).

Median ALT and AST remained near baseline through Day 10. Overall, 41.7% (60 of 144 patients) had increases in ALT and 47.8% (65 of 136 patients) had increases in AST. Most ALT and AST were Grade 1 or Grade 2. Grade 3 ALT increases were reported in 5.6% (8 patients), and there were no Grade 4 ALT increases. Grade 3 AST increases were reported in 6.6% (9 patients), and a Grade 4 AST increase was reported in 0.7% (1 patient). Nearly all of the Grade 3 or Grade 4 ALT or AST increases occurred in patients with invasive baseline oxygen support (IN-US-540-5755 Interim 1 Summary Report, Section 3.5.1).

2.4.1.2. Hepatic Safety in Healthy Participants

Across the Phase 1 studies, no hepatic AEs were reported in healthy participants.

Among healthy participants who received the proposed 5-day RDV dosing regimen (200 mg on Day 1 following by 100 mg on Days 2 through 5), no participant had increased ALT and 11.1% (1 of 9 participants) had transient Grade 1 increased AST (Study GS-US-399-5505). For the healthy participants who received the proposed 10-day RDV dosing regimen, transient Grade 1 or 2 elevations in ALT were observed in 45.0% (9 of 20 participants), accompanied by transient Grade 1 elevations in AST in 20.0% (4 participants; Study GS-US-399-5505). Within this cohort, mean ALT levels increased during RDV administration, peaked between Days 10 to 14 (approximately +30 U/L change from baseline), started decreasing after Day 14, and returned to baseline by Day 25.

With once-daily dosing of RDV 150 mg for 14 days (a higher dose than used in participants with COVID-19), transient Grade 1 or 2 elevations in ALT and transient Grade 1 elevations in AST were observed in 75% of healthy participants (Study GS-US-399-1954). In some participants, ALT and AST elevations were associated with transient Grade 1 increased prothrombin time; however, there was no other evidence of hepatic effects.

2.4.2. Renal Safety

Acute kidney injury has been commonly observed among patients with COVID-19 requiring hospitalization (5% to 22%) and intensive care unit care (23%), and among fatalities (25% to 50%) {Chen 2020b, Cheng 2020, Huang 2020, Pei 2020, Richardson 2020, Wang 2020, Zhou 2020a}. Proteinuria and hematuria have also been reported among COVID-19 patients at the time of hospital admission (43.9% to 65.8% and 26.7% to 41.7%, respectively), in addition to elevated creatinine and blood urea nitrogen (14.4% and 13.1%, respectively) {Cheng 2020, Pei 2020}. In US patient cohorts, new renal replacement therapy was applied in 3.2% to 7.5% of hospitalized patients and was more common among those requiring invasive mechanical ventilation (14.6%) {Goyal 2020, Richardson 2020}.

The kidney was identified as a target organ of toxicity for RDV in nonclinical studies.

For Studies GS-US-540-5773 and GS-US-540-5774, PTs for renal AEs were identified from a Standardized MedDRA Query (SMQ) for acute renal failure.

In Study GS-US-540-5773, the incidence of renal-related AEs and Grade 3 or 4 laboratory abnormalities were higher in the RDV 10-day group compared to in the RDV 5 day group. The difference was evident by Day 5 of treatment, suggesting it was not due to RDV but due to the imbalances between groups in baseline clinical status/disease severity. In Study GS-US-540-5774, the incidence of renal-related AEs was similar across RDV and SOC treatment groups, while the incidence of Grade 3 or 4 renal-related laboratory abnormalities was numerically lower in the RDV groups than in the SOC group. Overall, the incidence of renal-related AEs and Grade 3 or 4 laboratory abnormalities were lower in Study GS-US-540-5774 versus GS-US-540-5773, supporting disease severity as a driver of renal outcomes. The incidence of renal-related AEs was similar between RDV-treated participants and placebo-treated participants in Studies CO-US-540-5776 and CO-US-540-5758.

There were no renal AEs and few renal-related laboratory abnormalities reported in the Phase 1 studies.

2.4.2.1. Renal Safety in Individuals with COVID-19

2.4.2.1.1. Study CO-US-540-5776

The combined numbers of participants with 1 or more renal-related nonserious Grade 3 or 4 AEs (glomerular filtration rate decreased, acute kidney injury, blood creatinine increased, or creatinine renal clearance decreased) were 43 (8.1%) in the RDV 10-day group and 42 (8.1%) in the placebo group (Table 3). The combined numbers of participants with 1 or more renal-related SAEs (glomerular filtration rate decreased or acute kidney injury) were 8 (1.5%) in the RDV 10-day group and 10 (1.9%) in the placebo group (Table 4).

2.4.2.1.2. Study GS-US-540-5773

2.4.2.1.2.1. Renal Adverse Events

In Study GS-US-540-5773, renal-related AEs were reported in less than 2% of participants in both the RDV 5-day and RDV 10-day groups, with the exception of acute kidney injury (Table 18).

The incidence of renal-related SAEs was similar in the RDV 5-day group (1.5%; 3 participants) and in the RDV 10-day group (2.0%; 4 participants) (GS-US-540-5773 Interim [Final Part A] CSR, Table 15.11.4.5), none were considered related to study treatment by the investigator.

Table 18. GS-US-540-5773: Renal-Related Adverse Events by Preferred Term (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	8 (4.0%)	19 (9.6%)	27 (6.8%)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event by Preferred Term			
Acute kidney injury	4 (2.0%)	16 (8.1%)	20 (5.0%)
Blood creatinine increased	1 (0.5%)	2 (1.0%)	3 (0.8%)
Renal failure	1 (0.5%)	2 (1.0%)	3 (0.8%)
Glomerular filtration rate decreased	1 (0.5%)	1 (0.5%)	2 (0.5%)
Creatinine renal clearance decreased	0	1 (0.5%)	1 (0.3%)
Oliguria	1 (0.5%)	0	1 (0.3%)

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Renal events include preferred terms from MedDRA 22.1 SMQ for 'Acute renal failure'.
Source: Table req 10636.11

In an exploratory analysis, the difference in incidence between the groups was already evident at Day 5 of the study, when both groups had received the same duration of treatment. This suggests that differences between the groups were not due to RDV but to the imbalances between groups in baseline clinical status/disease severity.

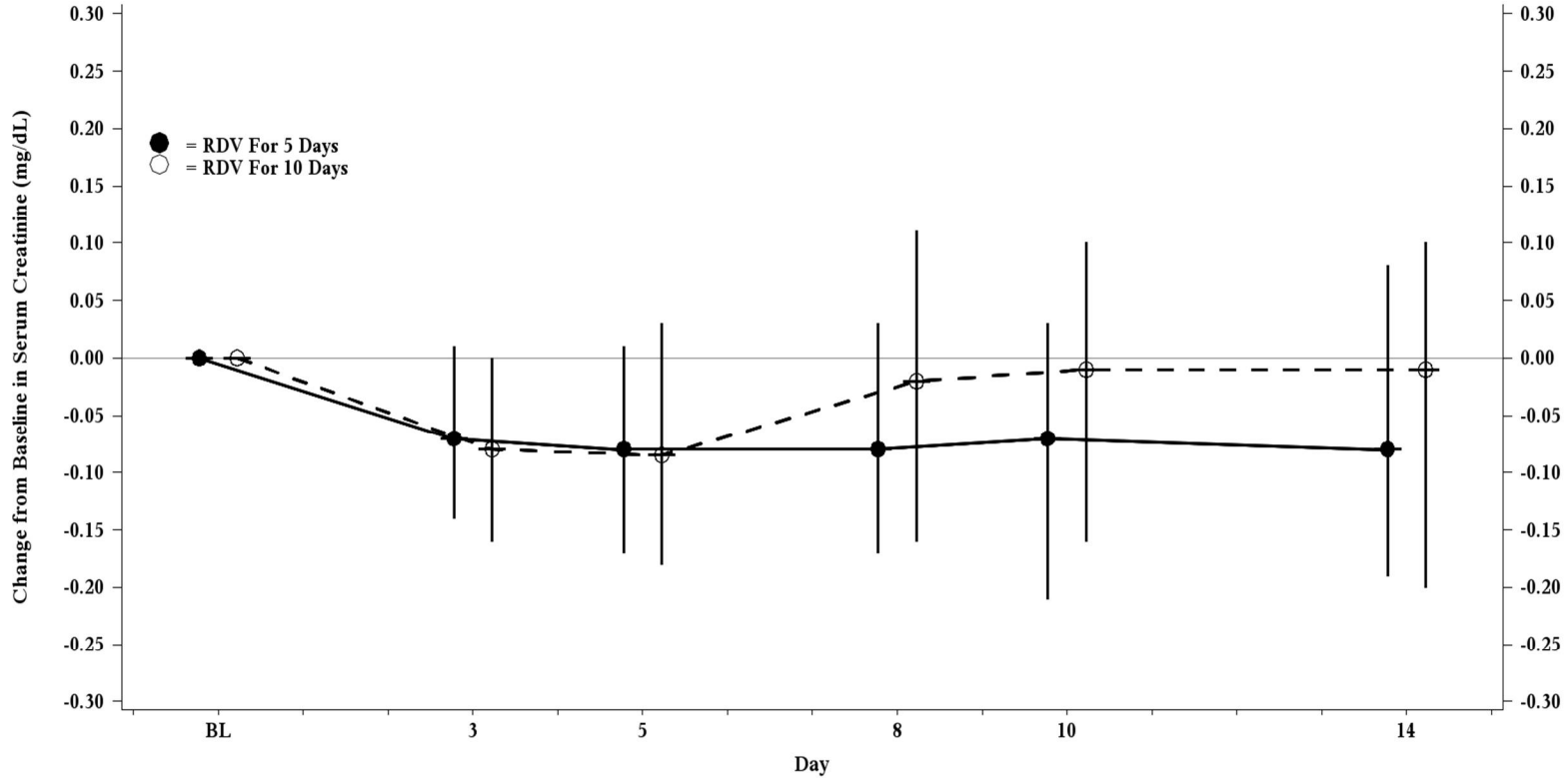
2.4.2.1.2.2. Renal-related Laboratory Parameters

Changes in creatinine and CrCl by Cockcroft-Gault during the study are presented in GS-US-540-5773 Interim (Final Part A) CSR, Table 15.11.6.1.9 and Table 15.11.6.1.10, respectively.

Between baseline and Day 14, median serum creatinine decreased and median CrCl increased in both treatment groups (Figure 5 and Figure 6). The differences between treatment groups in change from baseline were statistically significant for median serum creatinine at Days 8 and 10 ($p = 0.0466$ and $p = 0.0286$, respectively) and for median CrCl at Day 8 ($p = 0.0479$).

The incidence of Grade 3 or higher laboratory abnormalities in serum creatinine and CrCl was higher in the RDV 10-day group compared to in the RDV 5-day group (Table 20).

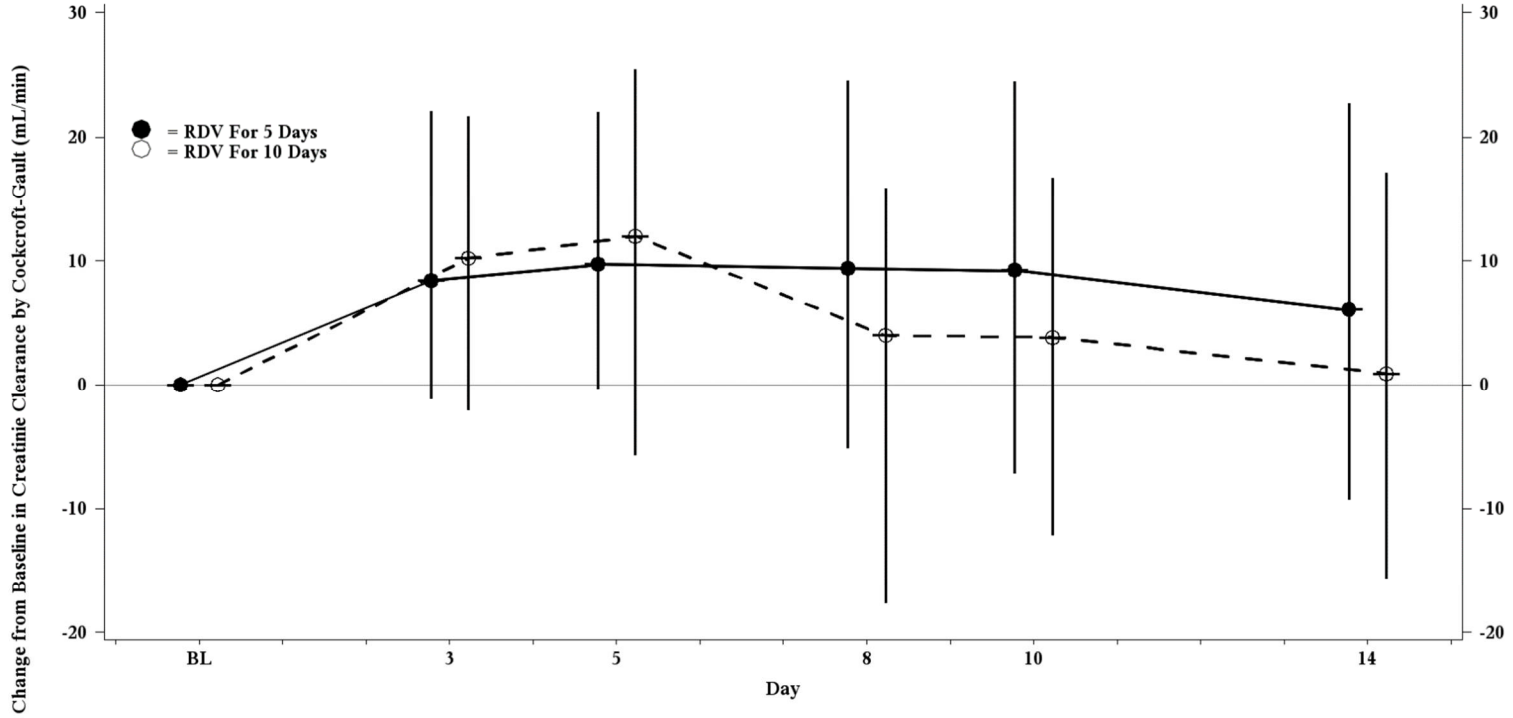
Figure 5. GS-US-540-5773: Median (Q1, Q3) Change from Baseline in Serum Creatinine (mg/dL) by Study Day (Safety Analysis Set)



RDV For 5 Days (n=):	200	186	179	115	87	59
RDV For 10 Days (n=):	195	186	164	131	107	65

BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5773 Interim (Final Part A) CSR, Figure 15.11.6.3.3

Figure 6. **GS-US-540-5773: Median (Q1, Q3) Change from Baseline in Creatinine Clearance by Cockcroft-Gault (mL/min) by Study Day (Safety Analysis Set)**



BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5773 Interim (Final Part A) CSR, Figure 15.11.6.3.4

2.4.2.1.3. Study GS-US-540-5774

2.4.2.1.3.1. Renal Adverse Events

In Study GS-US-540-5774, the incidence of renal-related AEs was low and similar across all treatment groups (Table 19).

There were no renal-related SAEs in the RDV 5-day or 10-day groups (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.4.5). One participant in the SOC group had an SAE of acute kidney injury.

Table 19. GS-US-540-5774: Renal-Related Adverse Events by Preferred Term (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	2 (1.0%)	4 (2.1%)	4 (2.0%)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event by Preferred Term			
Acute kidney injury	1 (0.5%)	1 (0.5%)	2 (1.0%)
Blood creatinine increased	0	2 (1.0%)	2 (1.0%)
Glomerular filtration rate decreased	1 (0.5%)	0	0
Urine output decreased	0	1 (0.5%)	0

Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Renal events include preferred terms from MedDRA 22.1 search term list 'Acute renal failure'.
Source: Table req 10643.11

2.4.2.1.3.2. Renal-related Laboratory Parameters

Change in serum creatinine and CrCl by Cockcroft-Gault during the study is presented by treatment group in GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.11.6.1.9 and 15.11.6.1.10, respectively.

Between baseline and Day 14, median serum creatinine decreased and median CrCl increased in both RDV treatment groups (Figure 7 and Figure 8). There were statistically significant differences between each RDV treatment group and the SOC only group in median changes from baseline in serum creatinine at Days 3 and 5 as follows:

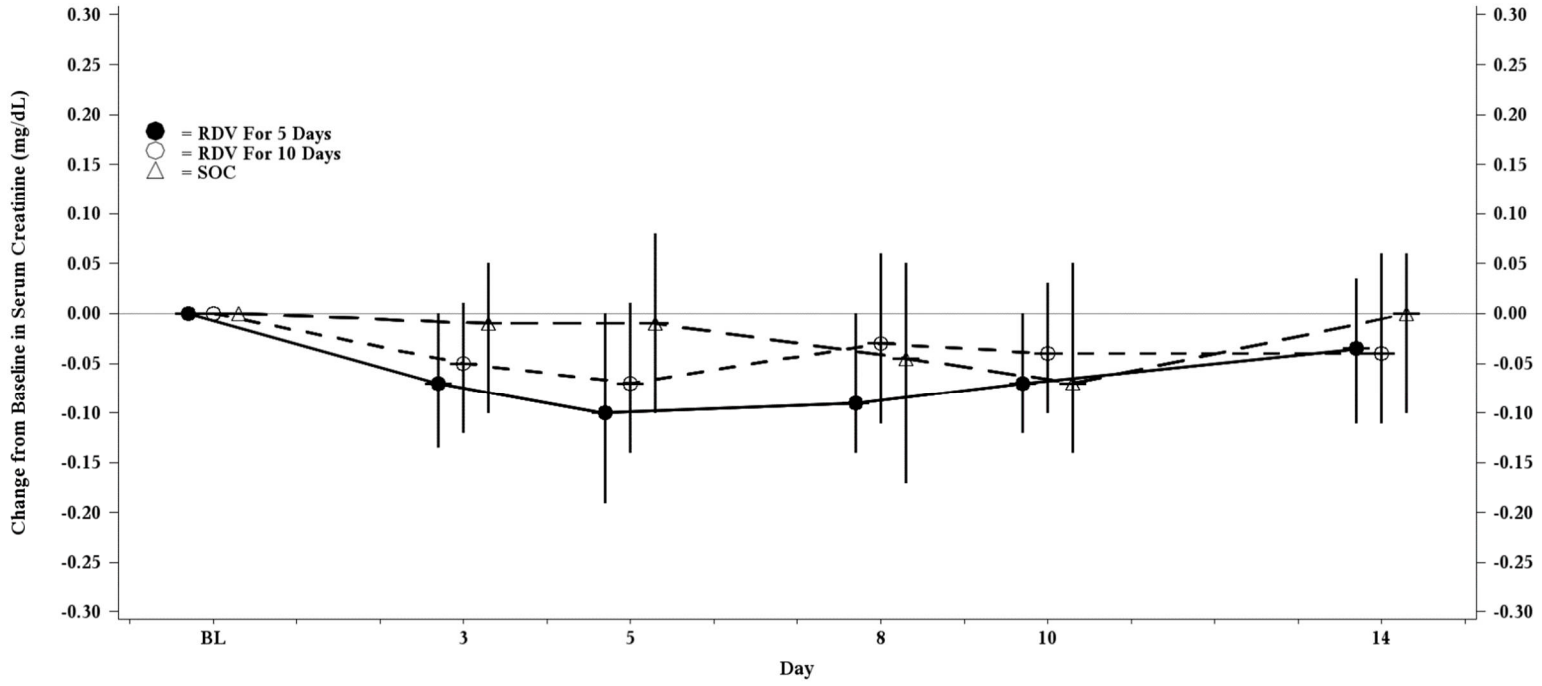
- Day 3: -0.07 mg/dL in the RDV 5-day group and -0.01 mg/dL in the SOC only group ($p = 0.0008$)
- Day 5: -0.10 mg/dL in the RDV 5-day group, -0.07 mg/dL in the RDV 10-day group, and -0.01 mg/dL in the SOC only group ($p < 0.0001$ for the RDV 5-day group vs SOC only group and $p = 0.0010$ for the RDV 10-day group vs SOC only group)

Likewise, there were statistically significant differences between the RDV treatment groups and the SOC only group in median changes from baseline in CrCl at Days 3 and 5 as follows:

- Day 3: 8.3 mL/min in the RDV 5-day group and 1.9 mL/min in the SOC only group ($p = 0.0021$)
- Day 5: 10.6 mL/min in the RDV 5-day group, 9.2 mL/min in the RDV 10-day group, and 0.8 mL/min in the SOC only group ($p < 0.0001$ for both RDV 5-day group vs SOC only group and RDV 10-day group vs SOC only group)

The incidence of Grade 3 or 4 laboratory abnormalities of creatinine increased and CrCl decreased was lower in the RDV 5-day and RDV 10-day groups compared to the SOC group (Table 21).

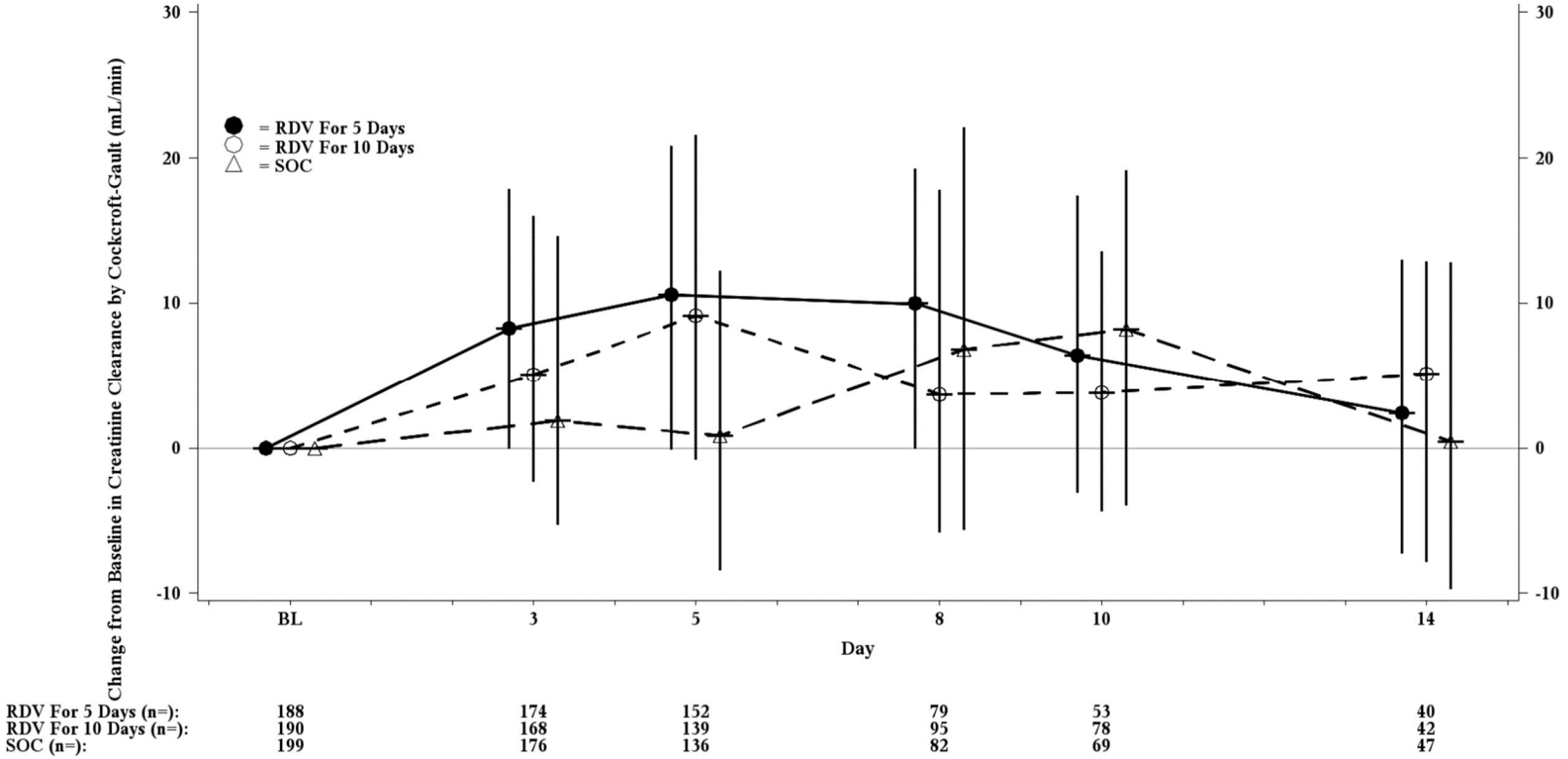
Figure 7. GS-US-540-5774: Median (Q1, Q3) Change from Baseline in Serum Creatinine (mg/dL) by Study Day (Safety Analysis Set)



RDV For 5 Days (n=):	191	176	154	79	53	40
RDV For 10 Days (n=):	193	171	140	97	80	43
SOC (n=):	200	177	137	82	69	47

BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Figure 15.11.6.3.3

Figure 8. **GS-US-540-5774: Median (Q1, Q3) Change from Baseline in Creatinine Clearance by Cockcroft-Gault (mL/min) by Study Day (Safety Analysis Set)**



BL = Baseline; Reference line represents no change from baseline (ie, y = 0).
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Figure 15.11.6.3.4

2.4.2.1.4. Study CO-US-540-5758

In Study CO-US-540-5758, the only renal-related AE reported in ≥ 2% of participants in a treatment group was increased blood urea nitrogen (6% of participants in both the RDV and placebo groups) {Wang 2020}. There was 1 SAE of acute kidney injury in the RDV group (not Grade 3 or 4) and no renal SAEs in the placebo group. One participant discontinued drug due to Grade 3 or 4 acute kidney injury in the RDV group.

2.4.2.1.5. Compassionate Use Program (IN-US-540-5755)

A total of 11.0% of patients (18 of 163 patients) in the compassionate use program (IN-US-540-5755) had renal AEs. Renal AEs observed in more than 2% of patients were reported more often in patients with invasive baseline oxygen support than patients with noninvasive baseline oxygen support: acute kidney injury (6.7% vs 1.7%), renal failure (3.8% vs 1.7%), and renal impairment (4.8% vs 0), consistent with the increased severity of illness in these patients.

Median serum creatinine remained near baseline through Day 10. Grade 3 increases in serum creatinine were reported in 6.1% (9 patients), and Grade 4 increases were reported in 10.1% (15 patients). Incidence of increased serum creatinine was lower among patients with noninvasive baseline oxygen support (20.8% [11 of 53 patients]) than it was among those with invasive baseline oxygen support (31.6% [30 of 95 patients]), particularly Grade 4 increases, which were reported in 3.8% (2 of 53 patients) with noninvasive baseline oxygen support and 13.7% (13 of 95 patients) with invasive baseline oxygen support (IN-US-540-5755 Interim 1 Summary Report, Section 3.5.2).

2.4.2.2. Renal Safety in Healthy Participants

No renal AEs were reported in the Phase 1 clinical studies. Grade 1 serum creatinine laboratory abnormalities were reported in 2 healthy participants (1.5%). There were no Grade 2 or higher serum creatinine laboratory abnormalities.

2.4.3. Infusion-Related Reactions and Hypersensitivity

A safety review was prompted by cases of potential IRRs and/or hypersensitivity reported during use of RDV through routine signal detection activities, cumulative to 31 May 2020 (Gilead Pharmacovigilance and Epidemiology Safety Review of IRRs and Hypersensitivity).

Of the more than 200 cases reviewed, 19 cases were identified with a plausible time to onset of clinical observations with respect to RDV administration and subsequent resolution or improvement following its interruption/discontinuation.

Based on data sources with available up-to-date exposure data, the frequency of serious cases with evidence of potential IRR (including hypersensitivity cases with overlapping signs and symptoms to the IRR cases) with a temporal association to the RDV infusion and without a clear alternative explanation was 0.036% (95% CI: 0.01 – 0.14%) in Gilead-sponsored clinical studies (GS-US-540-5773 and GS-US-540-5774; 2/5613 participants) and 0.097%

(95% CI: 0.03 - 0.29%) in the compassionate use program (IN-US-540-5755) and expanded access program (GS-US-540-5821) (3/3094 patients). Across these sources, the incidence was 0.057% (95% CI: 0.03 – 0.14%) (5/8707 participants). Infusion-related reactions were not observed in Studies CO-US-540-5776 and CO-US-540-5758.

While the signs and symptoms of IRRs and hypersensitivity ranged from throat itching to significant hypotension, where the final outcome was described, all cases described event resolution or improvement.

Based on the review of safety data, there was considered sufficient evidence of a causal relationship between events of potential IRRs and RDV to support the addition of IRR as an adverse drug reaction (ADR) for RDV.

Given the substantial overlap between the conditions of IRRs, which represented the majority of the events of interest described in this safety review, and events of hypersensitivity, for which events of interest generally described clinical observations and temporal relationship consistent with potential IRRs, the totality of the evidence reviewed was considered appropriately reflected by the ADR of IRR. There was considered insufficient evidence to identify a causal relationship between hypersensitivity and RDV independent of IRRs.

2.5. Narratives

For all Gilead-sponsored studies, narratives for deaths, SAEs, discontinuations due to AEs, and hepatic events, if applicable, are provided in the relevant reports.

3. CLINICAL LABORATORY EVALUATIONS

In the following sections, a summary of clinical laboratory evaluations is reported by study. All laboratory evaluations summarized herein were treatment emergent and are referred to as laboratory abnormalities.

Full details of clinical laboratory evaluations are provided in the individual CSRs and summary reports (GS-US-540-5773 Interim [Final Part A] CSR, Section 11.6, GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Section 11.6, IN-US-540-5755 Interim 1 Summary Report, Section 3.5, GS-US-399-1812 Final CSR, Section 11.6; GS-US-399-1954 Final CSR, Section 11.6; GS-US-399-4231 Final CSR, Section 11.6; and GS-US-399-5505 Final CSR; Section 11.6). Clinical laboratory evaluations are not included for Studies CO-US-540-5776 and CO-US-540-5758.

3.1. Clinical Laboratory Evaluations in Participants with COVID-19

3.1.1. GS-US-540-5773

3.1.1.1. Hematology

There were no clinically relevant changes from baseline within either treatment group or differences between the treatment groups in median values for hematology parameters, and median values were generally within reference ranges (GS-US-540-5773 Interim [Final Part A] CSR, Tables 15.11.6.1.1 to 15.11.6.1.4 and Listing 16.2.8.9).

3.1.1.2. Clinical Chemistry

Changes from baseline in clinical chemistry parameters are provided in GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.11.6.1.5 to 15.11.6.1.9. Median values for clinical chemistry parameters were generally within reference ranges (GS-US-540-5773 Interim [Final Part A] CSR, Listing 16.2.8.9). Changes from baseline in ALT, AST, and total bilirubin are presented in Section 2.4.1.1.2.2

3.1.1.3. Graded Laboratory Abnormalities

The majority of participants in each treatment group had at least 1 laboratory abnormality (RDV 5-day group 77.9%, 152 of 195 participants; RDV 10-day group 83.8%, 160 of 191 participants) (GS-US-540-5773 Interim [Final Part A] CSR Table 15.11.6.4.1).

The incidence of all graded individual laboratory abnormalities was generally similar across the 2 treatment groups with the exception of the following parameters, for which there was at least a 2-fold difference in the incidence between treatment groups:

- Grade 4 increased serum creatinine was less common in the RDV 5-day group (2.6%, 5 of 195 participants) than the RDV 10-day group (11.5%, 22 of 191 participants).

- Grade 4 decreased CrCl was less common in the RDV 5-day group (3.1%, 6 of 193 participants) than the RDV 10-day group (12.2%, 23 of 188 participants).

- Grade 2 increased total bilirubin was less common in the RDV 5-day group (2.6%, 5 of 194 participants) than the RDV 10-day group (5.3%, 10 of 190 participants).

- Grade 2 decreased hemoglobin was less common in the RDV 5-day group (4.1%, 8 of 195 participants) than the RDV 10-day group (8.4%, 16 of 191 participants).

Grade 3 or 4 laboratory abnormalities were reported in a similar percentage of participants in each treatment group (27.2%, 53 of 195 participants and 33.5%, 64 of 191 participants in the RDV 5-day and RDV 10-day groups, respectively) (Table 20). Grade 4 laboratory abnormalities were reported in a lower percentage of participants in the RDV 5-day group (6.2%, 12 participants) than the RDV 10-day group (13.6%, 26 participants).

The most common Grade 3 or 4 laboratory abnormality in the RDV 5-day group was hyperglycemia (10.8%, 20 of 186 participants). The most common Grade 3 or 4 laboratory abnormality in the RDV 10-day group was decreased CrCl (19.1%, 36 of 188 participants).

A summary of Grade 3 or higher liver-related laboratory abnormalities is provided in Section 2.4.1.1.2.2. A summary of Grade 3 or higher renal-related laboratory abnormalities is provided in Section 2.4.2.1.2.2.

Table 20. GS-US-540-5773: Grade 3 or Higher Laboratory Abnormalities (Safety Analysis Set)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)
Maximum Treatment-Emergent Toxicity	195	191	386
Grade 3	42 (21.5%)	38 (19.9%)	80 (20.7%)
Grade 4	12 (6.2%)	26 (13.6%)	38 (9.8%)
Grade 3 or 4	54 (27.7%)	64 (33.5%)	118 (30.6%)
Hematology			
Hemoglobin (Decreased)	195	191	386
Grade 3	11 (5.6%)	13 (6.8%)	24 (6.2%)
Grade 4	0	2 (1.0%)	2 (0.5%)
Grade 3 or 4	11 (5.6%)	15 (7.9%)	26 (6.7%)
Platelets (Decreased)	195	191	386
Grade 3	1 (0.5%)	1 (0.5%)	2 (0.5%)
Grade 4	1 (0.5%)	0	1 (0.3%)
Grade 3 or 4	2 (1.0%)	1 (0.5%)	3 (0.8%)

	RDV 5 Days (N = 200)	RDV 10 Days (N = 197)	Total (N = 397)
Chemistry			
ALT (Increased)	194	191	385
Grade 3	8 (4.1%)	11 (5.8%)	19 (4.9%)
Grade 4	4 (2.1%)	5 (2.6%)	9 (2.3%)
Grade 3 or 4	12 (6.2%)	16 (8.4%)	28 (7.3%)
AST (Increased)	194	190	384
Grade 3	11 (5.7%)	7 (3.7%)	18 (4.7%)
Grade 4	3 (1.5%)	4 (2.1%)	7 (1.8%)
Grade 3 or 4	14 (7.2%)	11 (5.8%)	25 (6.5%)
Creatinine (Increased)	195	191	386
Grade 3	5 (2.6%)	7 (3.7%)	12 (3.1%)
Grade 4	5 (2.6%)	22 (11.5%)	27 (7.0%)
Grade 3 or 4	10 (5.1%)	29 (15.2%)	39 (10.1%)
Creatinine Clearance (Decreased)	193	188	381
Grade 3	13 (6.7%)	13 (6.9%)	26 (6.8%)
Grade 4	6 (3.1%)	23 (12.2%)	29 (7.6%)
Grade 3 or 4	19 (9.8%)	36 (19.1%)	55 (14.4%)
Serum Glucose (Hyperglycemia)	186	187	373
Grade 3	20 (10.8%)	14 (7.5%)	34 (9.1%)
Grade 4	0	1 (0.5%)	1 (0.3%)
Grade 3 or 4	20 (10.8%)	15 (8.0%)	35 (9.4%)
Total Bilirubin (Hyperbilirubinemia)	194	190	384
Grade 3	1 (0.5%)	3 (1.6%)	4 (1.0%)
Grade 4	0	1 (0.5%)	1 (0.3%)
Grade 3 or 4	1 (0.5%)	4 (2.1%)	5 (1.3%)

The denominator for percentage is the number of subjects in the safety analysis set with at least 1 postbaseline value for the test under evaluation, specified in each laboratory test row.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Creatinine clearance is from Cockcroft-Gault.
Source: GS-US-540-5773 Interim (Final Part A) CSR, Table 15.11.6.4.2

3.1.2. GS-US-540-5774

3.1.2.1. Hematology

There were no clinically relevant changes from baseline within any treatment group or differences between the treatment groups in median values for hematology parameters, and median values were generally within reference ranges (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Tables 15.11.6.1.1 to 15.11.6.1.4 and Listing 16.2.8.9).

3.1.2.2. Clinical Chemistry

Changes from baseline in clinical chemistry parameters are provided in GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.11.6.1.5 to 15.11.6.1.10. Median values for clinical chemistry parameters were generally within reference ranges (GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Listing 16.2.8.9). Changes from baseline in ALT, AST, and total bilirubin are presented in Section 2.4.1.1.3.2.

3.1.2.3. Graded Laboratory Abnormalities

The majority of participants in each treatment group had at least 1 laboratory abnormality (RDV 5-day group 72.8%, 131 of 180 participants; RDV 10-day group 71.5%, 128 of 179 participants; SOC only group 73.1%, 136 of 186 participants; GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Table 15.11.6.4.1).

The majority of the reported laboratory abnormalities were Grade 1 or 2. The incidence of all graded individual laboratory abnormalities was generally similar across the treatment groups with the exception of the following parameter, for which there was at least a 2-fold difference in the incidence between treatment groups:

- Decreased CrCl was less common in the RDV 5-day group (14.6%, 26 of 178 participants) than the SOC only group (29.5%, 54 of 183 participants)

Grade 3 or 4 laboratory abnormalities were reported in a similar percentage of participants in each treatment group as follows: RDV 5-day group 12.8%, 23 participants; RDV 10-day group 16.2%, 29 participants; SOC only group 17.7%, 33 participants (Table 21).

The most common Grade 3 or 4 laboratory abnormality in the RDV 5-day group was hyperglycemia (3.9%, 7 of 180 participants). The most common Grade 3 or 4 laboratory abnormality in the RDV 10-day group was decreased CrCl (5.1%, 9 of 176 participants). The most common Grade 3 or 4 laboratory abnormalities in the SOC only group were increased ALT (7.1%, 13 of 182 participants) and decreased CrCl (7.1%, 13 of 183 participants).

A summary of Grade 3 or higher liver-related laboratory abnormalities is provided in Section 2.4.1.1.3.2. A summary of Grade 3 or higher renal-related laboratory abnormalities is provided in Section 2.4.2.1.3.2.

Table 21. GS-US-540-5774: Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC Only (N = 200)
Maximum Treatment-Emergent Toxicity Grade	180	179	186
Grade 3	18 (10.0%)	25 (14.0%)	25 (13.4%)
Grade 4	5 (2.8%)	4 (2.2%)	8 (4.3%)
Grade 3 or 4	23 (12.8%)	29 (16.2%)	33 (17.7%)
Hematology			
Hemoglobin (Decreased)	179	178	184
Grade 3	4 (2.2%)	2 (1.1%)	8 (4.3%)
Grade 4	2 (1.1%)	0	2 (1.1%)
Grade 3 or 4	6 (3.4%)	2 (1.1%)	10 (5.4%)
Platelets (Decreased)	179	178	184
Grade 3	0	0	1 (0.5%)
Grade 4	3 (1.7%)	0	0
Grade 3 or 4	3 (1.7%)	0	1 (0.5%)
WBC (Decreased)	179	178	184
Grade 3	1 (0.6%)	3 (1.7%)	2 (1.1%)
Grade 4	1 (0.6%)	1 (0.6%)	0
Grade 3 or 4	2 (1.1%)	4 (2.2%)	2 (1.1%)
Chemistry			
ALT (Increased)	179	177	182
Grade 3	4 (2.2%)	6 (3.4%)	10 (5.5%)
Grade 4	0	0	3 (1.6%)
Grade 3 or 4	4 (2.2%)	6 (3.4%)	13 (7.1%)
AST (Increased)	177	175	182
Grade 3	3 (1.7%)	2 (1.1%)	6 (3.3%)
Grade 4	1 (0.6%)	0	5 (2.7%)
Grade 3 or 4	4 (2.3%)	2 (1.1%)	11 (6.0%)
Creatinine (Increased)	180	179	184
Grade 3	1 (0.6%)	3 (1.7%)	4 (2.2%)
Grade 4	0	1 (0.6%)	4 (2.2%)
Grade 3 or 4	1 (0.6%)	4 (2.2%)	8 (4.3%)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC Only (N = 200)
Serum Glucose (Hyperglycemia)	180	177	181
Grade 3	7 (3.9%)	5 (2.8%)	4 (2.2%)
Grade 4	0	0	0
Grade 3 or 4	7 (3.9%)	5 (2.8%)	4 (2.2%)
Serum Glucose (Hypoglycemia)	180	177	181
Grade 3	0	0	0
Grade 4	0	0	0
Grade 3 or 4	0	0	0
Total Bilirubin (Hyperbilirubinemia)	177	176	181
Grade 3	1 (0.6%)	3 (1.7%)	1 (0.6%)
Grade 4	0	1 (0.6%)	1 (0.6%)
Grade 3 or 4	1 (0.6%)	4 (2.3%)	2 (1.1%)
Creatinine Clearance (Decreased)	178	176	183
Grade 3	4 (2.2%)	7 (4.0%)	9 (4.9%)
Grade 4	0	2 (1.1%)	4 (2.2%)
Grade 3 or 4	4 (2.2%)	9 (5.1%)	13 (7.1%)

The denominator for percentage is the number of subjects in the safety analysis set with at least 1 postbaseline value for the test under evaluation, specified in each laboratory test row.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Creatinine clearance is from Cockcroft-Gault.
Source: GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Table 15.11.6.4.2

3.1.3. Compassionate Use Program (IN-US-540-5755)

Hepatic and renal laboratory parameters are detailed in Sections 2.4.1.1.5 and 2.4.2.1.5, respectively.

3.2. Clinical Laboratory Evaluations in Healthy Participants

Hepatic and renal laboratory parameters are detailed in Sections 2.4.1.2 and 2.4.2.2, respectively. Overall, no other clinically relevant consistent patterns of laboratory abnormalities or changes from baseline in laboratory parameters were noted during the studies.

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

A description and summary of vital signs, physical findings, and other observations related to safety is provided in the individual CSRs (GS-US-540-5773 Interim [Final Part A CSR], Section 11.7, GS-US-540-5774 Interim 1 [Part A Day 11] CSR, Section 11.7, GS-US-399-1812 Final CSR, Section 11.7; GS-US-399-1954 Final CSR, Section 11.7; GS-US-399-4231 Final CSR, Section 11.7; and GS-US-399-5505 Final CSR, Section 11.7).

4.1. Electrocardiogram Findings

4.1.1. Electrocardiogram Findings in Individuals with COVID-19

Electrocardiogram (ECG) data were not collected in Studies CO-US-540-5776, GS-US-540-5773, GS-US-540-5774, CO-US-540-5758, or the compassionate use program (IN-US-540-5755).

4.1.2. Electrocardiogram Findings in Healthy Participants

No patterns of clinically relevant shifts in 12-lead ECGs were observed in studies in healthy participants.

4.2. Vital Signs

4.2.1. Vital Signs in Individuals with COVID-19

Vital signs data were not reported in Study CO-US-540-5776, CO-US-540-5758, or the compassionate use program (IN-US-540-5755).

There were no clinically relevant changes from baseline within any treatment group or differences between the treatment groups in median values for systolic blood pressure, diastolic blood pressure, pulse, respiration rate, or body weight in Studies GS-US-540-5773 and GS-US-540-5774.

4.2.2. Vital Signs in Healthy Participants

No patterns of clinically relevant changes from baseline in vital signs were observed in studies in healthy participants.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

5.1.1. Study GS-US-540-5773

Summaries of overall AEs are presented by age group (< 65 years; ≥ 65 years), sex at birth (male or female), and race in GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.11.2.1.1.2, 15.11.2.1.1.3, and req10636.12, respectively. Summaries of AEs by system organ class and PT are presented by age group, sex, and race in GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.11.2.1.2.1, 15.11.2.1.2.2, and req10636.13, respectively. In general, higher percentages of AEs were reported in participants aged ≥ 65 years than those aged < 65 years, regardless of the duration of RDV therapy. Deaths, SAEs, and severe (Grade 3 or higher) AEs were reported in higher percentages of older (≥ 65 years) versus younger participants. There were no meaningful differences identified for race.

Summaries of AEs by system organ class and PT by baseline CrCl (≥ 90 mL/min, 60 to < 90 mL/min, and 30 to < 60 mL/min) are presented in Table req10636.9. Summaries of laboratory abnormalities by baseline CrCl are presented in Table req10636.10. In general, higher rates of AEs were reported in participants with baseline CrCl 30 to < 60 mL/min than those with CrCl ≥ 90 mL/min or 60 to < 90 mL/min. There were no meaningful differences identified between the CrCl subgroups for laboratory abnormalities. However, the small number of participants in the 30 to <60 mL/min subgroup make it difficult to draw any meaningful conclusions.

5.1.2. Study GS-US-540-5774

Summaries of overall AEs are presented by age group (< 65 years or ≥ 65 years), sex at birth (male or female), and race in GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.11.2.1.1.2, 15.11.2.1.1.3, and req10643.12, respectively. Summaries of AEs by system organ class and PT are presented by age group, sex, and race in GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.11.2.1.2.1, 15.11.2.1.2.2, and req10643.13, respectively. Higher rates of AEs, Grade 3 or higher AEs, and SAEs were reported in older participants (≥ 65 years) compared with younger participants (< 65 years) across all treatment groups. Higher rates of AEs were reported in the RDV groups compared to SOC in those participants aged < 65 years but there was no meaningful difference between treatment groups in those participants aged ≥ 65 years. Higher rates of nausea were reported in females compared with males across all treatment groups. There were no meaningful differences identified for race.

Summaries of AEs by system organ class and PT by baseline CrCl (≥ 90 mL/min, 60 to < 90 mL/min, and 30 to < 60 mL/min) are presented in Table req10643.9. Summaries of laboratory abnormalities by baseline CrCl are presented in Table req10643.10. In general, higher rates of AEs were reported in participants with baseline CrCl 30 to < 60 mL/min and 60 to < 90 mL/min than those with CrCl ≥ 90 mL/min. In general, laboratory abnormalities were reported more frequently in participants treated with RDV with baseline CrCl 30 to < 60 mL/min than those with CrCl ≥ 90 mL/min or 60 to < 90 mL/min. However, the small number of

participants in the 30 to < 60 mL/min subgroup make it difficult to draw any meaningful conclusions.

5.2. Extrinsic Factors

5.2.1. Study GS-US-540-5773

Summaries of overall AEs are presented by baseline oxygen status (invasive mechanical ventilation, high-flow oxygen, low-flow oxygen, or room air) and country (USA, Italy, and ex-Italy) in GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.11.2.1.1.4 and 15.11.2.1.1.5, respectively. Summaries of AEs by system organ class and PT are presented by baseline oxygen status and country in GS-US-540-5773 Interim (Final Part A) CSR, Tables 15.11.2.1.2.3 and 15.11.2.1.2.4 to 15.11.2.1.2.6, respectively. Deaths, SAEs, and severe (Grade 3 or higher) AEs were reported in higher percentages of participants in sites in Italy versus those in the USA and outside Italy, and in a higher percentage of participants on mechanical ventilation or high-flow oxygen.

5.2.2. Study GS-US-540-5774

Summaries of overall AEs are presented by baseline oxygen status (invasive mechanical ventilation, high flow oxygen, low flow oxygen, or room air) and country (US, Italy, and ex-Italy) in GS-US-540-5774 Interim 1 (Part A Day 11) CSR, Tables 15.11.2.1.1.4 and 15.11.2.1.1.5, respectively. There were no meaningful differences identified in these subpopulations across all treatment groups.

5.2.3. Compassionate Use Program (IN-US-540-5755)

In the compassionate use program (IN-US-540-5755), safety data were summarized by baseline oxygen support status (noninvasive, invasive). Fewer patients on noninvasive baseline oxygen support had AEs and SAEs than did patients on invasive baseline oxygen support (41.4% vs 55.8% for AEs; 15.5% vs 27.9% for SAEs) (IN-US-540-5755 Interim 1 Summary Report, Section 3.4).

5.3. Drug Interactions

No clinical drug-drug interaction studies have been conducted with RDV.

5.4. Use in Pregnancy and Lactation

In nonclinical reproductive toxicity studies, RDV demonstrated no adverse effect on embryofetal development when administered to pregnant animals. In addition, nonclinical toxicity studies demonstrated no adverse effect on male fertility. Embryonic toxicity was seen when RDV was initiated in female animals prior to mating and conception, but only at a systemically toxic dose.

In animal studies, RDV metabolites have been detected in the nursing pups of mothers given RDV. It is not known whether RDV is secreted in human milk.

5.4.1. Pregnant Individuals with COVID-19

Pregnant women are included in the ongoing compassionate use program (IN-US-540-5755) and expanded access program if they meet the criteria for severe COVID-19, as outlined in the protocol. To date, RDV has been shipped to over 300 pregnant women through the compassionate use program. However, at this time, data are insufficient to determine the risk of RDV use in pregnant women.

No pregnancies were reported in the clinical studies in individuals with COVID-19.

5.4.2. Studies in Healthy Participants

No pregnancies were reported in studies in healthy participants.

5.5. Overdose

There is no known antidote for RDV. In the case of overdose, the patient should receive standard treatment for overdose and supportive therapy based on the patient's signs and symptoms.

5.6. Drug Abuse

There have been no reports of abuse or misuse of RDV throughout the RDV development program.

5.7. Withdrawal and Rebound

No formal clinical studies for withdrawal or rebound effects of RDV have been conducted.

5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies of the effect of RDV on the ability to drive or use machines have been conducted.

6. POSTMARKETING DATA

No postmarketing safety data are included in this submission.

7. SUMMARY OF SAFETY ACROSS STUDIES

This Summary of Clinical Safety provides data to support a marketing application for RDV for the treatment of COVID-19. The main focus of this Summary of Clinical Safety is the primary safety data from 3 pivotal Phase 3 studies, with supportive data from an investigator-sponsored Phase 3 study in China and a compassionate use program. Additional safety data are provided from a study in participants with EVD and 4 Phase 1 studies in healthy participants.

The demographic and baseline characteristics of the population enrolled in the pivotal studies was largely representative of the hospitalized population with COVID-19. Both males and females were represented with each of the 3 studies enrolling at least 35% female participants.

There were no specified upper limits on age and the oldest participant enrolled was 98 years of age; over 25% of participants were older than 65 years of age with higher proportions observed in the Studies CO-US-540-5776 and GS-US-540-5773 studies (36.2% and 42.3% respectively). Similarly, there were no specified upper limits on body mass index (BMI) and a high proportion of participants were obese (BMI $\geq$ 30 kg/m^2) with the maximum BMI of 76.9 kg/m^2. The mean BMI in Studies CO-US-540-5776 was 30.6 kg/m^2 while upper 25th percentile of participants in Studies GS-US-540-5773 and GS-US-540-5774 were 33.5 kg/m^2 and 31.1 kg/m^2, respectively. The studies also enrolled participants across 3 continents (Asia, Europe, and North America) and included a racially-diverse population tracking the pandemic.

Across the pivotal studies, the study populations had multiple comorbidities including hypertension (most common), Type 2 diabetes mellitus and cardiac disease. It is important to note that the exclusion criteria related to hepatic and renal function could have prevented the sickest patients from enrolling in these studies.

Treatment with RDV was generally safe and well tolerated irrespective of age, sex, race, or oxygen support class. Overall, the safety profile based on the incidence and types of AEs was generally consistent with the underlying manifestations of COVID-19 as observed in the placebo controlled studies. When compared to non-RDV containing SOC arms, no definitive RDV-associated findings were observed. There were more AEs and deaths reported in participants with more severe disease consistent with the natural history of COVID-19.

In the 2 studies that evaluated the 5 or 10 day treatment duration, treatment with RDV was generally well tolerated with similar incidence of AEs reported with the 2 treatment durations after accounting for baseline disease severity.

In participants with severe COVID-19 in Study GS-US-540-5773, there was a higher incidence of SAEs, Grade 4 AEs, and AEs leading to premature discontinuation of study treatment in those participants in RDV 10-day group compared to the RDV 5-day group. These findings were likely attributable to an imbalance in baseline disease severity.

Attention was given to a comprehensive analysis of liver-related laboratory abnormalities and renal events since these were identified in healthy participants and the nonclinical program respectively. While a signal of elevated transaminases was observed in healthy participants, it is important to note that across the pivotal studies, most hepatic events were laboratory abnormalities and occurred at similar rates in the RDV, placebo or SOC arms. Similarly, renal toxicity which was identified in nonclinical models was not associated with RDV in patients with COVID-19 or healthy volunteers. Across the pivotal studies, renal-related AEs and laboratory abnormalities were generally reported at a similar rates for participants receiving RDV and placebo or SOC. Consistent with published literature, hepatic and renal safety outcomes in studies of RDV are driven by disease severity.

In addition to the above, through continuous pharmacovigilance, a safety review identified an association between IRRs and RDV. Signs and symptoms ranged from throat itching to significant hypotension. Where the final outcome was described, all cases described event resolution or improvement.

Conclusions

In summary, RDV has been evaluated in a broad spectrum of hospitalized patients with moderate to severe COVID-19, and the conclusions are as follows:

- Remdesivir has a similar AE profile to placebo or SOC: Overall rates of AEs, AE severity, and AE frequency were similar to those of placebo or SOC

- Adverse event severity and death are driven by disease severity, with poorer outcomes in patients with more severe disease

- Remdesivir administered for 5 days or 10 days was generally safe and well tolerated

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9. APPENDICES

9.1. Tabular Summary of Studies Relevant for Safety

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-399-1812	• To evaluate the safety and tolerability of single-ascending IV doses of RDV (solution formulation or lyophilized formulation) compared with placebo in healthy participants • To evaluate the PK of RDV and its metabolites, GS-704277 and/or GS-441524, following single ascending IV doses of RDV in healthy participants	Phase 1, blinded, randomized, placebo-controlled, first-in-human, single-ascending dose study	• Cohort 1: RDV 3 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 2: RDV 10 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 3: RDV 30 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 4: RDV 75 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 5: RDV 150 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 6: RDV 225 mg solution formulation or placebo over 2 hours as an IV infusion • Cohort 7: RDV 75 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 8: RDV 150 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 9: RDV 75 mg or placebo lyophilized formulation over 30 minutes as an IV infusion	1 day	Enrolled: 96 Completed: 96	Healthy adults	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-399-1954	• To evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo • To evaluate the PK of RDV and its metabolites following multiple IV doses of RDV	Phase 1, blinded, randomized, placebo-controlled, multiple-dose study	• Cohort 1: IV RDV 150 mg or placebo administered, QD • Cohort 2: IV RDV 150 mg or placebo administered, QD	Cohort 1: 7 days Cohort 2: 14 days	Enrolled: 24 Completed: 22	Healthy adults	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-399-4231	To determine the mass balance of remdesivir following administration of a single, IV dose of radiolabeled [^{14C}]-RDV	Phase 1, single-center, open-label, mass balance study	Single dose of RDV 150 mg containing a mixture of both unlabeled and radiolabeled [^{14}C]-RDV administered via IV infusion over 0.5 hour on the morning of Day 1	1 day	Enrolled: 8 Completed: 8	Healthy male adults	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-399-5505	• To evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo • To evaluate the PK of RDV and its metabolites following multiple IV doses of RDV	Phase 1, blinded, randomized, placebo-controlled, multiple-dose study	• Cohort 1: IV RDV 200 mg or placebo administered QD for the first day, followed by IV RDV 100 mg or placebo administrated QD, for 4 days • Cohort 2: IV RDV 200 mg or placebo administered, QD for the first day, followed by IV RDV 100 mg or placebo administrated QD for 9 days • Cohort 3 (optional): IV RDV 200 mg or placebo administered QD for the first day, followed by IV RDV 100 mg or placebo administrated QD for up to 13 days. Cohort 3 was not enrolled	Cohort 1: 5 days Cohort 2: 10 days Cohort 3: up to 14 days (not enrolled)	Enrolled: 36 Completed: 30	Healthy adults	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Compassionate Use Data	IN-US-540-5755	To provide RDV for single-patient compassionate use for the treatment of COVID-19	Single-patient compassionate use	Single loading dose of IV RDV 200 mg on Day 1 followed by QD maintenance doses of IV RDV 100 mg for up to 9 days	Up to 10 days	163	Patients with PCR confirmed COVID-19 who were hospitalized with substantial clinical symptoms where the benefits of treatment with an investigational agent outweighed the risks	Study ongoing; Interim 1 Summary Report
Uncontrolled Clinical Studies	GS-US-540-5773	To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14	Phase 3, randomized study	Part A • Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Part B • Mechanically Ventilated Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected	Part A: • Treatment Group 1: 5 days • Treatment Group 2: 10 days Part B • Mechanically Ventilated Treatment Group: 10 days • Extension Treatment Group: either 5 or 10 days	Randomized: 401 Completed: 332	Adults with confirmed severe COVID-19	Study ongoing; Interim (Final Part A) CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	GS-US-540-5774	To evaluate the efficacy of 2 RDV regimens compared with SOC, with respect to clinical status assessed by a 7-point ordinal scale on Day 11	Phase 3, open-label, randomized, multicenter study	Part A • Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Treatment Group 3: continued SOC therapy Part B • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected	Up to 10 days	Randomized: 596 Completed: 228	Adults with confirmed moderate COVID-19	Study ongoing; Interim 1 (Part A Day 11) CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	CO-US-540-5776 (ACTT-1)	To evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19	Phase 3, multicenter, adaptive, randomized, double-blind, placebo-controlled study	Single loading dose of IV RDV 200 mg on Day 1, followed by QD maintenance doses of IV RDV 100 mg for the duration of the hospitalization for up to 10 days	Up to 10 days	Randomized: 1062 Completed: 774	Hospitalized adults with COVID-19	Study ongoing; Preliminary CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Active Controlled Study for Ebola Virus Disease	CO-US-399-5366 (PALM)	To assess the safety and effectiveness of 4 drugs for people with Ebola virus	Phase 2/3, multicenter, multi outbreak, randomized, controlled study	• ZMapp group: SOC therapy together with IV ZMapp 50 mg/kg every third day beginning on Day 1 • RDV group: SOC therapy together with a loading dose of IV RDV 200 mg on Day 1 (adjusted for body weight in pediatric participants) followed by QD maintenance doses of IV RDV 100 mg (in adults, adjusted for body weight in pediatric participants) starting on Day 2 and for 9 or 13 days. • MAb114 group: SOC therapy together with IV MAb114 50 mg/kg IV on Day 1 administered as a single infusion • REGN-EB3 group: SOC therapy together with IV REGN-EB3 150 mg/kg on Day 1 administered as a single infusion	Up to 13 days	Enrolled: 681 Included in the primary analysis: 673	Participants of any age, including pregnant women, with RT-PCR confirmed Ebola who did not receive other investigational agents (except experimental vaccines)	RDV group stopped; {Mulangu 2019}
Uncontrolled Clinical Studies	CO-US-540-5758	To assess time to clinical improvement up to Day 28, defined as time from randomization to the point of a decline of 2 levels on a 6-point ordinal scale of clinical status	Phase 3, randomized, double-blind, placebo-controlled, multicenter study	IV RDV 200 mg or placebo on Day 1, followed by IV RDV 100 mg or placebo on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10	10 days	Enrolled: 237 ITT population: 236	Adults admitted to hospital with RT-PCR-confirmed SARS-CoV-2 infection and radiologically confirmed pneumonia	Study completed; {Wang 2020}

ACTT = Adaptive COVID-19 Treatment Trial; COVID-19 = coronavirus disease 2019; CSR = clinical study report; ITT = intent-to-treat; IV = intravenous; mAb114 = single human monoclonal antibody derived from an Ebola survivor; PCR = polymerase chain reaction; PK = pharmacokinetic(s); QD = once daily; RDV = remdesivir (GS-5734™); REGN-EB3 = a coformulated mixture of 3 human IgG1 monoclonal antibodies; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; ZMapp = triple monoclonal antibody agent
Completed = number of subjects who completed the study

9.2. Additional Safety Analysis

Additional outputs presenting data from analyses that were not prespecified in the statistical analysis plans for Studies GS-US-540-5773 and GS-US-540-5774 are included in this submission.

SECTION 2.7
CLINICAL SUMMARY

SECTION 2.7.5—LITERATURE REFERENCES

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(GS-5734™)

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CONFIDENTIAL AND PROPRIETARY INFORMATION

1. LITERATURE REFERENCES

The following references are cited in the Clinical Summary documents (ie, m2.7.1 to m2.7.4). Copies of these references are available upon request if not provided with this submission.

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SECTION 2.7.6—SYNOPSES OF INDIVIDUAL STUDIES

REMDESIVIR
(GS-5734™)

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1. LISTING OF CLINICAL STUDIES

1.1. Remdesivir

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-399-1812	• To evaluate the safety and tolerability of single-ascending IV doses of RDV (solution formulation or lyophilized formulation) compared with placebo in healthy participants • To evaluate the PK of RDV and its metabolites, GS-704277 and/or GS-441524, following single ascending IV doses of RDV in healthy participants	Phase 1, blinded, randomized, placebo-controlled, first-in-human, single-ascending dose study	• Cohort 1: RDV 3 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 2: RDV 10 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 3: RDV 30 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 4: RDV 75 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 5: RDV 150 mg or placebo solution formulation over 2 hours as an IV infusion • Cohort 6: RDV 225 mg solution formulation or placebo over 2 hours as an IV infusion • Cohort 7: RDV 75 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 8: RDV 150 mg or placebo lyophilized formulation over 2 hours as an IV infusion • Cohort 9: RDV 75 mg or placebo lyophilized formulation over 30 minutes as an IV infusion	1 day	Enrolled: 96 Completed: 96	Healthy adults	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Healthy Subject PK and Initial Tolerability	GS-US-399-1954	• To evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo • To evaluate the PK of RDV and its metabolites following multiple IV doses of RDV	Phase 1, blinded, randomized, placebo-controlled, multiple-dose study	• Cohort 1: IV RDV 150 mg or placebo administered, QD • Cohort 2: IV RDV 150 mg or placebo administered, QD	Cohort 1: 7 days Cohort 2: 14 days	Enrolled: 24 Completed: 22	Healthy adults	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-399-4231	To determine the mass balance of remdesivir following administration of a single, IV dose of radiolabeled [^{14}C]-RDV	Phase 1, single-center, open-label, mass balance study	Single dose of RDV 150 mg containing a mixture of both unlabeled and radiolabeled [^{14}C]-RDV administered via IV infusion over 0.5 hour on the morning of Day 1	1 day	Enrolled: 8 Completed: 8	Healthy male adults	Study completed; Final CSR
Healthy Subject PK and Initial Tolerability	GS-US-399-5505	• To evaluate the safety and tolerability of multiple IV doses of RDV compared with placebo • To evaluate the PK of RDV and its metabolites following multiple IV doses of RDV	Phase 1, blinded, randomized, placebo-controlled, multiple-dose study	• Cohort 1: IV RDV 200 mg or placebo administered QD for the first day, followed by IV RDV 100 mg or placebo administrated QD, for 4 days • Cohort 2: IV RDV 200 mg or placebo administered, QD for the first day, followed by IV RDV 100 mg or placebo administrated QD for 9 days • Cohort 3 (optional): IV RDV 200 mg or placebo administered QD for the first day, followed by IV RDV 100 mg or placebo administrated QD for up to 13 days. Cohort 3 was not enrolled	Cohort 1: 5 days Cohort 2: 10 days Cohort 3: up to 14 days (not enrolled)	Enrolled: 36 Completed: 30	Healthy adults	Study completed; Final CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Compassionate Use Data	IN-US-540-5755	To provide RDV for single-patient compassionate use for the treatment of COVID-19	Single-patient compassionate use	Single loading dose of IV RDV 200 mg on Day 1 followed by QD maintenance doses of IV RDV 100 mg for up to 9 days	Up to 10 days	163	Patients with PCR confirmed COVID-19 who were hospitalized with substantial clinical symptoms where the benefits of treatment with an investigational agent outweighed the risks	Study ongoing; Interim 1 Summary Report
Uncontrolled Clinical Studies	GS-US-540-5773	To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14	Phase 3, randomized study	Part A • Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 Part B • Mechanically Ventilated Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected	Part A: • Treatment Group 1: 5 days • Treatment Group 2: 10 days Part B • Mechanically Ventilated Treatment Group: 10 days • Extension Treatment Group: either 5 or 10 days	Randomized: 401 Completed: 332	Adults with confirmed severe COVID-19	Study ongoing; Interim (Final Part A) CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Uncontrolled Clinical Studies	GS-US-540-5774	To evaluate the efficacy of 2 RDV regimens compared with SOC, with respect to clinical status assessed by a 7-point ordinal scale on Day 11	Phase 3, open-label, randomized, multicenter study	Part A • Treatment Group 1: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5 • Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 • Treatment Group 3: continued SOC therapy Part B • Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10 unless the 5-day dosing regimen used in Treatment Group 1 of Part A is selected	Up to 10 days	Randomized: 596 Completed: 228	Adults with confirmed moderate COVID-19	Study ongoing; Interim 1 (Part A Day 11) CSR
Controlled Clinical Studies Pertinent to the Claimed Indication	CO-US-540-5776 (ACTT-1)	To evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19	Phase 3, multicenter, adaptive, randomized, double-blind, placebo-controlled study	Single loading dose of IV RDV 200 mg on Day 1, followed by QD maintenance doses of IV RDV 100 mg for the duration of the hospitalization for up to 10 days	Up to 10 days	Randomized: 1062 Completed: 774	Hospitalized adults with COVID-19	Study ongoing; Preliminary CSR

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/ Entry Criteria	Study Status; Type of Report
Active Controlled Study for Ebola Virus Disease	CO-US-399-5366 (PALM)	To assess the safety and effectiveness of 4 drugs for people with Ebola virus	Phase 2/3, multicenter, multi outbreak, randomized, controlled study	• ZMapp group: SOC therapy together with IV ZMapp 50 mg/kg every third day beginning on Day 1 • RDV group: SOC therapy together with a loading dose of IV RDV 200 mg on Day 1 (adjusted for body weight in pediatric participants) followed by QD maintenance doses of IV RDV 100 mg (in adults, adjusted for body weight in pediatric participants) starting on Day 2 and for 9 or 13 days. • MAb114 group: SOC therapy together with IV MAb114 50 mg/kg IV on Day 1 administered as a single infusion • REGN-EB3 group: SOC therapy together with IV REGN-EB3 150 mg/kg on Day 1 administered as a single infusion	Up to 13 days	Enrolled: 681 Included in the primary analysis: 673	Participants of any age, including pregnant women, with RT-PCR confirmed Ebola who did not receive other investigational agents (except experimental vaccines)	RDV group stopped; {Mulangu 2019}
Uncontrolled Clinical Studies	CO-US-540-5758	To assess time to clinical improvement up to Day 28, defined as time from randomization to the point of a decline of 2 levels on a 6-point ordinal scale of clinical status	Phase 3, randomized, double-blind, placebo-controlled, multicenter study	IV RDV 200 mg or placebo on Day 1, followed by IV RDV 100 mg or placebo on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10	10 days	Enrolled: 237 ITT population: 236	Adults admitted to hospital with RT-PCR-confirmed SARS-CoV-2 infection and radiologically confirmed pneumonia	Study completed; {Wang 2020}

ACTT = Adaptive COVID-19 Treatment Trial; COVID-19 = coronavirus disease 2019; CSR = clinical study report; ITT = intent-to -treat; IV = intravenous; MAb114 = single human monoclonal antibody derived from an Ebola survivor; PCR = polymerase chain reaction; PK = pharmacokinetics; QD = once daily; RDV = remdesivir (GS-5734™); REGN-EB3 = a coformulated mixture of 3 human IgG1 monoclonal antibodies; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; ZMapp = triple monoclonal antibody agent
Completed = number of subjects who completed the study