Veklury®

(Remdesivir)

Authorization Number: 68026
Authorization Date: 25-Nov-2020
Indication Extension: 24-May-2022

Clinical Study Results

June 2022

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1. INTRODUCTION

As of 2020, Gilead discloses clinical study results of newly authorized products in Switzerland by Swissmedic according to the requirements laid out in Art. 71-73 TPO (Ordinance on Therapeutic Products).

Below you will find the information for clinical studies relevant for the marketing authorization for Veklury® (Remdesivir) in Switzerland dated 25 November 2020 as well as the indication extension approved on 24 May 2022.

2. OVERVIEW ON CLINICAL STUDIES

Study number	Study title:	Indication:	EudraCT-Number:
GS-US-540-5773 Part A	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19	Coronavirus Disease 2019 (COVID-19)	2020-000841-15
GS-US-540-5774 Part 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	COVID-19	2020-000842-32
GS-US-540-5776	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults	Coronavirus disease 2019 (COVID-19)	2020-001052-18
GS-US-540-9012	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient	Coronavirus disease 2019 (COVID-19)	2020-003510-12

3. STUDY SYNOPSIS GS-US-540-5773

INTERIM (FINAL PART A) CLINICAL STUDY REPORT

Study Title:	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Name of Test Drug:	Remdesivir (GS-5734™)
Dose and Formulation:	Remdesivir (GS-5734™) for injection, 100 mg, for intravenous (IV) administration
Indication:	Coronavirus Disease 2019 (COVID-19)
Sponsor:	Gilead Sciences, Inc 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-540-5773
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	147753 2020-000841-15
ClinicalTrials.gov Identifier:	NCT04292899
Study Start Date:	06 March 2020 (First Participant Screened)
Study End Date:	09 April 2020 (Last Participant Last Observation for the Primary Endpoint for Part A) 27 April 2020 (Last Participant Last Observation for this Report)
Principal or Coordinating Investigator:	Name: George A. Diaz, MD Affiliation: Providence Regional Medical Center Everett
Sponsor Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	24 June 2020

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-540-5773

Gilead Sciences, Inc. 333 Lakeside Drive
Foster City, CA 94404,
USA

Title of Study: A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19
Investigators: Multicenter study
Study Centers: Up to approximately 160 centers globally
Publications: Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020 May 27. doi: 10.1056/NEJMoa2015301.
Study Period: 06 March 2020 (First Participant Screened) 09 April 2020 (Last Participant Last Observation for the Primary Endpoint for Part A) 27 April 2020 (Last Participant Last Observation for this Report)
Phase of Development: Phase 3
Study Objectives: The purpose of this ongoing study is to provide remdesivir (RDV, GS-5734™) to participants with severe coronavirus disease 2019 (COVID-19). The primary objective of this study was as follows: • To evaluate the efficacy of 2 RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14 The secondary objective of this study was as follows: • To evaluate the safety and tolerability of RDV

Methodology:

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 infection. Eligible participants were randomized in equal proportions to 1 of 2 treatment groups. No stratification was performed. Part B is a 2–treatment-group multicenter study of RDV in participants with severe COVID-19 infection.

In Part A, approximately 400 participants meeting all eligibility criteria and who were not mechanically ventilated were randomized in a 1:1 ratio into 1 of the following treatment groups:

Treatment Group 1 (hereafter referred to as the RDV 5-day group): continued standard of care therapy together with intravenous (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 standard of care 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, up to an additional approximately 5600 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 standard of care 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 standard of care 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

This interim clinical study report (CSR) provides the final results for participants in Part A. All data for Part A collected by the data finalization date (19 May 2020) were included in this interim analysis. The study design, statistical analyses, and results for Part B are not included in this interim CSR.

At screening, after appropriate consent or assent was obtained, or the participant was enrolled under International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator, demographic and baseline characteristics, medical history, and concomitant medications were documented. Vital signs including temperature, respiratory rate, and oxygen saturation (SpO_2), were recorded. Radiographic imaging was performed if not already available. Severe acute respiratory syndrome (SARS) coronavirus-2 (CoV-2) (SARS CoV2) testing by polymerase chain reaction (PCR) testing was performed; if this testing had been performed within the previous 4 days, no repeat testing was required.

If safety laboratory results from the screening day were not already available, laboratory testing, including alanine aminotransferase (ALT), and aspartate aminotransferase (AST), creatinine, and creatinine clearance, were performed according to local practice.

The date of randomization was considered Day 1, and it was expected that all randomized participants would receive their initial dose of RDV on Day 1. In cases where participants received their initial dose of RDV on the day after randomization, Day 1 was the day of first

dose administration, as recorded on the Study Drug Administration electronic case report form.
Number of Participants (Planned and Analyzed): Planned: Approximately 6000 participants (approximately 400 participants in Part A) Analyzed (Part A): • All Randomized Analysis Set: 401 participants (201 in the RDV 5-day group and 200 in the RDV 10-day group) • Full Analysis Set (FAS) and Safety Analysis Set: 397 participants (200 in the RDV 5-day group and 197 in the RDV 10-day group)
Diagnosis and Main Criteria for Inclusion: Eligible participants had COVID-19 confirmed by PCR who were hospitalized with $SpO_2 \leq 94\%$ on room air or requiring supplemental oxygen, and radiographic evidence of pulmonary infiltrates, and who were willing and able to provide written informed consent, or with a legal representative who could provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (age ≥ 18) or willing and able to provide assent (age ≥ 12 to < 18, where locally and nationally approved) prior to performing study procedures. Participants in Part A must not have been mechanically ventilated.
Duration of Treatment: The duration of treatment with RDV in Part A was up to 5 days for participants in the RDV 5-day group and up to 10 days for participants in the RDV 10-day group.
Test Product, Dose, Mode of Administration, and Batch No.: Participants were treated with RDV 100 mg for injection, which was supplied as a lyophilized solid in sterile single-use, 30 mL Type I clear glass vials. This study treatment was reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion. In Part A, participants in both treatment groups received RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5. Participants in the RDV 10-day group also received RDV 100 mg on Days 6, 7, 8, 9, and 10. The batch numbers of the RDV 100 mg for IV injection were EW1802A1, EW1804A1, EW1805A1, and EW2001A1.
Reference Therapy, Dose, Mode of Administration, and Batch No.: None.

Criteria for Evaluation:

Efficacy: The primary endpoint of this study was clinical status assessed by a 7-point ordinal scale on Day 14. The ordinal scale is an assessment of the clinical status of a participant at a given study day, as follows:

1. Death
2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (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 requiring ongoing medical care (other than per-protocol RDV administration)
7. Not hospitalized

Other endpoints of interest included the following:

- Time to $SpO_2 > 94\%$ on room air
- Time to first negative SARS-CoV-2 PCR
- Duration of oxygen therapy (days)
- Duration of hospitalization (days)
- All-cause mortality at Day 28
- Time to clinical improvement (days): Clinical improvement is defined as a $\geq$ 2-point improvement from Day 1 on a 7-point ordinal scale
- Plasma concentrations of RDV and metabolites

Pharmacokinetics: Although pharmacokinetic (PK) sampling was included in the protocol, no samples were collected in Part A.

Safety: The secondary endpoint was the proportion of participants with treatment-emergent adverse events (AEs). Safety assessments included documentation of AEs and concomitant medications, monitoring of vital signs including respiratory status, and laboratory testing performed according to standard of care practice, with results for white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing reported to the sponsor. In addition, even if not performed as standard of care, white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, and AST data were collected at prespecified timepoints during the study.

Statistical Methods:

Efficacy: The primary analysis set for efficacy analysis was the FAS, which included all participants who were randomized into Part A of the study and received at least 1 dose of RDV. Participants were grouped according to the treatment to which they were randomized.

The primary efficacy endpoint was clinical status assessed by a 7-point ordinal scale on Day 14, which was analyzed using a proportional odds model with treatment as the independent variable and baseline clinical status as a continuous covariate. The assumption of odds proportionality was assessed using a score test. It would be concluded that 10-day treatment was superior to 5-day treatment if the lower bound of the 2-sided 95% confidence interval (CI) of the odds ratio (10-day/5-day) on Day 14 was more than 1.

As a supportive analysis of the primary endpoint, the clinical status at Day 14 was compared between treatment groups using a 2-sided Wilcoxon rank sum test, stratified on baseline clinical status. In addition, the primary endpoint was analyzed using a proportional odds model including treatment as the independent variable (dropping baseline score as a covariate).

The change from baseline in clinical status category on Days 5, 7, 11, 14, 28, and last available assessment was summarized by treatment groups using descriptive statistics and compared between the treatment groups using a 2-sided Wilcoxon rank sum test. The number and percentage of participants in each clinical status category for each day from baseline through Day 14, at Day 28, and at last available assessment were summarized by treatment group.

The number and percentage of participants in each clinical status category for each day from baseline through Day 14, at Day 28, and at last available assessment was summarized within each subgroup. The primary endpoint was analyzed for the subgroups by age, sex, oxygen support status, and country.

Analyses of other endpoints of interest were performed as described in the statistical analysis plan using the FAS.

Pharmacokinetics: No PK assessments were performed for this report.

Safety: The Safety Analysis Set included all participants who were randomized into Part A of the study and received at least 1 dose of RDV. Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1. Toxicity criteria specified in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, was used for assigning toxicity grades to AEs and laboratory results for analysis.

Adverse events were summarized by treatment group and listed by participant. The secondary endpoint, proportion of participants with treatment-emergent AEs, was compared between the 2 groups using the Cochran-Mantel-Haenszel test stratified on baseline clinical status. The point estimate of the treatment difference and the associated 95% CIs were calculated based on stratum-adjusted Mantel-Haenszel proportion where the stratum was baseline clinical status.

Laboratory data collected during the study were analyzed and summarized using both quantitative and qualitative methods and listed by participant. For numeric laboratory results, descriptive statistics were provided by treatment group. Baseline and change from baseline were compared between the treatment groups using the 2-sided Wilcoxon rank sum test.

Descriptive statistics were provided by treatment group for body weight and vital signs. Concomitant medications were summarized.

The incidence of AEs and time to all-cause mortality were each summarized for the subgroups age, sex, and country. The incidence of AEs was also summarized by baseline oxygen support status.

SUMMARY OF RESULTS:

Participant Disposition: 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 (RDV 5-day group, 200 participants; RDV 10-day group, 197 participants). 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 discretion)

Of the 397 participants treated in Part A, 35.0% (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% (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).

Participant Demographics and Other Baseline Characteristics: Demographic and baseline characteristics were similar between the 2 treatment groups. The majority of the participants were male (63.7%). The median age was 61 years (range 20 to 98 years); the majority of participants were white (75.0%) and were not Hispanic/Latino (78.0%). The median (first quartile [Q1], third quartile [Q3]) body mass index was 28.7 (25.3, 33.5) kg/m^2.

Although treatment groups were balanced in demographics, they were not balanced in baseline disease characteristics. Greater proportions of participants in the RDV 10-day group were in the highest disease severity categories on the 7-point ordinal scale. The differences in baseline clinical status (7-point ordinal scale) between the treatment groups were statistically significant, with a better (higher score) clinical status in participants in the RDV 5-day group compared with those in the RDV 10-day group ($p = 0.0230$). 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 ($p = 0.0175$).

There were statistically significant differences between the 2 treatment groups in the Italy subgroup in baseline clinical status ($p = 0.0471$) and baseline oxygen support status ($p = 0.0340$). Participants in the Italy subgroup also had a worse (lower score) baseline clinical status compared with participants in the ex-Italy subgroup.

Median baseline ALT was similar between the treatment groups (RDV 5-day group 32 U/L, RDV 10-day group 36 U/L); however, participants in the RDV 5-day group had significantly lower median baseline AST than participants in the RDV 10-day group (RDV 5-day group, 41 U/L, RDV 10-day group 46 U/L; $p = 0.0081$). Median (Q1, Q3) baseline serum creatinine was 0.82 (0.66, 1.00) mg/dL in the RDV 5-day group and 0.87 (0.70, 1.04) mg/dL in the RDV 10-day group ($p = 0.1125$), and median (Q1, Q3) baseline creatinine clearance by

Cockcroft-Gault was 106.3 (79.7, 141.7) mL/min in the RDV 5-day group and 103.4 (79.6, 139.8) mL/min in the RDV 10-day group (p = 0.6575).

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

The 3 most commonly reported medical history preferred terms in the RDV 5-day and RDV 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).

Efficacy Results: The primary efficacy endpoint for the study was clinical status assessed using a 7-point ordinal scale on Day 14 in the overall study population. Primary analysis of the primary endpoint demonstrated that treatment with RDV for 5 days and treatment with RDV for 10 days resulted in similar odds of improved clinical status at Day 14 (p = 0.1563).

Other endpoints of interest evaluated during the study included oxygen support status, duration of hospitalization, mortality, clinical improvement, recovery, and time to room air. There were no statistically significant differences between the RDV 5-day and 10-day treatment groups in the number of days of oxygen support at any level in participants who were discharged alive or who died on or before Day 14, and no notable differences between treatment groups in shift in oxygen support status from baseline.

Treatment with RDV beyond 5 days among participants who were receiving mechanical ventilation at 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 at 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%] in the RDV 10-day group vs 10 of 25 participants [40.0%] in the RDV 5-day group) and a higher proportion had improvements in oxygen support status at Day 14 (3 participants [7.3%] each improved to high-flow oxygen and low-flow oxygen, and 5 [12.2%] were discharged on or before Day 14 in the RDV 10-day group vs 2 participants [8.0%] who improved to low-flow oxygen, 1 [4.0%] who improved to room air, and 2 [8.0%] who were discharged on or before Day 14 in the RDV 5-day group).

The difference between treatment groups in the proportion of participants with a ≥ 2-point improvement from baseline in clinical status was not statistically significant at any time point. A higher proportion of participants in the RDV 5-day group had a ≥ 1-point improvement from baseline in clinical status than in the RDV 10-day group; the difference between treatment groups was statistically significant on Days 11, 14, and 28, with a higher proportion of participants in the RDV 5-day group with improvement (p = 0.0413, p = 0.0278, and p = 0.0418, respectively). The median time to ≥ 2-point and ≥ 1-point clinical improvement was shorter in the RDV 5-day group versus the RDV 10-day group; the differences between groups were statistically significant (p = 0.0298 and p = 0.0139, respectively).

While there were no statistically significant differences between the 2 treatment groups in the proportions of participants with recovery at any time point, higher proportions of participants in the RDV 5-day group than the RDV 10-day group achieved modified recovery, with

statistically significant differences between treatment groups for modified recovery on Day 28 and at the last available assessment (p = 0.0070 and p = 0.0208, respectively). Median times to recovery and modified recovery were shorter in the RDV 5-day group compared with the RDV 10-day group; the differences between groups were statistically significant (p = 0.0249 and p = 0.0227, respectively).

A higher proportion of participants in the RDV 5-day group than participants in the RDV 10-day group had improvement to room air on or prior to Day 28 (p = 0.0459).

There were no significant differences between the RDV 5-day and RDV 10-day treatment groups in duration of hospitalization or time to death.

Analysis of clinical status based on a 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 at Day 14 across all subgroups analyzed. 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 at Day 14. Consistent with analyses for the overall study population, there were no statistically significant differences in time to death between the RDV 5-day group and the RDV 10-day group in any subgroup.

Pharmacokinetics Results: No PK assessments were performed for this report.

Safety Results: Remdesivir administered for 5 days (median [Q1, Q3] exposure, 5 [5, 5] days) or 10 days (9 [5, 10] days) was generally well tolerated.

Adverse Events

Similar percentages of participants in RDV 5-day and RDV 10-day groups had AEs during the study (71.5% and 75.1%, respectively).

Through Day 5, Grade 3 or higher AEs and serious adverse events (SAEs) were reported in lower percentages of participants in the RDV 5-day group than the RDV 10-day group. When categorized by oxygen support status at Day 5, the percentage of participants with overall AEs occurring on or after Day 6 was similar between the groups.

Participants who were older (≥ 65 years) generally had higher percentages of AEs than those who were younger (< 65 years), and higher incidences of deaths, SAEs, and severe (Grade 3 or higher) AEs were reported in participants who were older, male, or at sites in Italy versus the USA or outside Italy.

The 3 most commonly reported AEs for each treatment group were as follows:

- 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 frequency of acute kidney injury in the RDV 5-day group compared with the RDV 10-day group (2.0%, 4 participants and 8.1%, 16 participants in the RDV 5-day and 10-day groups, respectively).

The incidence of Grade 3 or higher AEs was lower in the RDV 5-day group than the RDV 10-day group (31.5%, 63 participants and 42.6%, 84 participants, 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).

A similar percentage of deaths was reported in each treatment group (RDV 5-day group 12.5%, 25 participants; RDV 10-day group 14.2%, 28 participants).

The difference in percentages between treatment groups in reported SAEs was statistically significant (21.5%, 43 participants and 34.5%, 68 participants in the RDV 5-day and 10-day groups, respectively; $p = 0.0136$). The most commonly reported SAE in each treatment group was acute respiratory failure (5.0%, 10 participants and 9.1%, 18 participants in the RDV 5-day and 10-day groups, respectively).

The difference in the percentage of participants with reported AEs that led to premature discontinuation of study treatment was statistically significant (4.5%, 9 participants and 11.2%, 22 participants in the RDV 5-day and 10-day groups, respectively; $p = 0.0289$). The most common AE that led to premature study treatment discontinuation was acute kidney injury, reported in no participant in the RDV 5-day group and 2.5% (5 participants) in the RDV 10-day group.

Hepatic Safety

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. The overall pattern and types of hepatic AEs were similar in the 2 treatment groups; the 3 most commonly reported hepatic AEs in both 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). The combined numbers of participants in each treatment group with 1 or more transaminase-related AEs (ALT increased, AST increased, hepatic enzyme 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.

Grade 3 or higher hepatic AEs and hepatic SAEs were reported in a similar percentage of participants in each treatment group. Hepatic AEs leading to premature study treatment discontinuation were reported in 2.5% (5 participants) and 4.6% (9 participants) in the RDV 5-day and 10-day groups, respectively.

Median ALT increased and median AST decreased in both treatment groups during the study. Grade 3 or 4 increased ALT and Grade 3 or 4 increased AST were each reported in similar percentages of participants in the RDV 5-day and 10-day groups.

Laboratory Evaluations

There were no clinically relevant changes from baseline within either treatment group or differences between the treatment groups in median values for hematology parameters. Median values for hematology and chemistry parameters were generally within reference ranges.

Between baseline and Day 14, median serum creatinine decreased and median creatinine clearance increased in both treatment groups.

The majority of participants in each treatment group had at least 1 laboratory abnormality (77.9%, 152 of 195 participants and 83.8%, 160 of 191 participants in the RDV 5-day and RDV 10-day groups, respectively). The incidence of all graded individual laboratory abnormalities was generally similar across the 2 treatment groups. Grade 3 or 4 laboratory abnormalities were reported in a similar percentage of participants in each treatment group (27.7%, 54 participants and 33.5%, 64 participants in the RDV 5-day and 10-day groups, respectively). 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 creatinine clearance (19.1%, 36 of 188 participants). Grade 4 increased serum creatinine and Grade 4 decreased creatinine clearance were less common in the RDV 5-day group than the RDV 10-day group (2.6%, 5 of 195 participants vs 11.5%, 22 of 191 participants, respectively, for serum creatinine and 3.1%, 6 of 193 participants vs 12.2%, 23 of 188 participants, respectively, for creatinine clearance).

There were no clinically relevant changes from baseline in vital signs parameters or body weight.

CONCLUSIONS: The conclusions from this interim analysis of Study GS-US-540-5773 are as follows:

- 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.
- Patients on invasive mechanical ventilation may benefit from a treatment duration longer than 5 days.
- Remdesivir administered for 5 days or 10 days was generally safe and well tolerated in participants with severe COVID-19.

3.1. Protocol Amendments and Description

Amendment 1.0:	**Date: 15 March 2020**
Rationale:	Herein is a summary of the major changes made to the Original protocol dated 24 February 2020 and reflected in Amendment 1.0 dated 15 March 2020. • Revised primary endpoint to allow for more robust analysis • Expanded number of sites and subjects globally to meet urgent needs • Divided enrollment into two Parts: A and B • Included a Mechanically Ventilated Treatment Group and an Extension Treatment Group during enrollment to extend RDV therapy • Inserted EudraCT Number and Clinical Trials.gov identifiers • Provided further clarification to the inclusion and exclusion criteria • Included parameters for adolescent participants and adolescent dosing • Revised statistical methodology and analysis due to changes in endpoints and study design • Clarified requirements for oxygen supplementation • Additional formatting and administrative updates and minor grammatical corrections were made throughout the document but are not explicitly outlined in the changes below. Specific changes are presented herein as ***bold and italicized*** or ~~strikethrough~~.

Amendment 2.0:	**Date: 20 March 2020**
Rationale:	Herein is a summary of the major changes made to Amendment 1.0 dated 15 March 2020 and reflected in Amendment 2.0 dated 20 March 2020. • Revised informed consent language to include informed consent with a legal representative and those enrolled under ICH E6(R2) 4.8.15 emergency use provisions • Specific changes are presented herein as ***bold and italicized***

Amendment 3.0:	**Date: 12 April 2020**
Rationale:	Herein is a summary of the major changes made to Amendment 2.0 dated 20 March 2020 and reflected in Amendment 3.0 dated 12 April 2020: • Increased number of centers globally • Increased number of participants for enrollment • Removed enrollment limit for the mechanically ventilated treatment group • Revised section on pediatric dosing with minor edits • Added language around discontinuation of study medication • Clarified section on concomitant medications disallowed during study • Added further guidance on Pharmacokinetic (PK) assessments and sample collection timepoints • Clarified assessment guidance for laboratory abnormalities • Incorporated changes per the latest administrative amendment (v3) • Administrative changes and minor editorial updates were made, where appropriate, throughout the protocol to align with relevant sections, and may not be explicitly outlined in the changes below. Specific changes are presented herein as ***bold and italicized*** or ~~strikethrough~~

3.2. GS-US-540-5773: List of Principal Investigators

Geographic Region/ Country Principal Investigator	Study Site
Asia-Pacific / Hong Kong	Prince of Wales Hospital Rm 114037, Clinical Sciences Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong
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Asia-Pacific / South Korea	National Medical Center 245 Eulji-ro, Jung-gu Seoul, 04564, Republic of Korea
Asia-Pacific / Singapore	National University Hospital, National University Health System 1E Kent Ridge Road Singapore 119228 Singapore
Asia-Pacific / Singapore	Singapore General Hospital Outram Road Singapore 169608 Singapore
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EMEA / Italy	ASST Spedali Civili Di Brescia Piazza Spedali Civili 1, Brescia, 25123
EMEA / Italy	UOC Malattie Infettive e Tropicali, Azienda Ospedaliera di Padova Via Giustiniani 1, Padova, 35121
EMEA / Italy	Dipartimento di Malattie Infettive, Malattie Infettive I- Malattie Infettive III, ASST Fatebenefratelli Sacco Ospedale Luigi Sacco Via G.B. Grassi 74, Milano, 20157

Geographic Region/ Country Principal Investigator	Study Site
EMEA / Italy	UO Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma Via Gramsci 14, Parma, 43126
EMEA / Italy	ASST Cremona Viale Concordia 1, Cremona, 26100
EMEA / Spain	Hospital Universitario La Paz Paseo de la Castellana, 261, Madrid, 28046
EMEA / Spain	Hospital Universitario de Cruces Plaza de Cruces, 12, Barakaldo, Bizkaia, 48903
EMEA / Spain	Hospital Clinic de Barcelona Calle Villarroel 170, Barcelona, 08036
North America / United States	Jamaica Hospital Medical Center 8900 Van Wyck Expressway Jamaica, New York 11418
North America / United States	Hackensack University Medical Center 30 Prospect Avenue, Hackensack, New Jersey 07601
North America / United States	James J Peters VA Medical Center 130 West Kingsbridge Rd Bronx, New York 10468
North America / United States	Temple University Hospital 3401 North Broad Street, Philadelphia, Pennsylvania 19140
North America / United States	Providence Regional Medical Center Everett 1330 Rockefeller Avenue Everett, Washington 98201
North America / United States	Swedish Medical Center – First Hill 747 Broadway Seattle, Washington 98122
North America / United States	Baylor University Medical Center 3500 Gaston Ave Dallas,Texas 75246
North America / United States	Baylor Scott & White All Saints Medical Center – Fort Worth 1400 8th Ave, Fort Worth, Texas 76104
North America / United States	Houston Methodist Hospital 6565 Fannin Street Houston, Texas 77030
North America / United States	Providence Saint John's Health Center 2121 Santa Monica Blvd Santa Monica, California 90404

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	University Hospitals Cleveland Medical Center 11100 Euclid Ave Cleveland, Ohio 44106
North America / United States	Virginia Mason Medical Center 1100 9th Avenue Seattle, Washington 98101
North America / United States	MultiCare Tacoma General Hospital 315 Martin Luther King Jr Way Tacoma, Washington 98405
North America / United States	New York Presbyterian Hospital/Weill Cornell Medical Center 525 East 68th Street New York, New York 10065
North America / United States	Brigham and Women's Hospital 75 Francis Street Boston, Massachussets 02115
North America / United States	University of Chicago 5841 South Maryland Avenue Chicago, Illinois 60637
North America / United States	Robert Wood Johnson University Hospital Somerset 110 Rehill Avenue Somerville, New Jersey 08876
North America / United States	Danbury Hospital 24 Hospital Avenue Danbury, Connecticut 06810
North America / United States	Providence St. Vincent Medical Center 9205 Southwest Barnes Road Portland, Oregon 97225
North America / United States	Mayo Clinic 200 First St SW, Rochester, Minnesota 55905
North America / United States	Hoag Memorial Hospital Presbyterian One Hoag Drive Newport Beach, California 92663
North America / United States	VCU Health Medical Center 1250 East Marshall Street Richmond, Virginia 23298
North America / United States	Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center 330 Brookline Avenue, E/CLS 1036 Boston, Massachusetts 02215
North America / United States	Stanford Hospital 300 Pasteur Drive, Stanford, California 94305

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	The Miriam Hospital 164 Summit Avenue Providence, Rhode Island 02904
North America / United States	Kaiser Permanente Los Angeles Medical Center 1505 North Edgemont Street, Los Angeles, California 90027
North America / United States	Kaiser Permanente West Los Angeles Medical Center 6041 Cadillac Avenue, Los Angeles, California 90034
North America / United States	Kaiser Permanente Woodland Hills Medical Center 5601 De Soto Avenue, Woodland Hills, CA 91365
North America / United States	Kaiser Permanente Riverside Medical Center 10800 Magnolia Avenue Riverside, California 92505
North America / United States	Kaiser Permanente Moreno Valley Medical Center 27300 Iris Avenue Moreno Valley, California 92555
North America / United States	Kaiser Permanente Downey Medical Center 9333 Imperial Highway Downey, California 90241
North America / United States	Kaiser Permanente San Diego Medical Center 9455 Clairemont Mesa Blvd San Diego, California 92123
North America / United States	Kaiser Permanente Zion Medical Center 4647 Zion Avenue, San Diego, California 92120
North America / United States	Kaiser Permanente Fontana Medical Center 9961 Sierra Avenue Fontana, California 92335
North America / United States	Kaiser Permanente Orange County Anaheim Medical Center 3440 E. La. Palma Avenue Anaheim, California 92806
North America / United States	Kaiser Permanente Ontario Medical Center 2295 S. Vineyard Avenue Ontario, California 91761
North America / United States	Dartmouth-Hitchcock Medical Center One Medical Center Drive, Lebanon, New Hampshire 03756

a Blank cells in this column indicate no subjects transferred from another study site

4. STUDY SYNOPSIS GS-US-540-5774

INTERIM 2 (FINAL PART A) CLINICAL STUDY REPORT

Study 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
Name of Test Drug:	Remdesivir (GS-5734™)
Dose and Formulation:	Remdesivir (GS-5734™) for injection, 100 mg, for intravenous (IV) administration
Indication:	COVID-19
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-540-5774
Phase of Development:	Phase 3
IND No.: **EudraCT No.:**	147753 2020-000842-32
ClinicalTrials.gov Identifier:	NCT04292730
Study Start Date:	15 March 2020 (First Participant Screened)
Study End Date:	29 April 2020 (Last Participant Last Observation for the Primary Endpoint) 20 May 2020 (Last Participant Last Observation for this Report)
Principal or Coordinating Investigator:	Name: Christoph D. Spinner, MD Affiliation: Technical University of Munich School of Medicine University Hospital rechts der Isar
Gilead Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	05 August 2020
Previous Report Date(s):	26 June 2020 (Interim 1 [Part A Day 11] Clinical Study Report)

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-540-5774

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: 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
Investigators: Multicenter study
Study Centers: 105 centers globally
Publications: There were no publications at the time of this clinical study report (CSR).
Study Period: 15 March 2020 (First Participant Screened) 29 April 2020 (Last Participant Last Observation for the Primary Endpoint) 20 May 2020 (Last Participant Last Observation for this Report)
Phase of Development: Phase 3
Objectives: The purpose of this study was to provide remdesivir (RDV, GS-5734™) to participants with moderate coronavirus disease 2019 (COVID-19). The primary objective of this study was as follows: • To evaluate the efficacy of 2 RDV regimens compared to standard of care (SOC), with respect to clinical status assessed by a 7-point ordinal scale on Day 11 The secondary objective of this study was as follows: • To evaluate the safety and tolerability of RDV compared to SOC
Methodology: This Phase 3 study of RDV therapy in participants with moderate COVID-19 was conducted in 2 parts. Part A of this study was a randomized, open-label, multicenter study of RDV in adult participants with moderate COVID-19. Eligible participants were randomized in equal proportions to 1 of 3 treatment groups. No stratification was performed. Part B was a single-group multicenter study of RDV in participants with moderate COVID-19.

In Part A, approximately 600 participants meeting all eligibility criteria and who were not mechanically ventilated were randomized in a 1:1:1 ratio into 1 of the following treatment groups:

Treatment Group 1 (hereafter referred to as the RDV 5-day group): continued SOC therapy together with intravenous (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, up to an additional approximately 1000 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

This interim CSR provides the final results for participants in Part A. All data for Part A collected by the data finalization date (08 July 2020) were included in this interim analysis. The study design, statistical analyses, and results for Part B are not included in this interim CSR.

At screening, after appropriate consent or assent was obtained, or the participant was enrolled under International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator, demographic and baseline characteristics, medical history, and concomitant medications were documented. Vital signs including temperature, respiratory rate, and oxygen saturation (SpO_2) were recorded. Radiographic imaging was performed if not already available. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) testing by polymerase chain reaction (PCR) was performed; if this testing had been performed within the previous 4 days, no repeat testing was required.

If safety laboratory results from the screening day were not already available, laboratory testing, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and creatinine clearance were performed according to local practice.

Day 1 was the day of first dose administration, as recorded on the Study Treatment Administration electronic case report form.

Number of Participants (Planned and Analyzed):

Planned: Approximately 1600 participants (600 participants in Part A)

Analyzed (Part A):

- All Randomized Analysis Set: 596 participants (199 in the RDV 5-day group, 197 in the RDV 10-day group, and 200 in the SOC only group)
- Full Analysis Set (FAS) and Safety Analysis Set: 584 participants (191 in the RDV 5-day group, 193 in the RDV 10-day group, and 200 in the SOC only group)

Diagnosis and Main Criteria for Inclusion: Eligible participants had SARS-CoV-2 infection confirmed by PCR, were hospitalized with SpO_2 > 94% on room air, and had radiographic evidence of pulmonary infiltrates. Eligible participants were willing and able to provide written informed consent, had a legal representative who could provide informed consent, were enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (age ≥ 18), or willing and able to provide assent (ages ≥ 12 to < 18, where locally and nationally approved) prior to performing study procedures.
Duration of Treatment: The duration of treatment with RDV in Part A was up to 5 days for participants in RDV 5-day group and up to 10 days for participants in RDV 10-day group.
Test Product, Dose, Mode of Administration, and Batch No.: Participants were treated with RDV 100 mg for injection, which was supplied as a lyophilized solid in sterile single-use 30 mL Type I clear glass vials. This study treatment was reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion. In Part A, participants in the RDV 5-day group and the RDV 10-day group received RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5. Participants in the RDV 10-day group also received RDV 100 mg on Days 6, 7, 8, 9, and 10. The batch numbers of the RDV 100 mg for IV injection were EW1804A1, EW1805A1, EW2001A1, and EW2002A1.
Reference Therapy, Dose, Mode of Administration, and Batch No.: No study treatment was administered as a reference therapy. Participants in the SOC only group were treated according to local SOC practice.
Criteria for Evaluation: **Efficacy:** The primary endpoint of this study was clinical status assessed by a 7-point ordinal scale on Day 11. Each RDV group was compared to the SOC only group. The ordinal scale is an assessment of the clinical status of a participant at a given study day, as follows: 1. Death 2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation 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 required ongoing medical care (other than per-protocol RDV administration) 7. Not hospitalized Other endpoints of interest included the following: • Clinical status assessed by a 7-point ordinal scale on Day 14 • The proportion of participants with negative SARS-CoV-2 PCR

- Time to clinical improvement (days) defined as a ≥ 2-point improvement on the 7-point ordinal scale from baseline clinical status
- Time to ≥ 1-point improvement on the 7-point ordinal scale from baseline clinical status
- Time to recovery defined as an improvement in clinical status 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
- Time to modified recovery defined as an improvement in clinical status from a baseline score of 2 through 4 to a score of 5, 6, or 7, or an improvement from a baseline score of 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Time to room air defined as an improvement in clinical status from a baseline score of 2 through 4 to a score of 5, 6, or 7
- Duration of oxygen therapy (days)
- Shift in oxygen support status from baseline
- Duration of hospitalization (days)
- All-cause mortality at Day 28

Pharmacokinetics: Although optional pharmacokinetic (PK) sampling was included in the protocol, no samples were collected in Part A.

Safety: The secondary endpoint was the proportion of participants with treatment-emergent adverse events (TEAEs). Safety assessments included monitoring of vital signs including respiratory status, documentation of adverse events (AEs) and concomitant medications, laboratory testing performed according to SOC practice with results for white blood cell count, hemoglobin and/or hematocrit, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, AST, and any SARS-CoV-2 testing reported to the sponsor.

In addition, even if not performed as SOC, white blood cell count, hemoglobin, platelets, creatinine, creatinine clearance, glucose, total bilirubin, ALT, and AST data were collected at prespecified time points during the study.

The other endpoint of interest was the proportion of participants in the Extension Treatment Group with TEAEs.

Statistical Methods:

Efficacy: The primary analysis set for efficacy analysis was the FAS, which included all participants who were randomized into Part A of the study and received at least 1 dose of RDV if randomized to 1 of the RDV treatment groups. Participants in the SOC group who had the protocol-specified Day 1 visit were included in the FAS. Participants were grouped according to the treatment to which they were randomized for Part A.

The primary efficacy endpoint was clinical status assessed by a 7-point ordinal scale on Day 11, which was analyzed using a proportional odds model with treatment as the independent variable. The assumption of odds proportionality was assessed using a score test.

As a supportive analysis of the primary endpoint, the clinical status on Day 11 was compared between each RDV group (5-day or 10-day) and the SOC only group using a 2-sided Wilcoxon rank sum test. In addition, the primary endpoint was analyzed using a proportional odds model including treatment as the independent variable and baseline clinical status as a nominal covariate.

The change from baseline in clinical status category on Days 5, 7, 11, 14, 28, and last available assessment was summarized by treatment group using descriptive statistics and compared between each RDV group and the SOC only group using a 2-sided Wilcoxon rank sum test. The number and percentage of participants in each clinical status category for each day from baseline through Day 14, at Day 28, and at last available assessment were summarized by treatment group and within each subgroup.

The primary endpoint was analyzed for the subgroups by age, sex at birth, baseline oxygen support status, and race.

Analyses of other endpoints of interest were performed as described in the statistical analysis plan using the FAS.

Pharmacokinetics: No PK assessments were performed for this report.

Safety: The Safety Analysis Set included all participants who were randomized into Part A of the study and received at least 1 dose of RDV if randomized to 1 of the RDV treatment groups. Participants in the SOC only group who had the protocol-specified Day 1 visit were included in the Safety Analysis Set.

Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.1. Toxicity criteria specified in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 were used for assigning toxicity grades to AEs and laboratory results for analysis.

Adverse events were summarized by the number and percentage of participants. The secondary endpoint of the proportion of participants with any TEAEs was compared between each RDV group (5-day or 10-day) and the SOC only group using a Fisher's exact test. The point estimate of the treatment difference and the associated 95% CIs were provided.

Laboratory data collected during the study were analyzed based on values reported in conventional units and summarized using both quantitative and qualitative methods. For numeric laboratory results, descriptive statistics were provided by treatment group. Baseline and change from baseline were compared between each RDV group and the SOC group using the 2-sided Wilcoxon rank sum test.

Descriptive statistics were provided by treatment group for body weight, body mass index (BMI), and vital signs. Concomitant medications were summarized.

The incidence of all TEAEs was summarized for the subgroups age, sex at birth, and race.

SUMMARY OF RESULTS:

Participant Disposition: A total of 612 participants were screened, of whom 596 were randomized, and 384 received at least 1 dose of study treatment (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 any study treatment (3 were enrolled in violation of the study protocol, 8 withdrew consent, and 1 was withdrawn due to investigator discretion).

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

discontinued study treatment in the RDV 10-day group. Of the 584 participants in the Safety Analysis Set, 8.7% (51 participants) prematurely discontinued from the study (RDV 5-day group 6.3%, 12 participants; RDV 10-day group 8.8%, 17 participants; SOC only group 11.0%, 22 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), participant decision (RDV 5-day group 2.6%, 5 participants; RDV 10-day group 3.1%, 6 participants), and AE (RDV 5-day group 2.1%, 4 participants; RDV 10-day group 4.1%, 8 participants). Participants in the SOC only group were not receiving RDV and could not prematurely discontinue study treatment.

Participant Demographics and Other Baseline Characteristics: Demographic and baseline characteristics were similar among the 3 treatment groups. The majority of the participants were male (61.1%). The median age was 57 years (range: 12 to 95); the majority of the participants were White (61.3%), and the majority were not Hispanic or Latino (81.9%). The median (first quartile [Q1], third quartile [Q3]) BMI was 27.1 (24.1, 31.1) kg/m^2.

Treatment groups were balanced in other baseline disease characteristics. There were no statistically significant differences in baseline clinical status (7-point ordinal scale) among the 3 treatment groups. There were no statistically significant differences among the 3 treatment groups in baseline oxygen support status, which was derived from the 7-point ordinal scale used to assess clinical status. Most participants were on room air (not requiring oxygen support) across the 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).

Median (Q1, Q3) baseline ALT was similar among the 3 treatment groups (RDV 5-day group 30 [19, 51] U/L; RDV 10-day group 28 [21, 47] U/L; SOC only group 30 [19, 49] U/L). Median (Q1, Q3) baseline AST was similar among the treatment groups (RDV 5-day group 32 [25, 48] U/L; RDV 10-day group 34 [23, 48] U/L; SOC only group 34 [24, 49] U/L).

Median (Q1, Q3) baseline serum creatinine was 0.83 (0.71, 1.03) mg/dL in the RDV 5-day group, 0.81 (0.70, 0.93) mg/dL in the RDV 10-day group, and 0.86 (0.70, 1.00) mg/dL in the SOC only group; and median (Q1, Q3) creatinine clearance by Cockcroft-Gault was (75.0, 130.3) mL/min in the RDV 5-day group, 109.7 (86.3, 142.7) mL/min in the RDV 10-day group, and 102.7 (78.1, 129.5) mL/min in the SOC only group.

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 among the 3 treatment groups.

The 3 most commonly reported medical history preferred terms (PTs) 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 (14.5%, 28 participants)
- SOC only group — hypertension (39.0%, 78 participants), cough (14.5%, 29 participants), and pyrexia (13.5%, 27 participants)

Efficacy Results: The primary efficacy endpoint for the study was clinical status assessed using a 7-point ordinal scale on Day 11 in the FAS. Primary analysis of the primary endpoint demonstrated that treatment with RDV for 5 days resulted in greater odds of improved clinical status at Day 11 compared with treatment with only SOC ($p = 0.0174$). The comparison of treatment with RDV for 10 days versus treatment with only SOC resulted in similar odds of improved clinical status at Day 11 ($p = 0.1826$).

For participants on room air at baseline, the results were similar to results from the primary analyses. Odds of improved clinical status at 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 ($p = 0.5197$).

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 at Day 6, following completion of up to 5 days of RDV treatment ($p = 0.0361$), and at Days 8 through 14 ($p < 0.05$ at each time point). Similar results were observed in clinical status on the 7-point ordinal scale by study day for participants on room air at baseline. There were statistically significant differences between the RDV 10-day and SOC only groups in clinical status on a 7-point ordinal scale at baseline ($p = 0.0337$), Day 1 ($p = 0.0405$), Day 14 ($p = 0.0323$), Day 28 ($p = 0.0335$), and at the last available assessment ($p = 0.0227$).

There was a difference observed in the rates of hospital discharge between Days 4 and 6 in the RDV 5-day and 10-day groups. At Day 4, the percentage of participants discharged was lower in the RDV 5-day group (18.8%, 36 of 191 participants) compared with the RDV 10-day group (26.4%, 51 of 193 participants). At Day 6, this trend had reversed, with the percentage of participants discharged higher in the RDV 5-day group (48.7%, 93 participants) compared with the RDV 10-day group (40.4%, 78 participants).

Other endpoints of interest evaluated during the study included clinical status assessed using a 7-point ordinal scale on Day 14, oxygen support status, duration of hospitalization, mortality, clinical improvement, recovery, and time to room air. There were greater odds of improved clinical status at Day 14 in the RDV 5-day and 10-day groups versus the SOC only group ($p = 0.0293$ and $p = 0.0328$, respectively). There were no significant differences between either RDV group and the SOC only group in days of high-flow and low-flow oxygen support in participants who were discharged alive on or prior to Day 14. Most participants across the treatment groups showed an improvement from baseline in oxygen support status at Days 11, 14, and 28. This was particularly notable in the RDV 5-day group compared with the SOC only group through Day 14.

There were no statistically significant differences between the RDV 5-day group and the SOC only group in the proportion of participants with a $\geq$ 2-point improvement from baseline in clinical status at any time point. Higher proportions of participants in the RDV 10-day group than the SOC only group had a $\geq$ 2-point improvement from baseline in clinical status at Day 14 ($p = 0.0440$), Day 28 ($p = 0.0398$), and at the last available assessment ($p = 0.0262$). A higher proportion of participants in the RDV 5-day group had a $\geq$ 1-point improvement from baseline in clinical status compared with the SOC only group. The difference between treatment groups was statistically significant on Day 11 ($p = 0.0257$) and at the last available assessment ($p = 0.0349$). Higher proportions of participants in the RDV 10-day group than the SOC only group had a

≥ 1-point improvement from baseline in clinical status at Day 28 (p = 0.0238) and at the last available assessment (p = 0.0341). There were no statistically significant differences in the median times to ≥ 2-point and ≥ 1-point clinical improvement in the RDV 5-day and 10-day groups compared with the SOC only group.

Higher proportions of participants in the RDV 5-day group than the SOC only group achieved recovery and modified recovery, with statistically significant differences between treatment groups on Day 11 (p = 0.0386 and p = 0.0257, respectively). There were also differences between the RDV 10-day group and the SOC only group in the proportion of participants with recovery and modified recovery at Day 28 (p = 0.0269 and p = 0.0238, respectively) and at the last available assessment (p = 0.0238 and p = 0.0341, respectively), with higher proportions of participants in the RDV 10-day group than the SOC only group achieving recovery and modified recovery, respectively. There were no significant differences in the median times to recovery and modified recovery in the RDV 5-day and 10-day groups compared with the SOC only group.

There were no significant differences between the RDV 5-day group and the SOC only group in the proportion of participants with improvement to room air at any time point. Higher proportions of participants in the RDV 10-day group than the SOC only group had improvement to room air on Day 14 (p = 0.0107), Day 28 (p = 0.0186), and at the last available assessment (p = 0.0186). Median time to room air was shorter in the RDV 10-day group compared with the SOC only group (p = 0.0195). There was no statistically significant difference between the RDV 5-day and SOC only groups in time to room air.

There were no significant differences between either RDV group and the SOC only group in duration of hospitalization.

A similar percentage of participants in each treatment group died by Day 28 (RDV 5-day group 1.0%, 2 participants; RDV 10-day group 1.6%, 3 participants; SOC only group 2.0%, 4 participants). There were no statistically significant differences in time to death between either RDV group and the SOC only group.

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 at Day 11 compared with treatment with SOC only for the following subgroups: age (< 65 years; p = 0.0487) and baseline oxygen support status (room air; p = 0.0483).

Pharmacokinetics Results: No PK or pharmacodynamic assessments were performed for this report.

Safety Results: Remdesivir administered for 5 days (median [Q1, Q3] exposure, 5 [5, 5] days) and 10 days (6 [3, 10] days) was generally well tolerated.

Adverse Events

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 51.3%, 98 of 191 participants; RDV 10-day group 58.5%, 113 of 193 participants; SOC only group 46.5%, 93 of 200 participants). The difference in percentages between the RDV 10-day and SOC only groups was statistically significant (p = 0.0201).

Participants who were older (≥ 65 years) had higher rates of AEs, Grade 3 or higher AEs, and serious adverse events (SAEs) compared with those who were younger (< 65 years). Higher rates of AEs were reported in the RDV treatment groups compared with the SOC only group in participants aged < 65 years, but there were no meaningful differences among the treatment groups in participants aged ≥ 65 years.

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

- RDV 5-day group — nausea (9.9%, 19 participants), diarrhea (6.3%, 12 participants), and hypokalemia and headache (each 5.2%, 10 participants)
- RDV 10-day group — nausea (9.3%, 18 participants), hypokalemia (6.7%, 13 participants), and diarrhea and headache (each 5.2%, 10 participants)
- SOC only group — diarrhea (7.0%, 14 participants), constipation (4.5%, 9 participants), and insomnia and pyrexia (each 3.5%, 7 participants)

The incidence and types of common AEs were generally similar among the treatment groups.

The incidence of Grade 3 or higher AEs was generally similar among the treatment groups (RDV 5-day group 10.5%, 20 participants; RDV 10-day group 12.4%, 24 participants; SOC only group 12.0%, 24 participants). Adverse events considered related to study treatment were reported in 18.8% of participants (36 participants) in the RDV 5-day group and 13.0% of participants (25 participants) in the RDV 10-day group.

Similar percentages of deaths were reported in each treatment group (RDV 5-day group 1.0%, 2 participants; RDV 10-day group 1.6%, 3 participants; SOC only group 2.0%, 4 participants).

Lower percentages of participants in the RDV treatment groups had SAEs compared with the SOC only group (RDV 5-day group 4.7%, 9 participants; RDV 10-day group 5.2%, 10 participants; SOC only group 9.0%, 18 participants).

Similar percentages of AEs leading to study treatment discontinuation were reported in each RDV treatment group (RDV 5-day group 2.1%, 4 participants; RDV 10-day group 4.1%, 8 participants). Adverse events that led to premature study treatment discontinuation in > 1 participant in each RDV treatment group were as follows:

- RDV 5-day group — rash (1.0%, 2 participants)
- RDV 10-day group — ALT increased (1.6%, 3 participants) and AST increased (1.0%, 2 participants)

Hepatic Safety

Hepatic AEs were reported in a similar percentage of participants in each treatment group (RDV 5-day group 7.9%, 15 of 191 participants; RDV 10-day group 10.4%, 20 of 193 participants; SOC only group 5.5%, 11 of 200 participants). The overall pattern and types of hepatic AEs were generally similar among the treatment groups; the most commonly reported hepatic AEs for each treatment group were as follows:

- RDV 5-day group — ALT increased (4.2%, 8 participants), AST increased (2.6%, 5 participants), and hypertransaminasemia and transaminases increased (each 1.6%, 3 participants)

- RDV 10-day group — ALT increased (3.6%, 7 participants) and AST increased and hypertransaminasemia (each 3.1%, 6 participants)
- SOC only group — ALT increased and AST increased (each 2.5%, 5 participants) and hypertransaminasemia (1.5%, 3 participants)

The combined numbers of participants in each treatment group with 1 or more transaminase-related AEs (using the s ALT increased, AST increased, hepatic enzymes increased, hypertransaminasemia, liver function test increased, and transaminases increased) were 15 participants (7.9%) in the RDV 5-day group, 18 participants (9.3%) in the RDV 10-day group, and 10 participants (5.0%) in the SOC only group.

The only hepatic SAE was reported in 1 participant in the RDV 10-day group (Grade 3 ALT increased) and was considered not related to study treatment. Grade 3 or higher study treatment-related hepatic AEs were reported in a similar percentage of participants in each treatment group. Hepatic AEs that led to premature study treatment discontinuation were reported as follows: RDV 5-day group 0.5%, 1 participant; RDV 10-day group 3.1%, 6 participants.

Median ALT increased and median AST decreased in all treatment groups during the study. 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 10-day groups compared with the SOC only group.

Renal Safety

The incidence of renal-related AEs was similar among the treatment groups (RDV 5-day group 1.6%, 3 of 191 participants; RDV 10-day group 2.1%, 4 of 193 participants; SOC only group 2.0%, 4 of 200 participants).

The only renal-related SAE was reported in 1 participant in the SOC only group (Grade 4 acute kidney injury).

Between baseline and Day 14, median serum creatinine decreased and median creatinine clearance increased in both RDV treatment groups. The incidence of Grade 3 or 4 laboratory abnormalities of increased creatinine and decreased creatinine clearance was lower in the RDV 5-day and 10-day groups compared with the SOC only group.

Laboratory Evaluations

There were no clinically relevant changes from baseline within any treatment group or differences among the treatment groups in median values for hematology parameters. Median values for hematology and chemistry parameters were generally within reference ranges.

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). The incidence of all graded individual laboratory abnormalities was generally similar among the treatment groups. Decreased creatinine clearance was less common in the RDV 5-day group (14.6%, 26 of 178 participants) compared with the SOC only group (30.1%, 55 of 183 participants). Grade 3 or 4 laboratory abnormalities were reported in a similar percentage of participants in each treatment group (RDV 5-day group 12.8%, 23 participants; RDV 10-day group 16.2%, 29 participants; SOC only group 18.3%, 34 participants).

Vital Signs, Physical Findings, and Other Observations Related to Safety There were no clinically relevant changes from baseline in vital signs parameters or body weight.
CONCLUSIONS: The conclusions from this interim analysis of Study GS-US-540-5774 are as follows: 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. 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.

4.1. Protocol Amendments and Description

Amendment 1.0:	**Date: 15 March 2020**
Rationale:	Herein is a summary of the major changes made to the Original protocol dated 24 February 2020 and reflected in Amendment 1.0 dated 15 March 2020. • Revised primary endpoint to allow for more robust analysis • Expanded number of sites and subjects globally to meet urgent needs • Divided enrollment into two Parts: A and B • Included an Extension Treatment Group during enrollment to extend RDV therapy • Inserted EudraCT Number and Clinical Trials.gov identifiers • Provided further clarification to the inclusion and exclusion criteria • Included parameters for adolescent participants and adolescent dosing • Revised statistical methodology and analysis due to changes in endpoints and study design • Clarified requirements for oxygen supplementation • Additional formatting and administrative updates and minor grammatical corrections were made throughout the document but are not explicitly outlined in the changes below. Specific changes are presented herein as ***bold and italicized*** or ~~strikethrough~~.

Amendment 2.0:	**Date: 29 April 2020**
Rationale:	Herein is a summary of the major changes made to Protocol Amendment 1.0 dated 15 March 2020 and reflected in Protocol Amendment 2.0 dated 29 April 2020. • Increased number of centers globally • Revised section on pediatric dosing with minor edits • Added language around discontinuation of study medication • Clarified exclusion criteria requirements • Clarified section on concomitant medications disallowed during study and revised concomitant medication assessment window • Added further guidance on pharmacokinetic (PK) assessments and sample collection timepoints • Added further guidance on virologic testing • Clarified assessment guidance for laboratory abnormalities • Revised sections on other endpoints of interest and planned analyses • Incorporated changes per the latest administrative amendment (v3) • Additional formatting and administrative updates and minor grammatical corrections were made throughout the document but are not explicitly outlined in the changes below. Specific changes are presented herein as ***bold and italicized*** or ~~strikethrough~~.

4.2. GS-US-540-5774: List of Principal Investigators

Geographic Region/ Country Principal Investigator	Study Site
Asia Pacific / South Korea	Seoul Medical Center 156 Sinnae-ro, Jungnang-gu, Seoul, 02053, Korea
Asia Pacific / South Korea	National Medical Center 245, Eulji-ro, Jung-gu, Seoul, 04564, Republic of Korea
Asia Pacific / South Korea	Kyungpook National University Hospital 130 Dongdeok-ro, Jung-gu, Daegu, 41944, Korea
Asia Pacific / Hong Kong	Prince of Wales Hospital Room 114037, Clinical Sciences Building, Shatin, New Territories, Hong Kong
Asia Pacific / Hong Kong	Princess Margaret Hospital Department of Medicine and Geriatrics, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong
Asia Pacific / Singapore	National University Hospital 1E Kent Ridge Road, Singapore, 119228, Singapore
Asia Pacific / Singapore	Singapore General Hospital Outram Rd, Singapore, 169608, Singapore
Asia Pacific / Singapore	National Centre for Infectious Diseases, Tan Tock Seng Hospital 16 Jalan Tan Tock Seng, Singapore, 308442, Singapore
Asia Pacific / Taiwan	National Taiwan University Hospital No.7, Chung Shan S. Rd, Zhongzheng Dist, Taipei City, Taiwan, 10002, Taiwan
Asia Pacific / Taiwan	Kaohsiung Veterans General Hospital No. 386, Da-Chung 1st. Road., Zuoying Dist. Kaohsiung, Taiwan, 81362, Taiwan
Asia Pacific / Taiwan	China Medical University Hospital No.2, Yuh-Der Road, North District, Taichung, Taiwan, 40447, Taiwan
EMEA / France	CHU Pellegrin Service des Maladies Infectieuses et Tropicales, Bordeaux Cedex, 33076
EMEA / France	CHU de Nantes-Hôtel Dieu, Place Alexis Ricordeau, Nantes Cedex 1, 44093
EMEA / France	CHU de Montpellier-Hôpital Gui de Chauliac 80 Avenue Augustin Fliche, Montpellier Cedex 05, 34295
EMEA / Germany	Universitatsklinikum Duesseldorf, Klinik fur Gastroenterologie, Hepatologie und Infektiologie Moorenstrasse 5, Germany, 40225 Duesseldorf

Geographic Region/ Country Principal Investigator	Study Site
EMEA / Germany	Klinikum St. Georg gGmbH Klinik fur Infektiologie, Tropenmedizin, Nephrologie und Rheumatologie Delitzscher Strasse 141, Germany, 04129 Leipzig
EMEA / Germany	Universitatsklinikum Hamburg-Eppendorf, Martinistr. 52, Germany, 20246 Hamburg
EMEA / Germany	Universitatsklinikum Schleswig-Holstein, Campus Kiel, Klinik fur Innere Medizin I, Arnold-Heller-Strasse 3, Germany, 24105 Kiel
EMEA / Germany	Klinikum rechts der Isar der TU Munchen, Klinik und Poliklinik Innere Medizin 2, Ismaningerstr. 22, Germany, 81675 Munchen
EMEA / Germany	Munchen Klinik Schwabing, Klinik fur Hamatologie, Onkotogie, Immunologie, Palliativmedizin, Infektiologie und Tropenmedizin Koener Platz 1, Germany, 80804 Munchen
EMEA / Italy	UOC Malattie Infettive I, Fondazione IRCCS Policlinico San Matteo Piazzale Golgi, 19, Pavia, 27100
EMEA / Italy	UO Malattie Infettive, IRCCS Ospedale San Raffaele , via Stamira D'Ancona 20, Milano 20127
EMEA / Italy	ASST Spedali Civili Di Brescia Piazza Spedali Civili 1, Brescia, 25123
EMEA / Italy	UOC Malattie Infettive e Tropicali, Azienda Ospedaliera di Padova Via Giustiniani 1, Padova, 35121
EMEA / Italy	Ospedale Guglielmo da Saliceto AUSL di Piacenza, via Taverna 49, Piacenza, 29100
EMEA / Italy	Clinica Universitaria Malattie Infettive, Ospedale Amedeo di Savoia, Corso Svizzera 164, Torino, 10149
EMEA / Italy	Dipartimento di Malattie Infettive, Malattie Infettive I- Malattie Infettive III, ASST Fatebenefratelli Sacco Ospedale Luigi Sacco Via G.B. Grassi 74, Milano, 20157
EMEA / Italy	UO Malattie Infettive, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, via Francesco Sforza, 28, Milano, 20122
EMEA / Italy	UO Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma Via Gramsci 14, Parma, 43126
EMEA / Italy	UOC Malattie Infettive ad Alta Intensita di Cure, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani IRCCS, via Portuense 292, Rome, 00149
EMEA / Italy	ASST Cremona Viale Concordia 1, Cremona, 26100
EMEA / Netherlands	Leids Universitair Medisch Centrum Albinusdreef 2, Leiden, 2333 ZA

Geographic Region/ Country Principal Investigator	Study Site
EMEA / Spain	Hospital Universitario La Paz Paseo de la Castellana, 261, Madrid, 28046
EMEA / Spain	Hospital Regional Universitario de Malaga, Avda. Carlos Haya s/n, Malaga, 29010
EMEA / Spain	Hospital Universitario Virgen del Rocio, Avenida Manuel Siurot, s/n, Sevilla, 41013
EMEA / Spain	Hospital Universitario de Cruces Plaza de Cruces, 12, Barakaldo, Bizkaia, 48903
EMEA / Spain	Hospital Universitario Fundacion Jimenez Diaz, Av. Reyes Católicos 2 Madrid, 28040
EMEA / Spain	Hospital Universitario 12 de Octubre, Avenida de Cordoba s/n, Madrid, 28041
EMEA / Spain	Hospital Universitario Ramon y Cajal, Ctra. De Colmenar Viejo. Km. 9.100, Madrid, 28034
EMEA / Spain	Hospital Universitario Principe de Asturias, Carretera Alcala Meco s/n, Alcalca de Henares, Madrid, 28805
EMEA / Spain	Hospital Clinic de Barcelona Calle Villarroel 170, Barcelona, 08036
EMEA / Switzerland	Servizio Malattie Infettive, Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano, Sede Civico, Via Tesserete 46, Lugano Ticino, 6903
EMEA / Switzerland	Hôpitaux Universitaires de Genève, Rue Gabrielle- Perret-Gentil 4, Geneve 14, 1211
EMEA / Switzerland	Universitaets Spital Zuerich, Raemistrasse 100, Zuerich 8091
EMEA / United Kingdom	Royal Free London Hospital Pond Street, Hampstead, London, NW3 2QG
EMEA / United Kingdom	University College Hospital 235 Euston Road, London NW1 2BU
EMEA / United Kingdom	Imperial College Healthcare NHS Trust Praed Street London, W2 1NY
EMEA / United Kingdom	NHS Greater Glasgow & Clyde Queen Elizabeth University Hospital, 1345 Govan Road Glasgow, G51 4TF

Geographic Region/ Country Principal Investigator	Study Site
EMEA / United Kingdom	Hull University Teaching Hospitals NHS Trust Castle Road, Cottingham, Hull, HU16 5JQ
EMEA / United Kingdom	King's College Hospital NHS Foundation Trust King's College Hospital, Denmark Hill, London, SE5 9RS
EMEA / United	North Manchester General Hospital Delaunays Road Manchester, M8 5RB
EMEA / United Kingdom	London North West University Healthcare NHS Trust Northwick Park Hospital Watford Road, Harrow, HA1 3UJ
North America / United States	Icahn School of Medicine at Mount Sinai One Gustave L. Levy Place Box 1642 New York, NY 10029
North America / United States	Mount Sinai West 1000 10th Avenue Suite 2T New York, NY 10019
North America / United States	Mount Sinai Beth Israel 350 East 17th Street 3rd Floor New York, NY 10003
North America / United States	Hackensack University Medical Center 30 Prospect Avenue, Hackensack, New Jersey 07601
North America / United States	Henry Ford Hospital 2799 West Grand Boulevard, Detroit, Michigan,48202
North America / United States	James J Peters VA Medical Center 130 West Kingsbridge Road, Bronx, New York 10468
North America / United States	The Center for Cancer Prevention and Treatment at St. Joseph Hospital of Orange 1100 West La Veta Avenue, Orange County, California 92868

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	University of Colorado Denver, University of Colorado Hospital 12605 East 16th Ave Aurora, Colorado,80045
North America / United States	MultiCare Deaconess Hospital 800 W 5th Ave Spokane, Washington 99204
North America / United States	Temple University Hospital 3401 North Broad Street, Philadelphia, Pennsylvania 19140
North America / United States	Hospital of the University of Pennsylvania 3400 Spruce Street Philadelphia, Pennsylvania, 19104
North America / United States	Providence Regional Medical Center Everett 1330 Rockefeller Avenue, Suite 440, Everett, Washington 98201
North America / United States	Swedish Medical Center – First Hill 747 Broadway, Seattle, Washington, 98122
North America / United States	Baylor University Medical Center 3500 Gaston Ave Dallas, Texas,75246
North America / United States	Baylor Scott & White All Saints Medical Center -Forth Worth 1400 8th Ave Fort Worth, Texas, 76104
North America / United States	Baylor Scott & White Medical Center -Temple 2401 S 31st St Temple, Texas, 76508
North America / United States	Houston Methodist Hospital 6565 Fannin Street, Houston, Texas, 77030
North America / United States	IU Health Methodist Hospital 1701 N Senate Boulevard, Indianapolis, Indiana,46202
North America / United States	Providence Saint John's Health Center 2121 Santa Monica Blvd, Santa Monica, California, 90404

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	University Hospitals Cleveland Medical Center 11100 Euclid Ave, Cleveland, Ohio, 44106
North America / United States	John H. Stroger Jr. Hospital of Cook County 1969 West Ogden Ave, Chicago, Illinois 60612
North America / United States	University of Iowa Hospitals and Clinics 200 Hawkins Drive, Iowa City, Iowa 52242
North America / United States	UT Southwestern Medical Center Amelia Court, HIV Research Clinic 1936 Amelia Court 2nd Floor Dallas, Texas, 75235
North America / United States	William P. Clements Jr. University Hospital 6201 Harry Hines Blvd Dallas, Texas 75390
North America / United States	The University of Michigan Hospitals & Health System 1500 East Medical Center Drive, Ann Arbor, Michigan, 48109
North America / United States	Inova Fairfax Medical Campus 3300 Gallows Road, Falls Church, Virginia 22042
North America / United States	Sutter Medical Center Sacramento 2825 Capitol Ave, Sacramento, California 95816
North America / United States	North Shore University Hospital 300 Community Drive Manhasset, New York, 11030
North America / United States	Long Island Jewish Medical Center 270-05 76th Ave New Hyde Park, NY 11040
North America / United States	Virginia Mason Medical Center 1100 9th Avenue, Seattle, Washington 98101
North America / United States	MultiCare Tacoma General Hospital 315 Martin Luther King Jr. Way, Tacoma, Washington 98405

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	New York Presbyterian Hospital/Weill Cornell Medical Center 525 East 68th Street, New York, New York 10065
North America / United States	Brigham and Women's Hospital 75 Francis Street, Boston, Massachusetts 02115
North America / United States	Kaiser Permanente Northwest – Center for Health Research 3800 N. Interstate Ave, Portland, Oregon 97227
North America / United States	University of Chicago 5841 South Maryland Avenue, Chicago, Illinois 60637
North America / United States	Robert Wood Johnson University Hospital New Brunswick 1 RWJ Place, New Brunswick, New Jersey 08901
North America / United States	Danbury Hospital 24 Hospital Avenue, Danbury, Connecticut 06810
North America / United States	Yale-New Haven Hospital 20 York Street, New Haven, Connecticut 06510
North America / United States	Tufts Medical Center 800 Washington Street, Boston, Massachusetts 02111
North America / United States	Providence St. Vincent Medical Center 9205 SW Barnes Road, Portland, Oregon 97225
North America / United States	St. Joseph's University Medical Center 703 Main Street, Paterson, New Jersey 07503
North America / United States	Mayo Clinic 200 First St SW, Rochester, Minnesota 55905

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	Hoag Memorial Hospital Presbyterian One Hoag Drive, Newport Beach, California 92663
North America / United States	VCU Health Medical Center 1250 East Marshall Street, Richmond Virginia 23298
North America / United States	Rush University Medical Center 1653 W Congress Parkway, Chicago, Illinois 60612
North America / United States	El Camino Hospital 2500 Grant Road, Mountain View, California 94040
North America / United States	Kaiser Permanente Oakland Medical Center 3600 Broadway Oakland, California, 94611
North America / United States	Kaiser Permanente San Francisco Medical Center 2425 Geary Blvd San Francisco, California 94115
North America / United States	Kaiser Permanente South San Francisco Medical Center 1200 El Camino Real San Francisco, California 94080
North America / United States	Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center 330 Brookline Avenue, Boston, Massachusetts 02215
North America / United States	Stanford University School of Medicine 300 Pasteur Drive, Stamford, California 94305
North America / United States	The Miriam Hospital 164 Summit Avenue Providence, Rhode Island 02904
North America / United States	Dartmouth-Hitchcock Medical Center One Medical Center Drive, Lebanon, New Hampshire 03756

5. STUDY SYNOPSIS GS-US-540-5776

FINAL CLINICAL STUDY REPORT

Study 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
Short Title:	Adaptive COVID-19 Treatment Trial (ACTT)
Name of Test Drug:	Remdesivir (RDV, GS-5734™)
Dose and Formulation:	Remdesivir (GS-5734) for injection, 150 mg or 100 mg, for intravenous (IV) administration
Indication:	Coronavirus disease 2019 (COVID-19)
Sponsor:	Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) 5601 Fishers Lane Bethesda, MD 20892 USA
Study No.:	DMID Protocol Number 20-0006 INSIGHT Protocol Number 010 Gilead Protocol Number CO-US-540-5776
Phase of Development:	Phase 3
IND No.:	147771
EudraCT No.:	2020-001052-18
ClinicalTrials.gov Identifier:	NCT04280705
Study Start Date:	21 February 2020 (First Participant Screened)
Study End Date:	21 May 2020 (Last Participant Last Observation)
Principal or Coordinating Investigator:	Name: John Beigel, MD Affiliation: Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Gilead Medical Monitor:	Name: PPD Telephone: PPD
Report Date:	23 August 2020

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

DMID Protocol Number 20-0006/INSIGHT Protocol Number 010/
Gilead Study CO-US-540-5776

Sponsor

Division of Microbiology and Infectious Diseases (DMID)

National Institute of Allergy and Infectious Diseases

National Institutes of Health
5601 Fishers Lane
Bethesda, MD 20892
USA

Sponsor of European Union/United Kingdom Sites

University of Minnesota
Regents of the University of Minnesota
600 McNamara Alumni Center
200 Oak Street SE
Minneapolis, MN 55455
USA

Study Drugs Provided By:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults **Short Title**: Adaptive COVID-19 Treatment Trial (ACTT)
Investigators: Multicenter study
Study Centers: A total of 60 main study sites globally
Publications: Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. N Engl J Med 2020a. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report [Supplementary Appendix]. N Engl J Med 2020b.

Study Period:

21 February 2020 (First Participant Screened)
21 May 2020 (Last Participant Last Observation)

Phase of Development: Phase 3

Objectives:

The primary objective of this study was as follows:

- To evaluate the clinical efficacy, as assessed by time to recovery, of remdesivir (RDV, GS-5734™) compared with the control arm in adults hospitalized with coronavirus disease 2019 (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

Additional secondary objectives were as follows:

- To evaluate the clinical efficacy of RDV compared with the control arm as assessed by:

— Clinical Severity

  - Ordinal scale:
    - Time to an improvement of 1 category and 2 categories from Day 1 (baseline) using an ordinal scale
    - Clinical status using ordinal scale at Days 3, 5, 8, 11, 15, 22, and 29
    - Mean change in the ordinal scale from Day 1 to Days 3, 5, 8, 11, 15, 22, and 29
  - National Early Warning Score (NEWS):
    - Time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurred first
    - Change from Day 1 to Days 3, 5, 8, 11, 15, and 29
  - Oxygenation:
    - Oxygenation use up to Day 29
    - Incidence and duration of new oxygen use during the study
  - Noninvasive ventilation/high-flow oxygen:
    - Noninvasive ventilation/high-flow oxygen use up to Day 29
    - Incidence and duration of new noninvasive ventilation or high-flow oxygen use during the study
  - Invasive mechanical ventilation/extracorporeal membrane oxygenation (ECMO):
    - Ventilator/ECMO use up to Day 29

- Incidence and duration of new mechanical ventilation or ECMO use during the study
- Hospitalization
  - Duration of hospitalization (days)
- Mortality
  - 14-day mortality
  - 28-day mortality

- To evaluate the safety of RDV compared with the control arm as assessed by:
  - Cumulative incidence of serious adverse events (SAEs) through Day 29
  - Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events (AEs) through Day 29
  - Discontinuation or temporary suspension of infusions (for any reason)
  - Changes in white blood cell count with differential, hemoglobin, platelets, creatinine, glucose, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and prothrombin time over time (analysis of laboratory test values in addition to AEs noted above)

Methodology: This study was a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. The study was designed as an adaptive trial. The first novel therapeutic agent tested was RDV with placebo as the comparator arm. There was interim monitoring to allow early stopping for futility, efficacy, or safety. An independent Data and Safety Monitoring Board actively monitored interim data to make recommendations about early study closure or changes to study arms.

The study randomized participants 1:1 to placebo or RDV. In the absence of an established treatment, the use of placebo was justified. Randomization was stratified by site and severity (severe versus mild-to-moderate). Severe disease was defined as requiring mechanical ventilation, requiring oxygen, a peripheral oxygen saturation (SpO_2) ≤ 94% on room air, or 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.

Number of Participants (Planned and Analyzed):
Planned: Approximately 572 participants to achieve 400 recoveries Analyzed:

- Intent-to-Treat (ITT) Population: 1062 (RDV, 541 participants; placebo, 521 participants)
- As Treated Population: 1048 (RDV, 532 participants; placebo, 516 participants)

Diagnosis and Main Criteria for Inclusion: Eligible participants were male and nonpregnant female adults aged ≥ 18 years at the time of enrollment who had been admitted to hospital with symptoms suggestive of COVID-19, had laboratory-confirmed documented severe acute respiratory syndrome coronavirus 2 infection as determined by polymerase chain reaction or other commercial or public health assay in any specimen, illness of any duration, and at least 1 of the following: radiographic infiltrates by imaging (chest x-ray, computed tomography scan, etc), SpO_2 levels ≤ 94% on room air, requiring supplemental oxygen, or requiring mechanical ventilation.
Duration of Treatment: The duration of treatment with RDV or placebo was up to 10 days.
Test Product, Dose, Mode of Administration, and Batch No.: Remdesivir provided as a lyophilized formulation containing 150 mg or 100 mg of RDV reconstituted with sterile water for injection and diluted into intravenous (IV) infusion fluids prior to IV infusion. Remdesivir 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, infusions were no longer administered. The total treatment course was not to exceed 10 calendar days even if an infusion was missed. The following batch numbers of RDV were used in this study: EW1603A1 (150 mg); EW1802A1, EW1805A1, and EW2002A1 (100 mg).
Reference Therapy, Dose, Mode of Administration, and Batch No.: Matching placebo lyophilized formulation (150 mg or 100 mg equivalent), administered as IV infusion, was identical in physical appearance to the active lyophilized formulation and contained the same inactive ingredients. An equal volume of matching placebo was administered at the same schedule as the active study treatment, given at the same time each day (± 2 hours for medication scheduling). Due to limitations on placebo supply, normal saline was given at some sites at an equal volume as a placebo in place of the lyophilized formulation; IV bags of study treatment (both the active and the placebo) were masked with an opaque bag to maintain the blind. The following batch numbers of placebo-to-match were used in this study: EW1601A1 (lyophilized); EW1801A1 (lyophilized).
Criteria for Evaluation: **Efficacy:** 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. The key secondary endpoint was the distribution of clinical status (8-point ordinal scale) on Day 15.

The other secondary efficacy endpoints were as follows: ordinal outcome assessed daily while hospitalized and on Days 15, 22, and 29; NEWS assessed daily while hospitalized and on Days 15 and 29; days of supplemental oxygen (if applicable); days of noninvasive ventilation/high-flow oxygen (if applicable); days of invasive mechanical ventilation/ECMO (if applicable); days of hospitalization; and date and cause of death (if applicable).

Pharmacokinetics (PK)/Pharmacodynamics (PD): No PK/PD assessments were performed for this report.

Safety: The safety endpoints included the cumulative incidence of SAEs through Day 29, cumulative incidence of Grade 3 and 4 clinical, and/or laboratory AEs through Day 29. Other safety evaluations include discontinuation or temporary interruption of study treatment infusions (for any reason), clinical laboratory evaluations (changes in laboratory values for hematology and chemistry parameters), pre-existing medical conditions, prior/concomitant medications, pregnancy, vital signs, and physical examinations.

Statistical Methods: This study was designed to achieve 85% power for detecting a recovery rate ratio (RRR, the instantaneous "risk" of recovery ratio) of 1.35 with a 2-sided type I error rate of 5%. Enrollment continued through 20 April 2020 to ensure at least 400 recoveries and to address subgroup analysis.

Efficacy: The primary analysis was performed on the ITT Population, which included all participants who were randomized. The primary analysis used the stratified log-rank test to compare treatment to control with respect to time to recovery. The treatment RRR estimate and its CI were estimated from a stratified Cox model. Stratification was based on mild-to-moderate versus severe disease at randomization. Multiple supplemental and sensitivity analyses were performed, including but not limited to the following: an estimation of RRR using Cox proportional hazards models, in which participants who died prior to recovering were treated as experiencing a competing risk in the Fine-Gray proportional hazards regression model; an analysis in which a Cox model was fit with binary indicators for treatment group and disease severity, as well as their interaction term; a sensitivity analysis for unsustained recoveries (readmittance for hospitalization); an analysis in which participants who took medications of interest were censored at time of medication use; an analysis in which participants who were unblinded were censored at the time of unblinding; and an analysis in which participants in the placebo group who had crossover treatment with RDV were censored at the time of retreatment.

For the key secondary endpoint, the outcome was analyzed using a proportional odds model with treatment arm and disease severity as covariates for both the ITT and As Treated Populations. Similar analyses were conducted by replacing disease severity with other subgroups as a covariate. Sensitivity analyses were performed on the ITT Population to account for participants who were unblinded and placebo participants who were crossover-treated with RDV. A sensitivity analysis was performed on the ITT Population to account for participant use of any medications of interest prior to the Day 15 assessments; the participant's last clinical status score prior to medication of interest use was used as their

Day 15 outcomes. Multiple supplemental analyses of this key secondary outcome were performed to determine time to improvement by at least 1 and 2 categories in the clinical 8-point ordinal scale. The log-rank test was performed to test whether the Kaplan-Meier (KM) curves differ between treatment arms, as well as to estimate the median improvement time and its 95% CI. Improvement rate ratio (IRR) and its 95% CI were estimated from a Cox proportional hazards model. These analyses for time to improvement (at least 1 and 2 categories) were repeated such that participants who were unblinded and retreated with RDV were censored at the time of RDV treatment initiation. In addition, a subgroup analysis for time to improvement among participants enrolled with a clinical score of 7 was performed using the retreatment censoring plan. Moreover, these analyses for time to improvement by at least 2 categories were repeated on a 7-point ordinal scale such that categories 1 and 3 of the 8-point ordinal scale were combined into the lowest category. The distribution (ie, number, percentage, and 95% CI) of clinical 8-point ordinal scale was summarized by treatment group and study visit Days 1, 3, 5 8, 11, 15, 22, and 29 in both the ITT and As Treated Populations.

The median time to discharge or to a NEWS of ≤ 2 and 95% CI were summarized by treatment group with the hazard ratio (HR) and log-rank p-values for both the ITT and As Treated Populations; differences in time-to-event endpoints by treatment arm were summarized with KM curves with number at risk, HR, and log-rank p-values. The mean (standard deviation) of change from baseline in NEWS was reported by treatment arm and study visit Days 3, 5, 8, 11, 15, and 29 in both the ITT and As Treated Populations.

For the secondary analyses that involved duration (ie, days of oxygenation, noninvasive ventilation/high-flow oxygen, invasive mechanical ventilation/ECMO, and hospitalization), the total duration was the sum of all reported days, regardless of whether the days occurred consecutively or in disjointed intervals. The analyses were performed on the ITT and As Treated Populations. Median days and quartiles were presented by treatment arm.

For the secondary analyses that involved incidence of new use of respiratory support (oxygen use, noninvasive ventilation/high-flow oxygen, invasive mechanical ventilation/ECMO) among participants who were not on the modality of oxygen support under evaluation at baseline, the number of participants reporting new use, incidence rate, and 95% CI were reported by treatment arm. The analyses were performed on both the ITT and As Treated Populations. The median days and quartiles of duration of new use were reported by treatment arm.

Subgroup analyses for the efficacy outcomes evaluated the treatment effect across the following subgroups: geographic region, race, comorbidities, age, sex, duration of symptoms prior to enrollment, and severity of disease.

Pharmacokinetics/Pharmacodynamics: No PK/PD assessments were performed for this report.

Safety: Safety was analyzed on the As Treated Population, which included all randomized participants who received any study treatment infusion, even if the infusion was halted or slowed. Safety endpoints included death through Day 29, SAEs, and nonserious Grade 3 and 4 AEs. These events were analyzed univariately and as a composite endpoint.

An overall summary by treatment arm and disease severity of AEs included participants with at least 1 of the following: AE, related AE, SAE, related SAE, AE leading to early termination, and unanticipated problem. Serious adverse events or nonserious AEs occurring in 5% of participants (by Medical Dictionary for Regulatory Activities preferred term) in any treatment arm are presented by system organ class and preferred term for each treatment arm, disease severity and overall. Each AE was counted once for a given participant and graded by severity and relationship to COVID-19 or study treatment. Adverse events were coded using the Medical Dictionary for Regulatory Activities (Version 23.0). Rates of Grade 3 and 4 AE occurrence and rates of SAE occurrence were compared between treatment arms using Barnard's exact test.

Analyses of mortality were performed on the ITT and As Treated Populations. The number of participants who died by Day 15 and Day 29, and the 14- and 28-day crude mortality rate, are presented by treatment arm; the analysis was repeated treating participants who died after unblinding as alive; and a similar analysis was repeated treating placebo participants who died after crossover treatment with RDV as alive. Mortality through Day 15 and Day 29 was analyzed as a time-to-event endpoint and presented with median time to event along with 95% CIs for each treatment group along with the HR estimate and stratified log-rank p-values. Differences in time-to-event endpoints by treatment were summarized with KM curves. The ITT summaries were repeated censoring placebo participants who were retreated with RDV at the time of retreatment. Similarly, the summaries were repeated censoring participants who were unblinded at the time of unblinding.

Further, the composite endpoint of the occurrence of death, an SAE, or Grade 3 or 4 AE was analyzed as a time-to-event outcome and is presented with median time-to-event with 95% CI for each treatment arm, the HR estimate, and log-rank p-values. Differences in time-to-event endpoints by treatment will be summarized with KM curves.

Laboratory safety parameters were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (July 2017). The distribution of abnormal chemistry and hematology laboratory results, and Grade 3 and 4 chemistry and hematology laboratory results, are presented by maximum severity, time point, disease severity, and treatment group. Descriptive statistics for the absolute results and change from baseline for each chemistry and hematology laboratory parameter were summarized by time point, disease severity, and treatment group. Vital signs were assessed as part of the NEWS and were listed. The use of concomitant medications during the study was summarized by Anatomical Therapeutic Classification (ATC) code (ATC1 and ATC2), disease severity, and treatment group for the As Treated Population. Participants reporting use of medications of interest was summarized by disease severity and treatment group.

SUMMARY OF RESULTS:

Participant Disposition and Demographics:

A total of 1114 participants were screened, of whom 1062 were randomized and 1048 received at least 1 dose of study treatment (RDV 10-day group, 531 participants; placebo group, 517 participants). One participant was randomized to placebo but received RDV. A total of 14 randomized participants did not receive study treatment because they did not meet the eligibility criteria or withdrew consent.

A total of 517 participants in the RDV 10-day group and 508 participants in the placebo group completed the study through Day 29, recovered, or died. A total of 23 participants (RDV 10-day group, 14 participants; placebo group, 9 participants) discontinued the study before Day 29.

A total of 51 participants (RDV 10-day group, 16 participants; placebo group, 35 participants) were unblinded to their treatment and 26 participants in the placebo group were treated with RDV during follow-up.

Demographics and baseline characteristics were similar between the RDV 10-day and placebo groups. Most participants in the ITT Population were male (64%), mean age was 58.9 years (range: 21 to 95 years); most were white (53%) and not Hispanic/Latino (71%). The mean (SD) body mass index was 30.60 (7.52) kg/m^2.

Most participants (85%, 903 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.

Most participants had 1 (26%) or 2 or more (55%) of the 13 prespecified coexisting conditions at enrollment. The most commonly reported comorbidities were hypertension (51%), obesity (45%), and type 2 diabetes mellitus (31%). Baseline clinical status score distribution (8-point ordinal scale) was similar between the 2 treatment groups. A total of 285 participants (27%) had a clinical status of 7 (hospitalized, receiving invasive mechanical ventilation or ECMO), 193 participants (18%) had a clinical status of 6 (hospitalized, receiving noninvasive ventilation or high-flow oxygen devices), 435 participants (41%) had a clinical status of 5 (hospitalized, requiring supplemental oxygen), and 138 participants (13%) had a clinical status of 4 (hospitalized, not requiring supplemental oxygen, requiring ongoing medical care [COVID-19-related or otherwise]). There were 11 participants (1%) who had missing ordinal scale data at enrollment.

Efficacy Results:

Primary Endpoint

A statistically significant shorter median time to recovery was observed for participants in the RDV 10-day group (10 days [95% CI: 9, 11]) than those in the placebo group (15 days [95% CI: 13, 18]) (RRR 1.29; 95% CI: 1.12, 1.49; $p < 0.001$). The KM curves, representing estimates of cumulative recoveries, diverged at Day 5 and remained separated through Day 28, suggesting a higher proportion of recoveries in the RDV 10-day group versus the placebo group starting from Day 5 up to Day 28.

When time to recovery was analyzed within each randomized disease severity stratum, the following were observed:

- Severe disease stratum at randomization: The median time to recovery was shorter in the RDV 10-day group (n = 459) than in the placebo group (n = 444), with a median of 12 days (95% CI: 10, 14) to recovery in the RDV 10-day group versus 19 days (95% CI: 16, 21) in the placebo group (RRR 1.34; 95% CI: 1.14, 1.58). The KM curves diverged after approximately Day 4, suggesting a higher proportion of recoveries in the RDV 10-day group versus the placebo group starting from Day 4.
- Mild-to-moderate disease stratum at randomization: The median time to recovery was numerically shorter in the RDV 10-day group (5 days; 95% CI: 4, 6; n = 82) than in the placebo group (7 days; 95% CI: 5, 9; n = 77) (RRR 1.10; 95% CI: 0.80, 1.53).

In general, the results of the analysis on the As Treated Population and the prespecified sensitivity analyses of the primary endpoint were consistent with that of the primary analysis in the ITT Population.

Key Secondary Endpoint

The odds of improvement in the ordinal score at Day 15 were significantly higher in the RDV 10-day group than in the placebo group, as determined by a proportional odds model (odds ratio for improvement, 1.6; 95% CI: 1.3, 1.9; $p < 0.001$). Results of 3 sensitivity analyses accounting for participants who were unblinded, for participants who received placebo then were unblinded and crossed over to RDV treatment, and for participants who took restricted medications before Day 15 (ie, the participant's last clinical status score prior to medication/therapy use was used as the participant's Day 15 outcome), were consistent with those from the overall study population.

The median time to improvement by ≥ 1 category or ≥ 2 categories in the clinical status 8-point ordinal scale in the ITT Population was significantly shorter in the RDV 10-day group than the placebo group, as follows:

- ≥ 1 category: median of 7 days (95% CI: 6, 8) versus 9 days (95% CI: 8, 11), respectively (IRR 1.23; 95% CI: 1.08, 1.41; p = 0.002)
- ≥ 2 categories: 11 days (95% CI: 10, 13) versus 14 days (95% CI: 13, 15), respectively (IRR 1.29; 95% CI: 1.12, 1.48; $p < 0.001$)

Results of a sensitivity analysis accounting for participants who received placebo then were unblinded and crossed over to RDV treatment were consistent with those from the overall study population.

Other Secondary Endpoints

The median time to discharge or to a NEWS of ≤ 2 in the ITT Population was significantly shorter for participants in RDV 10-day group than for those in the placebo group, with a median of 8 days (95% CI: 7, 9) in the RDV 10-day group versus 12 days (95% CI: 10, 15) in the placebo group (HR 1.27; 95% CI: 1.10, 1.46; p < 0.001).

With respect to oxygen use, among participants in the ITT Population requiring oxygen at enrollment (ie, ordinal score of 5, 6, or 7), those in the RDV 10-day group were on oxygen for a lower median number of days (Q1, Q3) than those in the placebo group (13 [5, 28] days versus 21 [8, 28] days, respectively, when including imputations for participants who died). The incidence rate (95% CI) of new oxygen use was lower among participants not on oxygen at baseline in the RDV 10-day group than those in the placebo group; the population with nonoverlapping 95% CIs between treatment groups was participants with a baseline ordinal score 4 (no supplemental oxygen), 5 (supplemental oxygen), or 6 (noninvasive ventilation/high-flow oxygen) requiring new invasive mechanical ventilation/ECMO use (13% [10%, 17%] in the RDV 10-day group versus 23% [19%, 27%] in the placebo group).

With respect to duration of initial hospitalization, the median (Q1, Q3) days were numerically fewer in the RDV 10-day group (n = 541) than in the placebo group (n = 521): 12 (6, 28) versus 17 (8, 28) days, respectively, when including imputations for participants who died.

With respect to mortality, the mortality rate (95% CI) of participants by Day 15 was numerically lower in the RDV 10-day group (n = 541) than in the placebo group (n = 521) (7% [5%, 9%] versus 12% [9%, 15%], respectively) in the ITT Population. The mortality rate (95% CI) of participants by Day 29 was numerically lower in the RDV 10-day group than in the placebo group) (11% [9%, 15%] versus 15% [12%, 19%], respectively).

In the ITT Population, the risk of death by Day 15 was significantly lower in the RDV 10-day group compared with the placebo group (HR 0.55; 95% CI: 0.36, 0.83; p = 0.004). The risk of death by Day 29 was numerically lower in the RDV 10-day group compared with the placebo group (HR 0.73; 95% CI: 0.52, 1.02; p = 0.066). Results were similar in the As Treated Population.

Subgroup Analyses

The results of subgroup analyses were generally consistent with the main analyses in terms of demonstrating a benefit in the RDV 10-day group compared with the placebo group. A number of subgroups for which the 95% CI for the event rate ratio of interest did not include 1 included, but were not limited to, the following:

- Median time to recovery: third quartile (10 to ≤ 12 days) duration of symptoms prior to enrollment, > median (9 days) duration of symptoms prior to enrollment, any comorbidities, 1 comorbidity, 2 or more comorbidities, obesity, severe disease (actual or randomized stratum), and baseline ordinal score 5

- Odds of improvement in ordinal score: any comorbidities, 1 comorbidity, 2 or more comorbidities, obesity, severe disease at baseline (actual or randomized stratum), or baseline ordinal score 5
- Median times to ≥ 1 or ≥ 2 clinical status categories of improvement: third quartile (10 to ≤ 12 days) duration of symptoms prior to enrollment, > 10 days duration of symptoms prior to enrollment, > median (9 days) duration of symptoms prior to enrollment, any comorbidities, 2 or more comorbidities, obesity, severe disease at baseline (actual or randomized stratum), or baseline ordinal score 5
- Median times to discharge or to NEWS ≤ 2: severe disease (actual or randomized stratum) or a baseline ordinal score 5

In subgroup analyses of oxygen use in the ITT Population, the subgroups for which the RDV 10-day group had lower incidence rates with nonoverlapping 95% CIs than the placebo group in new invasive mechanical ventilation/ECMO use were those with ≤ median (9 days) duration of symptoms prior to enrollment and severe disease (actual or randomized stratum).

In ad hoc subgroup analyses of mortality by actual disease stratum or ordinal score, the greatest differences in percentages of deaths among participants with known mortality status at Day 29 in the RDV 10-day group compared with that in the placebo group was observed in the subgroup with baseline ordinal score 5 (4.1% [9 of 222 participants] versus 12.8% [25 of 195 participants], respectively; HR [95% CI] = 0.30 [0.14, 0.64], p <0.001 [without adjustments for multiplicity]) and in the actual severe disease stratum (12.5% [57 of 457 participants] versus 16.3% [74 of 453 participants], respectively).

Pharmacokinetics/Pharmacodynamics Results: No PK/PD assessments were performed for this report.

Safety Results:

The median (Q1, Q3) exposure to study treatment was 8 (4, 10) days in both the RDV 10-day group and placebo group with no crossover to RDV.

Grade 3 or 4 AEs were reported in 51% of participants in the RDV 10-day group and 57% of participants in the placebo group.

Participants who had more severe disease had higher rates of AEs, treatment-related AEs, treatment-related Grade 3 or 4 AEs, SAEs, and AEs leading to premature discontinuation of study treatment than those who had mild-to-moderate disease.

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

- RDV 10-day group: decreased glomerular filtration rate (11%, 60 of 532 participants), decreased hemoglobin (9%, 49 participants), and decreased lymphocyte count (8%, 45 participants).
- Placebo group: decreased glomerular filtration rate (15%, 76 of 516 participants), decreased hemoglobin (12%, 62 participants), and respiratory failure (12%, 60 participants).

The incidence and types of common AEs were generally similar between the 2 treatment groups.

A lower percentage of participants in the RDV 10-day group had SAEs reported compared with the placebo group (RDV 10-day group 25%, 131 participants; placebo group 32%, 163 participants; ($p = 0.010$). The only SAE reported in ≥ 5% of participants in any treatment group was respiratory failure (RDV 10-day group: 7%, 35 participants; placebo group: 11%, 58 participants).

Similar percentages of AEs leading to discontinuation of study treatment were reported in each treatment group (RDV 10-day group 11%, 57 participants; placebo group 15%, 77 participants).

An analysis of time to death, SAEs, or Grade 3 or Grade 4 AEs through Day 29 showed that the median time was significantly longer in the RDV 10-day group than in the placebo group (9 days versus 4 days, respectively; HR 0.85, 95% CI: 0.73, 0.99, $p = 0.031$). The KM curve representing time to death, SAE, or Grade 3 or 4 AE, diverged at Day 3 and remained separated through Day 28, suggesting a lower proportion of events in the RDV 10-day group versus the placebo group starting from Day 3.

Hepatic Safety

Hepatic AEs were reported in a similar percentage of participants in each treatment group (RDV 10-day group 13%, 71 of 532 participants; placebo 16%, 80 of 516 participants). The overall pattern and types of hepatic AEs were generally similar between the treatment groups; the most commonly reported hepatic AEs for each treatment group were as follows:

- RDV 10-day group: PT prolonged (5%, 26 of 532 participants), AST increased (3%, 18 participants) and ALT increased and blood bilirubin increased (each 2%, 12 and 9 participants, respectively)
- Placebo group: AST increased (6%, 33 of 516 participants), ALT increased (5%, 24 participants), and blood bilirubin increased (3%, 16 participants)

Only 1 participant in the placebo group had a hepatic SAE (Grade 4 hepatitis) which was considered related to study treatment. Nonserious hepatic AEs that led to study treatment discontinuation were reported as follows: RDV 10-day group 2% (10 participants), placebo group 2% (12 participants). No hepatic SAEs leading to study treatment discontinuation were reported.

Median ALT and median AST decreased between baseline and Day 29 in both treatment groups during the study. However, these data may be confounded by missing data due to discharge or death. Grade 3 or 4 increased ALT and Grade 3 or 4 increased AST were each reported in similar percentages of participants in the RDV 10-day and placebo groups.

Renal Safety

Renal AEs were reported in a similar percentage of participants in each treatment group (RDV 10-day group 18%, 94 of 532 participants; placebo 23%, 118 of 516 participants). The overall pattern and types of renal AEs were generally similar between the treatment groups; the most commonly reported renal AEs for each treatment group were as follows:

- RDV 10-day group: glomerular filtration rate decreased (11%, 60 of 532 participants), blood creatinine increased (6%, 32 participants), and acute kidney injury (5%, 28 participants)
- Placebo group: glomerular filtration rate decreased (15%, 76 of 516 participants), blood creatinine increased (7%, 36 participants), and acute kidney injury (6%, 33 participants)

Renal SAEs were reported in 3% (15 of 532 participants) in the RDV 10-day group versus 4% (20 of 516 participants) in the placebo group. The most commonly reported renal SAE was acute kidney injury (RDV 10-day group: 2%, 7 participants; placebo group: 2%, 12 participants). Nonserious renal AEs that led to study treatment discontinuation were reported as follows: RDV 10-day group 4% (22 participants), placebo group 5% (28 participants). Renal SAEs leading to study treatment discontinuation were reported in 2% in both the RDV 10-day group (8 participants) and the placebo group (10 participants).

Median creatinine and creatinine clearance by Cockcroft-Gault were similar between baseline and Day 29 in both treatment groups during the study. However, these data may be confounded by missing data due to discharge or death. Graded abnormalities reported for increased creatinine were reported for all grades (Grades 1 to 4) in similar percentages of participants in the RDV 10-day and placebo groups. Graded abnormalities reported for decreased creatinine clearance were reported for Grades 2 to 4 in similar percentages of participants in the RDV 10-day and placebo groups.

Laboratory Evaluations

There were no clinically relevant changes from baseline within each treatment group or differences between the treatment groups in median values for hematology parameters. Median values for hematology and chemistry parameters were generally within reference ranges.

The majority of participants in each treatment group had at least 1 treatment-emergent laboratory abnormality (RDV 10-day group: 89%, 465 of 520 participants; placebo group: 92%, 464 of 504 participants). The incidence of all graded individual laboratory abnormalities was generally similar, except for increased PT and increased prothrombin international normalized ratio (INR) which were less common in the placebo group, across the 2 treatment groups. Increases in PT and prothrombin INR were predominately Grade 1 or 2. The percentage of participants reporting treatment-emergent Grade 3 or 4 laboratory abnormalities was similar between treatment groups (RDV 10-day group: 45%, 232 participants; placebo group: 51%, 255 participants). Treatment-emergent Grade 4 laboratory abnormalities were reported in a lower percentage of participants in the RDV 10-day group (RDV 10-day group: 18%, 93 participants; placebo group: 24%, 121 participants). The most common treatment-emergent Grade 3 or 4 laboratory abnormality was decreased creatinine clearance (18%, 90 of 487 participants) in the RDV 10-day group and decreased hemoglobin (22%, 110 of 504 participants) in the placebo group.

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.
- Treatment with RDV compared with placebo for up to 10 days led to a statistically significant 45% reduction in the risk of death by Day 15. By Day 29, the risk of death was numerically lower by 27% in the RDV 10-day group compared with the placebo group.
- Remdesivir was safe and well tolerated, with a safety profile similar to placebo, in hospitalized participants with COVID-19.

5.1. Protocol Amendment History

Version/Date		
Section	**Description of Change**	**Brief Rationale**
2.0 2MAR2020		
	Overall	This version addresses the comments received from the US FDA, Japanese PDMA, DSMB, IRBs, and NIAID scientific review.
	Improved clarity and brevity	Multiple areas throughout the document were reworded to improve clarity (recognized after implementation) and edited to minimize redundant statements.
1.1	Number of sites increased from 50 to approximately 75	Given the currently unpredictable epidemiology, additional sites will improve the ability to enroll the study in a timely manner.
	Sample size increased	Version 1 sample size table and statements in the text did not align. The new assumptions use a slightly smaller treatment effect (OR 1.75) and the 8-category scale and give the sample size of 440.
	Addition of phone call on Day 22	Recent information from the outbreak in China suggest some COVID-19 patients worsen between 2 and 4 weeks of illness. We added Day 22 because of concerns that the peak illness may be missed. There are also concerns if the more severe population will be discharged by Day 29.
	Ordinal scale was increased to 8 categories.	This addresses the concern raised by several reviews that "Hospitalized not on oxygen" is two separate populations – those still needing medical care and those kept in hospital just for infection control.
	Objectives and endpoints were put into table format	Multiple comments that the tabular form of objectives and endpoints (that was previously in Section 4) was much easier to read and understand.

	Added inclusion criteria for admission to hospital	This was implied throughout the document, but never stated in the inclusion criteria.
	Inclusion criteria #8	Contraceptive requirement aligned to new IB from February 21, 2020
	Phase of study	Changed to phase 3. After discussion with company, and new IB that outlines safety data of > 500 subjects, the company thought this was more accurately called a phase 3 trial.
1.2	Schedule of Assessments updated	To include Day 22. Footnotes also revised for clarity.
2.2	Background updated	To reflect current understanding of SARS-CoV, COVID-19, and new data from IB.
3.	Separating objectives about non-invasive from invasive mechanical ventilation	Elsewhere in the protocol, it was mentioned that this data would be captured separately, but it mistakenly never made into an endpoint.
	Added Day 14 mortality	To allow better assessment of short and long term mortality.
4	Rewritten for clarity	These paragraphs were substantially rewritten, but aside from the changes note above the content is not different.
8	Screening is more detailed	These edits reflect so ambiguity discovered with the first enrollment.
8.1.2	Efficacy assessments more detailed	More detail is provided to facilitate these assessments. Also, each component that contribute to the categories will not be captured separately. This will allow the ordinal scale as structured, but also will allow analysis of alternative ordinal scales.
8.1.3.1	Viral load in plasma and resistance	The assessment of viral load in plasma and detection of resistance was previously noted on the SOA, but never discussed in the text. This has now been added in this section.
9.2	Sample size calculations	With the addition of one category to the ordinal scale, the estimates per category must change leading to new tables.
3.0 27MAR2020		
	Improved clarity	Multiple areas throughout the document were reworded to improve clarity (issues that arose with implementation)
	Flexibility	The pandemic has limited ability for people to be seen in followup due to infection control and restrictions on travel. Additionally, staff at some sites have limited ability to go into rooms due to limited

		personal protective equipment. So flexibility has been added where possible while still ensuring safety and good scientific data.
1.1	Sample Size Increase	The sample size was changed to reflect ensuring sufficient samples for the endpoint of interest which 400 subjects with a "recovered" status (per the primary objective). Additionally, enrollment is permitted after the 400 recoveries up to April 20 to provide additional data about important subgroups.
	Primary Endpoint	Given evolving data, the precise day of assessment of the primary endpoint is not clear. Modeling of the prior endpoint suggested if the day is chosen incorrectly, the power is significantly decreased. So the primary endpoint has been changed from a ordinal scale on a given day to days to recovery (the best three categories of the ordinal scale.
	Key secondary endpoint	The prior primary endpoint has been labeled as the key secondary endpoint.
	Inclusion Criteria #5	Given delays of PCR results in some sites (given number of tests and throughput within the lab), the PCR positive requirement has been written to allow flexibility if the PCR results are delayed.
	Inclusion Criteria #6	Removed auscultation requirement given challenges of accurate auscultation while in full PPE.
	Exclusion Criteria #2	Cutoff of eGFR to 30 was decreased after discussion with the manufacturer and FDA.
	Sites	Increased to 100 given unpredictable epidemiology of COVID-19
	DSMB	Given the rapid pace of enrollment, the prior plans for DSMB oversight are not practical, so this has been modified with input from the DSMB on when they would like to have interim reviews.
2.3.2	Drug interaction	Corrected erroneous statements about CYP inhibition.
5.3	Vulnerable Subjects	Allow inclusion of those that are incapable of consent such as cognitively impaired. Prior version noted consent by a LAR, but it was not described in this section.
6	Study Product	Updated throughout for 2 issues. First, the newly manufactured lot of remdesivir is in 100mg vials. Second, there is limited supply of placebo and the options for using saline with an opaque bag for the control infusion was added.
6.5	Concomitant Therapy	There has been significant increased in use of off label therapies for COVID-19, including many repurposed agents and therapies targeting immune

		response. So additional wording was added to cover these scenarios to minimize additional confounding medications.
8.1.3	Sample Processing	Some sites are reporting needing to process samples in BSL-3 and/or have limitations on processing, shipping, storage, etc. of samples. So wording was added to allow exclusion of these samples (which may be cost prohibitive)
8.2	Venipuncture volume	This table was corrected for total volumes, but not new samples were added.
9	Statistical Considerations	This section was rewritten to given the change in sample size.
10.1.1	Informed consent	Given isolation and infection control issues with COVID-19, traditional consenting documentation is not always possible. This section was rewritten to allow alternative consent processes and documentation as long as these are acceptable to the site's IRB.

5.2. GS-US-540-5776: List of Principal Investigators

Geographic Region/ Country Principal Investigator	Study Site
Asia/ Japan	National Center for Global Health and Medicine Hospital Disease Control and Prevention Center 1-21-1 Toyama, Shinjuku-ku Tokyo, 162-8655 Japan (SIT20)
Asia/ Republic of Korea	Seoul National University Bundang Hospital Division of Infectious Diseases 82 Gumi-ro, 173 Beon-gil Bundang-gu, Seongnam-si Gyeonggi-do Republic of Korea 13620 (SIT14)
Asia/ Republic of Korea	Seoul National University Hospital 101 Daehak-ro, Jongno-gu Seoul Republic of Korea 03080 (SIT05)
Asia/ Singapore	National Centre for Infectious Diseases (NCID) 16 Jalan Tan Tock Seng Singapore 308442 (SIT25)
Europe/ Denmark	University of Copenhagen/ Rigshospitalet Centre of Excellence for Health, Immunity and Infections (CHIP) Department of Infectious Diseases Section 2100, Oster Alle 56 5th Floor, Copenhagen, 2100 Denmark (SIT50)
Europe/ Germany	U. Koeln (University Hospital of Cologne) Klinik I fur Innere Medizin Klinisches Studienzentrum fur Infektiologie I Kerpener Str. 62 Cologne, 50937 Germany (SIT56)
Europe/ Germany	Universitatsklinikum Bonn (University Hospital Bonn) Medizinische Klinik I Bereich Infektiologie/ HIV der Medizinischen Klinik Gebaude 26, EG, Raum 132 Bonn Nordrhein-Westfalen 53127 Germany (SIT58)
Europe/ Germany	U. Frankfurt (University Hospital Frankfurt) Zentrum der Inneren Medizin Medizinische Klinik II Infektiologie Theodor-Stern-Kai 7, Haus 23 Frankfurt, 60590 Germany (SIT57)
Europe/ Greece	AHEPA University Hospital 1st Department of Internal Medicine St. Kiriakidis 1, Thessaloniki Central Macedonia, P.O. 54636 Greece (SIT62)

Geographic Region/ Country Principal Investigator	Study Site
Europe/ Greece	Medical School of Athens University Evangelismos General Hospital Department of Critical Care and Pulmonary Services 45-47 Ipsilandou Street Athens, GR-10675 Greece (SIT59)
Europe/ Greece	Athens Hospital for Diseases of the Chest "Sotiria" (satellite location to Evangelismos General Hospital) Greece (SIT60)
Europe/ Greece	Attikon University General Hospital (satellite location to Evangelismos General Hospital) Greece (SIT61)
Europe/ Spain	Hospital Clinic de Barcelona Servicio de Salud Internacional Carrer De Villarroel 170 08036 Barcelona Spain (SIT64)
Europe/ Spain	Hospital Germans Trias i Pujol Servei Malalties Infeccioses Carretera del Canyet s/n 08916 Badalona Spain (SIT63)
Europe/United_Kingdom	John Radcliffe Hospital/ Churchill Hospital Level 4 JR Main Building Headley Way, Headington Oxford, OX3 9DU United Kingdom (SIT53)
Europe/United_Kingdom	Guy's & St. Thomas' NHS Foundation Trust Directorate of Infection 5th Floor, North Wing Saint Thomas Hospital Westminster Bridge Rd London, City of London SE1 7EH United Kingdom (SIT52)
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Europe/United_Kingdom	Royal Sussex County Hospital Department of Intensive Care Medicine Eastern Road, East Sussex Brighton, BN2 5BE United Kingdom (SIT54)
Europe/ United Kingdom	Royal Victoria Infirmary Department of Infectious Diseases Queen Victoria Road, Level 6 Ward 19, Newcastle upon Tyne NE1 4LP United Kingdom (SIT51)
North America/ Mexico	Instituto Nacional de Enfermedades Respiratorias (INER) Ismael Cosío Villegas Calz. de Tlalpan 4502 Del. Tlalpan, Col. Seccion XVI Mexico City, 14080 Mexico (SIT71)

Geographic Region/ Country Principal Investigator	Study Site
North America/ Mexico	Investigacion del Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran (NUTRICION) Departamento de Infectologia Avenida Vasco de Quiroga No. 15, Col. Belisario Domínguez Sección XVI Alcaldía Tlalpan Mexico City 14080 Mexico (SIT70)
North America/ United States	Stanford University Stanford Hospital and Clinics - Pediatrics - Infectious Diseases 730 Welch Road, 2nd Floor Palo Alto, CA 94304-1503 United States (SIT37)
North America/ United States	Valley Care Medical Center (satellite location to Stanford University) United States (SIT74)
North America/ United States	Providence Sacred Heart Medical Center 101 W 8th Avenue Spokane, WA 99204 United States (SIT02)
North America/ United States	University of Washington Virology Research Clinic 908 Jefferson Street Seattle, WA 98104-2433 United States (SIT12)
North America/ United States	University of California Davis Medical Center - Internal Medicine - Infectious Disease 4150 V Street, Sacramento CA 95817-1460 United States (SIT27)
North America/ United States	Madigan Army Medical Center Infectious Disease Clinic First Floor, Medical Mall 9040 Jackson Avenue Tacoma, WA 98431 United States (SIT08)
North America/ United States	Vanderbilt University Medical Center Inf Dis 1161 21st Avenue S Medical Center North Nashville, TN 37232-0011 United States (SIT17)
North America/ United States	NIH Clinical Center NIAID Laboratory of Immunoregulation Clinical Research Section 10 Center Drive, Room 4-1479 MSC 1460 Bethesda, MD 20892-1504 United States (SIT04)
North America/ United States	New York University School of Medicine Langone Medical Center – Microbiology 550 First Avenue New York, NY 10016-6402 United States (SIT38)

Geographic Region/ Country Principal Investigator	Study Site
North America/ United States	NYC Health + Hospitals/Bellevue (satellite location to New York University Langone) United States (SIT69)
North America/ United States	Baylor College of Medicine Molecular Virology and Microbiology One Baylor Plaza Houston, TX 77030-3411 United States (SIT19)
North America/ United States	Ben Taub Hospital (satellite location to Baylor College of Medicine) United States (SIT41)
North America/ United States	University of Rochester Medical Center Vaccine Research Unit 601 Elmwood Avenue, Box 689 Rochester, NY 14642-0001 United States (SIT30)
North America/ United States	University of Massachusetts Medical School Infectious Diseases and Immunology 55 Lake Avenue N Room S6-105 Worcester, MA 01655-0002 United States (SIT47)
North America/ United States	Denver Health Division of Hospital Medicine Main Campus 777 Bannock Street Denver, CO 80204 United States (SIT32)
North America/ United States	Saint Louis University Center for Vaccine Development 1100 S Grand Boulevard 1st Floor Edward A. Doisy Research Center Saint Louis, MO 63104-1015 United States (SIT22)
North America/ United States	University of Alabama at Birmingham School of Medicine - Infectious Disease 1802 6th Avenue South Birmingham, AL 35233 United States (SIT40)
North America/ United States	Massachusetts General Hospital Infectious Diseases 55 Fruit Street Boston, MA 02114-2621 United States (SIT16)
North America/ United States	VA Palo Alto Health Care System InfDis. 3801 Miranda Avenue Palo Alto, CA 94304-1207 United States (SIT39)

Geographic Region/ Country Principal Investigator	Study Site
North America/ United States	University of California Irvine MedCtr. - InfDis. 101 The City Drive Orange, CA 92868-3298 United States (SIT33)
North America/ United States	Walter Reed National Military Medical Center 8901 Wisconsin Avenue Bethesda, MD 20889 United States (SIT11)
North America/ United States	Johns Hopkins Hospital School of Medicine - Infectious Diseases 600 N Wolfe Street Baltimore, MD 21287-0005 United States (SIT18)
North America/ United States	University of Virginia Acute Care Surgery 1215 Lee Street PO Box 800709 Charlottesville VA 22908-0816 United States (SIT44)
North America/ United States	University of Nebraska Medical Center Infectious Diseases 985400 Nebraska Medical Center Omaha, NE 68198-5400 United States (SIT01)
North America/ United States	University of Minnesota Medical Center Fairview - Infectious Diseases and International Medicine 420 Delaware Street SE Minneapolis, MN 55455-0341 United States (SIT26)
North America/ United States	Naval Medical Center Portsmouth Infectious Disease Division 620 John Paul Jones Circle Building 3, 3rd Floor Portsmouth, VA 23708 United States (SIT09)
North America/ United States	Brook Army Medical Center 3551 Roger Brooke Drive Fort Sam Houston, TX 78234 United States (SIT07)
North America/ United States	Evergreen Health Infectious Disease Service 12303 NE 130th Lane Kirkland, WA 98034 United States (SIT06)
North America/ United States	University of California San Francisco Zuckerberg San Francisco General Hospital - Division of HIV, ID, and Global Medicine 995 Potrero Avenue Building 80, Ward 84 San Francisco, CA 94110-2859 United States (SIT23)
North America/ United States	Naval Medical Center San Diego Infectious Disease Clinic 34800 Bob Wilson Drive San Diego, CA 92314 United States (SIT10)

Geographic Region/ Country Principal Investigator	Study Site
North America/ United States	University of Texas Medical Branch Division of Infectious Disease 301 University Boulevard Galveston, TX 77555-0435 United States (SIT03)
North America/ United States	Emory University Emory Vaccine Ctr. - The Hope Clinic 500 Irvin Court, Suite 200 Decatur, GA 30030-1705 United States (SIT15)
North America/ United States	Grady Memorial Hospital (satellite location to Emory University) United States (SIT72)
North America/ United States	University of Illinois at Chicago Division of Infectious Diseases UIC Infectious Diseases 835 South Wolcott Street Chicago, IL 60612 United States (SIT21)
North America/ United States	University of Maryland School of Medicine Center for Vaccine Development, Baltimore 200 Forbes Street, Suite 200 Annapolis, MD 21401-1527 United States (SIT31)
North America/ United States	University of Texas Health Science Center at San Antonio - Infectious Diseases 7703 Floyd Curl Drive San Antonio, TX 78229-3901 United States (SIT43)
North America/ United States	Penn State Health Milton S. Hershey Medical Center Division of Infectious Diseases 500 University Drive Hershey, PA 17033 United States (SIT49)
North America/ United States	Hospital of the University of Pennsylvania InfDis. 3400 Spruce Street Silverstein Building, Suite D Philadelphia, PA 19104- 4238 United States (SIT35)
North America/ United States	University of California San Diego Health Jacobs Medical Center 9300 Campus Point Drive La Jolla, CA 29037 United States (SIT24)
North America/ United States	Southeast Louisiana Veterans Health Care System (SLVHCS) Section of Infectious Diseases 2400 Canal Street New Orleans, LA 70119 United States (SIT68)

Geographic Region/ Country Principal Investigator	Study Site
North America/ United States	Northwestern University Hospital Infectious Disease 251 East Huron Street Chicago, IL 60611-2908 United States (SIT34)
North America/ United States	Cedars-Sinai Medical Center 8700 Beverly Boulevard Room 1738 West Hollywood CA 90048-1804 United States (SIT42)
North America/ United States	Duke University, Human Vaccine Institute - Duke Vaccine and Trials Unit 2608 Erwin Road, Suite 210 Durham, NC 27704 United States (SIT36)
North America/ United States	University of California Los Angeles (UCLA) MedCtr. - Westwood Clinic 200 Medical Plaza, Suite 365C Los Angeles, CA 90095 United States (SIT28)
North America/ United States	Montefiore Medical Center Albert Einstein College of Medicine Division of Infectious Diseases 111 East 210th Street Bronx, NY 10467-2401 United States (SIT29)

Investigator numbers were not assigned in this study
Blank cells in this column indicate no participants transferred from another study site

6. STUDY SYNOPSIS GS-US-540-9012

FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting	
Name of Test Drug:	Remdesivir (GS-5734™)	
Dose and Formulation:	Remdesivir (GS-5734™) for injection, 100 mg, for intravenous (IV) administration	
Indication:	Coronavirus disease 2019 (COVID-19)	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
Study No.:	GS-US-540-9012	
Phase of Development:	Phase 3	
IND No.:	147753	
EudraCT No.:	2020-003510-12	
ClinicalTrials.gov Identifier:	NCT04501952	
Study Start Date:	18 September 2020 (first participant screened)	
Study End Date:	06 May 2021 (last participant last observation for the primary endpoint and for this report)	
Principal or Coordinating Investigator:	Name: Affiliation:	Carlos Vaca, MD Nuren Medical and Research Center
Sponsor Responsible Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Report Date:	01 October 2021	

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-540-9012
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Investigators: Multicenter study

Study Centers: Participants were enrolled across 64 centers: 55 in the United States (US), 5 in Denmark, 2 in Spain, and 2 in the United Kingdom.

Publication: Hill JA, Paredes R, Vaca C, Mera J, Webb BJ, Perez G, et al. Remdesivir for the treatment of high-risk non-hospitalized individuals with COVID-19: A randomized, double-blind, placebo-controlled trial [Abstract]. IDWeek 2021 Annual Meeting; 30 September 2021. Abstract LB-1.

Study Period:

18 September 2020 (first participant screened)
06 May 2021 (last participant last visit for the primary endpoint and for this report)

Phase of Development: Phase 3

Study Objectives and Endpoints:

The purpose of this study was to evaluate treatment with intravenous (IV) administered remdesivir (RDV [GS-5734™]) in an outpatient setting in participants with confirmed coronavirus disease 2019 (COVID-19) who were at risk for disease progression.

Primary Objectives	Primary Endpoints
• To evaluate the efficacy of RDV in reducing the rate of COVID-19-related hospitalization or all-cause death in non-hospitalized participants with early stage COVID-19 • To evaluate the safety of RDV administered in an outpatient setting	• Composite endpoint of COVID-19-related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28 • Proportion of participants with treatment-emergent AEs

Secondary Objectives	Secondary Endpoints
• To evaluate the efficacy of RDV in reducing the rate of COVID-19–related medically-attended visits (MAVs; medical visits attended in person by the participant and a health care professional) or all-cause death in non-hospitalized participants with early stage COVID-19 • To determine the antiviral activity of RDV on severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 viral load • To assess the impact of RDV on symptom duration and severity	• Composite endpoint of COVID-19–related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 28 • All-cause mortality at Day 28 • Proportion of participants hospitalized by Day 28 • Composite endpoint of COVID-19-related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 14 • Composite endpoint of COVID-19–related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 14 • Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7 • Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19-adapted InFLUenza Patient-Reported Outcome (FLU-PRO) Plus© • Proportion of participants progressing to requiring oxygen supplementation by Day 28
Exploratory Objectives	**Exploratory Endpoints**
• To assess the impact of RDV on other clinical outcomes • To evaluate the emergence of viral resistance to RDV • To identify and assess associations of host biomarkers with disease progression and treatment response • To assess the pharmacokinetics (PK) of RDV and its metabolites in patients with COVID-19 • To assess patient-reported outcome using the COVID-19-adapted FLU-PRO Plus questionnaire and validate the questionnaire (if available)	• Time to alleviation (mild or absent) of baseline symptoms in each domain of the COVID-19-adapted FLU-PRO Plus • Change from baseline in COVID-19-adapted FLU-PRO Plus total score and score in each domain • Psychometric validity of COVID-19-adapted FLU-PRO Plus questionnaire • Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 14 • Time to first negative SARS-CoV-2 polymerase chain reaction (PCR) • Proportion of participants with negative SARS-CoV-2 PCR at each study visit • Emergence of viral resistance to RDV • Baseline levels and change from baseline for inflammation/immune-related, acute respiratory distress syndrome-related and coagulation-related biomarkers • Proportion of participants admitted to the intensive care unit (ICU) by Day 28 • Proportion of participants started on mechanical ventilation by Day 28 • The plasma concentrations and PK parameters of RDV and metabolites

Methodology:

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of RDV therapy for outpatients with early stage COVID-19 who were at higher risk of disease progression. Participants who met all eligibility criteria were randomized in a 1:1 ratio to RDV or placebo. Randomization was stratified by participants who reside in a skilled nursing facility, by participant's age (< 60 vs ≥ 60 years), and by region (US vs ex-US):

Treatment Group A (hereafter referred to as the RDV IV for 3 days group) received a single dose of IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3

Treatment Group B (hereafter referred to as the placebo group) received IV placebo-to-match (PTM) RDV on Days 1 to 3

Number of Participants (Planned and Analyzed):
Planned: Approximately 1264 participants
Analyzed: Enrollment was halted on 08 April 2021 after 584 participants were randomized, 292 to receive RDV IV for 3 days and 292 to receive placebo for 3 days. A total of 562 participants (279 in the RDV IV for 3 days and 283 in the placebo group) received at least 1 dose of study drug and were included in the Full Analysis Set and Safety Analysis Set.

Diagnosis and Main Criteria for Inclusion: Eligible participants who met the following eligibility criteria:

Key Inclusion Criteria:

- Willing and able to provide written informed consent (≥ 18 years of age) or assent (≥ 12 to < 18 years of age, where locally and nationally approved) or with a legal representative able to provide informed consent
- Age ≥ 18 years (at all sites) or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant independent ethics committee or institutional review board) with at least 1 of the preexisting risk factors for progression to hospitalization (chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (body mass index [BMI] ≥ 30), immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease) or age ≥ 60 years, regardless of the presence of other preexisting risk factors for progression
- SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [eg, PCR] or antigen testing) ≤ 4 days prior to screening
- At least 1 symptom consistent with COVID-19 for ≤ 7 days prior to randomization (such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia)
- Did not receive, require, or expect to require supplemental oxygen during time of study
- Did not require hospitalization (hospitalization defined as ≥ 24 hours of acute care)

Duration of Treatment:

The duration of treatment was up to 3 days for participants in the RDV IV for 3 days group and up to 3 days for participants in the placebo group. The last study follow-up was on Day 28.

Test Product, Dose, Mode of Administration, and Batch No.:

Participants were treated with RDV 100 mg for injection, which was supplied as a lyophilized solid in sterile single-use, 30 mL type I clear glass vials. This study treatment was reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion.

Participants in the RDV IV for 3 days group received RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3.

The batch number of the RDV 100 mg for IV injection was EW2009A1.

Reference Therapy, Dose, Mode of Administration, and Batch No.:

The supplied PTM RDV for injection, was identical in physical appearance to the active formulation and contained the same inactive ingredients.

Participants in the placebo group received PTM RDV on Days 1 through 3.

The batch numbers of the PTM for IV injection were EW2004A1 and EW2022A1.

Criteria for Evaluation:

Efficacy: Hospitalizations, MAVs, and deaths up to Day 28 were used to assess disease progression. COVID-19 symptoms recorded by participants on the COVID-19-adapted FLU-PRO Plus questionnaire daily on Days 1 through 14 were used to assess the impact of RDV on symptom alleviation. Nasopharyngeal swabs were taken at prespecified time points through Day 14 for SARS-CoV-2 qRT-PCR testing to assess change in SARS-CoV-2 viral load and possible viral resistance testing.

Pharmacokinetics: Sparse PK was collected from participants at selected sites at Day 2: end of infusion and optional 2 hours after end of infusion and Day 3: predose (within 30 minutes of dosing) and end of infusion. Intensive PK was collected from participants at selected sites at Day 1 and Day 3, at the following time points relative to the start time of infusion: 0 (predose), 0.5, 0.75, 3, 6, 8, 12 (optional), and 24 hours.

Safety: Safety assessments included the monitoring of adverse events (AEs) and concomitant medications, clinical laboratory tests, vital signs measurements (including respiratory status), body weight, and physical examinations.

Statistical Methods:

Efficacy: The primary analysis set for the efficacy analysis was defined as the Full Analysis Set (FAS), which included all participants who were randomized into the study and who received at least 1 dose of study treatment. A modified Full Analysis Set (mFAS) included all participants who were randomized into the study, received at least 1 dose of study treatment, and enrolled under protocol amendment 2 or later. Participants were grouped according to the treatment to which they were randomized.

Analysis of Primary Efficacy Endpoint

The primary endpoint of the study was the composite endpoint of COVID-19-related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28. The null hypothesis being tested was whether the hazard ratio (HR) of COVID-19-related hospitalization or all-cause death by Day 28 between the 2 treatment groups was equal to 1. This was estimated using a Cox model with randomization stratification factors as covariates.

Analysis of Secondary Efficacy Endpoints

The FAS was the primary analysis set for secondary endpoints. The mFAS was used for the secondary composite endpoint of COVID-19-related MAVs or death.

All-cause mortality by Day 28 was compared between the 2 treatment groups using the Fisher exact test.

COVID-19-related hospitalizations or all-cause death by Day 14, COVID-19-related MAVs or death by Day 28, and COVID-19-related MAVs or death by Day 14 were analyzed using the same method as used for the primary endpoint.

The proportion of participants hospitalized (COVID-19-related) by Day 28 was estimated using the Kaplan-Meier method and compared between the 2 treatment groups using a log-rank test. Hazard ratio and 2-sided 95% CI estimated using the Cox regression with baseline stratification factors as covariates were provided.

Number and percentage of participants progressing to requiring oxygen supplementation by Day 28 were summarized and compared between treatment groups using the Fisher exact test.

The Kaplan-Meier product limit method was used to estimate and log-rank test was used to compare treatment groups for the time to alleviation of baseline COVID-19 symptoms. Hazard ratio and 2-sided 95% CI estimated using the Cox regression with baseline stratification factors as covariates were provided.

Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7 was summarized by treatment groups and compared between treatment groups using an analysis of covariance model with baseline viral load as covariate; the analysis was based on the Virology Analysis Set.

Safety: The proportion of participants with treatment-emergent AEs (TEAEs) was the primary safety endpoint of the study. Clinical and laboratory AEs were coded using the MedDRA, Version 24.0. Descriptive summary statistics were provided for safety data. No formal statistical testing was performed. The Safety Analysis Set was used to summarize safety data.

SUMMARY OF RESULTS:

Participant Disposition and Demographics:

Of the 630 participants screened, a total of 584 participants were randomized, 292 to receive RDV IV for 3 days and 292 to receive placebo for 3 days. Of the 562 participants who received at least 1 dose of study drug, 20 participants (3.6%) prematurely discontinued study treatment. The most common reasons for premature discontinuation of study treatment were participant decision for 8 participants (1.4%) and AEs for 7 participants (1.2%). Fewer participants in the RDV IV for 3 days group discontinued study treatment due to AEs (1 participant [0.4%]) compared with the placebo group (6 participants [2.1%]).

A total of 24 participants (4.3%) prematurely discontinued from the study. The most common reasons for premature discontinuation from the study were withdrawal of consent and lost to follow-up in 9 participants (1.6%) each.

Baseline risk factors, symptom severity, demographics, and other baseline characteristics were balanced across both treatment groups. Most enrolled participants exhibited mild to moderate symptoms at baseline on the COVID-19-adapted FLU-PRO Plus questionnaire. A similar proportion of male and female participants (52.1% and 47.9%, respectively) enrolled in the study. The mean (SD) age was 50 (15.1) years (range: 13 to 98 years); the majority of participants (68.3%) were ≥ 18 to < 60 years of age and 170 participants (30.2%) were ≥ 60 years of age. The majority of participants were White (82.3%) and there was a notably high enrollment of participants of Hispanic or Latino ethnicity (43.6%). The median (first quartile, third quartile) BMI was 30.7 (26.5, 34.2) kg/m^2.

Of the 8 adolescent participants, 5 were male and 3 were female. The mean (SD) age was 14 (2.3) years (range: 13 to 17 years) in the RDV IV for 3 days group and 16 (1.1) years (range: 14 to 17 years) in the placebo group. All 8 participants were White. Three participants were not Hispanic/Latino and 5 were Hispanic/Latino.

Efficacy Results:

Primary Efficacy Endpoint: Composite Endpoint of COVID-19-related Hospitalization or All-Cause Death by Day 28

The RDV IV for 3 days group met the primary endpoint of a reduction in COVID-19-related hospitalization or all-cause death by Day 28 compared with placebo. COVID-19-related hospitalizations or all-cause death by Day 28 were reported for 2 of 279 participants (0.7%) in the RDV IV for 3 days group and 15 of 283 participants (5.4%) in the placebo group, resulting in an 87% reduction with RDV compared with placebo ($P = 0.0076$; Cox model using FAS). No deaths occurred in either group by Day 28. There was a consistent benefit of treatment with RDV IV for 3 days compared with placebo across each subgroup by region, age, resident of skilled nursing facility, sex, race, baseline risk factor, and ethnicity.

Results from the sensitivity analysis of the primary endpoint confirmed the results of the primary analysis ($P = 0.0015$; Cochran-Mantel-Haenszel [CMH] analysis using FAS).

No adolescent participant (12 to < 18 years of age) had COVID-19-related hospitalization or all-cause death by Day 28.

Secondary Efficacy Endpoints

An 81% reduction in COVID-19-related MAVs or all-cause death by Day 28 was observed with RDV compared with placebo ($P = 0.0024$; Cox model using mFAS). COVID-19-related MAVs or all-cause death by Day 28 were reported for 4 of 246 participants (1.7%) in the RDV IV for 3 days group and 21 of 252 participants (8.5%) in the placebo group. Similar results were observed for COVID-19-related MAVs or all-cause death by Day 28 using the CMH analysis for the mFAS ($P = 0.0006$).

Results for the composite endpoints of COVID-19–related hospitalization or all-cause death by Day 14, COVID-19–related MAVs or all-cause death by Day 14, and COVID-19–related hospitalizations by Day 28 also demonstrated statistically significant reductions with RDV IV for 3 days compared with placebo.

There was no statistically significant difference between the groups for change from baseline in nasopharyngeal SARS-CoV-2 viral load.

Overall 126 participants (66 in the RDV IV for 3 days group and 60 in the placebo group) had baseline COVID-19-adapted FLU-PRO Plus questionnaire data captured prior to the first dosing time. A trend towards faster time to baseline COVID-19 symptom alleviation through Day 14 in the RDV IV for 3 days group with a 41% greater probability of symptom alleviation was observed (HR: 1.405; 95% CI: 0.733 to 2.693; $P = 0.2987$). In a post hoc analysis that included 334 participants (169 in the RDV IV for 3 days group and 165 in the placebo group) who had baseline data captured prior to or on the first dosing date, participants in the RDV IV for 3 days group had a significantly faster time to alleviation of baseline symptoms through Day 14, with a 92% greater probability of symptom alleviation observed (HR: 1.924; 95% CI: 1.259 to 2.939; $P = 0.0014$).

The proportion of participants requiring oxygen supplementation as reported at each study visit by Day 28 or prior to study discontinuation was 1 of 279 participants (0.4%) in the RDV IV for 3 days group and 5 of 283 participants (1.8%) in the placebo group ($P = 0.2163$). One additional participant in the placebo group required mechanical ventilation on Day 16.

Exploratory Efficacy Endpoints

There was a similar mean decrease from baseline in total score of the COVID-19-adapted FLU-PRO Plus questionnaire through Day 14 in both groups.

Median time to negative SARS-CoV-2 viral load and mean changes from baseline in viral load were similar between the treatment groups.

Pharmacokinetics Results: Pharmacokinetic data will be summarized in a separate report.

Safety Results:

Treatment with RDV was well tolerated. Participants in the RDV IV for 3 days group had similar type, incidence, and severity of AEs as participants in the placebo group.

At least 1 AE was reported in 118 of 279 participants (42.3%) in the RDV IV for 3 days group and 131 of 283 participants (46.3%) in the placebo group. The most commonly reported AEs in the RDV IV for 3 days group were nausea (30 participants [10.8%]) and headache (16

participants [5.7%]), and in the placebo group were nausea (21 participants [7.4%]), cough (18 participants [6.4%]), headache (17 participants [6.0%]), dyspnea (15 participants [5.3%]).

Grade 3 or higher AEs were reported in fewer participants in the RDV IV for 3 days group (10 participants [3.6%]) than the placebo group (20 participants [7.1%]). The most common Grade 3 or higher AEs were COVID-19 pneumonia (6 participants [2.1%] in the placebo group), pneumonia (2 participants [0.7%] in each group), COVID-19 (1 participant [0.4%] in the RDV IV for 3 days group and 2 participants [0.7%] in the placebo group), and dyspnea (3 participants [1.1%] in the placebo group). The only Grade 3 AEs that were considered related to study drug were the AEs of alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased at Day 9 in 1 participant who had elevated alkaline phosphatase levels at baseline; these AEs were not considered to be serious and resolved with no further intervention. Grade 4 AEs were reported in 1 participant (0.4%) in the RDV IV for 3 days group (pneumonia) and 7 participants (2.5%) in the placebo group (COVID-19 pneumonia and/or pneumonia, acute myocardial infarction, lumbar vertebral fracture, dyspnea, and respiratory failure, hypoxia).

Study drug-related AEs were reported in more participants in the RDV IV for 3 days group (34 participants [12.2%]) than the placebo group (25 participants [8.8%]). The only study drug-related AEs reported in ≥ 2% of participants in either treatment group were nausea and chills.

Serious AEs were reported in fewer participants in the RDV IV for 3 days group (5 participants [1.8%]) than the placebo group (19 participants [6.7%]); no SAE was considered to be related to study drug.

Adverse events leading to premature study drug discontinuation were reported in 2 participants (0.7%) in the RDV IV for 3 days group and 5 participants (1.8%) in the placebo group; no AE was considered to be related to study drug.

No treatment-emergent death was reported; however, 1 participant in the placebo group had a death due to worsening of COVID-19 disease on Day 59.

Of the 8 adolescent participants in the study, 1 participant in the placebo group reported an AE (mild fatigue).

There were no clinically relevant changes from baseline for hematology, chemistry, and coagulation parameters. Grade 3 or 4 laboratory abnormalities were reported in a similar proportion of participants in both treatment groups (RDV IV for 3 days group, 29 participants [10.5%]; placebo group, 23 participants [8.3%]). The most common Grade 3 or 4 laboratory abnormalities were hyperglycemia (nonfasting), which occurred in a similar proportion of participants in each group, and creatinine clearance decreased and creatinine increased, both of which occurred in more participants in the RDV IV for 3 days group. Most decreases in creatinine clearance occurred while creatinine was within normal range, occurred after completion of RDV therapy, and resolved on follow-up where data were available. No renal AEs were observed during the study. Median changes from baseline to Day 14 in ALT and AST were similar between the treatment groups.

There were no clinically relevant changes from baseline for any vital signs or respiratory status parameter and no notable differences between treatment groups.

CONCLUSIONS:

The conclusions from Study GS-US-540-9012 are as follows:

- Remdesivir was effective at preventing disease progression in high-risk nonhospitalized COVID-19 patients. The primary efficacy endpoint was met, whereby treatment with RDV IV for 3 days resulted in a statistically significant 87% reduction in COVID-19-related hospitalization or all-cause death by Day 28 compared with placebo (2 of 279 participants [0.7%] with RDV and 15 of 283 participants [5.4%] with placebo, $P = 0.0076$). Sensitivity analysis confirmed the results of the primary analysis. There was a consistent benefit of treatment with RDV IV for 3 days compared with placebo across each subgroup by region, age, resident of skilled nursing facility, sex, race, baseline risk factor, and ethnicity.
- Treatment with RDV IV for 3 days resulted in a statistically significant 81% reduction in COVID-19-related MAVs or all-cause death by Day 28 compared with placebo (4 of 246 participants [1.7%] in the RDV IV for 3 days group and 21 of 252 participants [8.5%] in the placebo group) ($P = 0.0024$).
- No significant differences were observed for $DAVG_7$ or $DAVG_{14}$ in nasopharyngeal SARS-CoV-2 viral load, suggesting that upper respiratory viral load was an inadequate efficacy surrogate for RDV.
- In the 22% of participants who had baseline COVID-19-adapted FLU-PRO Plus questionnaire data captured prior to the first dosing time, a trend towards faster time to baseline COVID-19 symptom alleviation through Day 14 in the RDV IV for 3 days group with a 41% greater probability of symptom alleviation was observed. In a post hoc analysis that included 59% of participants who had baseline data on or prior to the first dosing date, participants in the RDV IV for 3 days group had a significantly faster time to alleviation of baseline COVID-19 symptoms through Day 14, with a 92% greater probability of symptom alleviation observed.
- Remdesivir was generally safe and well tolerated with a safety profile similar to that of placebo in outpatients with early stage COVID-19 who were at higher risk of disease progression.

Protocol Amendment History

333 Lakeside Drive
Foster City, CA 94404

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #1

STUDY GS-US-540-9012

A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Original Protocol Date:	21 July 2020
Amendment 1 Date:	11 August 2020

Rationale:	Herein is a summary of the major changes made to the original protocol dated 21 July 2020 and reflected in Amendment #1 dated 11 August 2020. Changes made to the original protocol include modifications for clarification and in response to FDA comments. • Added ClinicalTrials.gov identifier • Increased the number of planned study centers to 150 • Removed restriction on percentage of participants that may be enrolled from skilled nursing facilities • Decreased minimum age to include adolescent participants ages ≥ 12 • Modified inclusion and exclusion criterion • Added sputum samples for SARS-CoV-2 RT-qPCR viral load testing and possible resistance testing • Added study drug administration instructions • Revised Section 7.3.2 Adverse Events • Removed Appendix 2 Pandemic Risk Assessment and Mitigation Plan as it is not applicable for this study Specific changes contained in Amendment 1 are presented herein as ***bold and italicized*** or ~~strikethrough~~. These changes were made to enhance the clarity of the protocol and to perform administrative updates. Study synopsis and all applicable sections are updated to align with above mentioned changes in the protocol. In addition, the opportunity is taken to correct typographical or grammatical errors.

333 Lakeside Drive
Foster City,
CA 94404

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #1.1 (UNITED KINGDOM)

Study GS-US-540-9012

A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Original Protocol Date:	21 July 2020
Amendment 1 Date:	11 August 2020
Amendment 1.1 (United Kingdom) Date:	07 October 2020

Rationale:	Herein is a summary of the major changes made to the protocol amendment 1 dated 11 August 2020 and reflected in Amendment 1.1 (United Kingdom) dated 07 October 2020. Changes made to the protocol amendment include modifications for clarification and in response to comments from the Medicines and Healthcare products Regulatory Agency (MHRA) and the Expert Advisory Group (EAG). Specific changes contained in Amendment 1.1 (United Kingdom) are presented herein as ***bold and italicized*** or ~~strikethrough~~. The opportunity was taken to correct typographical, formatting, or grammatical errors.

333 Lakeside Drive
Foster City, CA 94404

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #1.1 (GERMANY)

STUDY GS-US-540-9012

A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Original Protocol Date:	21 July 2020
Amendment 1 Date:	11 August 2020
Amendment 1.1 (United Kingdom) Date:	07 October 2020
Amendment 1.1 (Germany) Date:	14 October 2020

Rationale:	Herein is a summary of the major changes made to the protocol amendment 1 dated 11 August 2020 and reflected in Amendment 1.1 (Germany) dated 14 October 2020. Changes made to the protocol amendment include modifications for clarification and in response to comments from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). Specific changes contained in Amendment 1.1 (Germany) are presented herein as ***bold and italicized*** or ~~strikethrough~~. The opportunity was taken to correct typographical, formatting, or grammatical errors.

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Foster City, CA 94404

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #2

STUDY GS-US-540-9012

A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Original Protocol Date:	21 July 2020
Amendment 1 Date:	11 August 2020
Amendment 1.1 (United Kingdom):	07 October 2020
Amendment 1.1 (Germany):	14 October 2020
Amendment 2 Date:	06 November 2020

Rationale:	Herein is a summary of the major changes made to the protocol amendment #1 dated 11 August 2020 and reflected in Amendment #2 dated 06 November 2020. The majority of changes reflect updates to the endpoints of the study made in response to evolving treatment paradigms and understanding of COVID-19. Compared to the available data at the time the study was designed, diagnosed patients with risk factors for developing severe COVID-19 are less likely to be immediately hospitalized and are more likely to receive care in an outpatient setting. In addition, mortality for symptomatically treated COVID-19 appears to have been reduced both in hospitalized patients and those who have not been hospitalized. The revised endpoints allow the overall potential for treatment with remdesivir (RDV) to reduce the burden throughout the health care system to be assessed by including all medically attended visits, those visits where the participant and a health care professional are physically present, to be included in the composite endpoint. In addition, endpoints have been aligned with recently reported studies of potential COVID-19 treatment, eg, {Chen 2020} and {Regeneron 2020}, to better allow potential inter-study comparisons to be made in the absence of direct comparative trials.

	Additional changes made to Amendment #2 include modifications for clarification and in response to FDA and other regulatory agencies' comments. • Updated General Information section to refer to the latest IB • Addition, update, and clarification of study endpoints • Addition of coagulation panel • Clarification and/or update of inclusion and exclusion criteria • Addition of complete physical examination requirements section Specific changes contained in Amendment #2 are presented herein as ***bold and italicized*** or ~~strikethrough~~. The protocol synopsis, study procedures table, and all applicable sections were updated to align with above-mentioned changes in the protocol. In addition, the opportunity was taken to correct typographical or grammatical errors.

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Foster City, CA 94404

PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #3

STUDY GS-US-540-9012

A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Original Protocol Date:	21 July 2020
Amendment 1 Date:	11 August 2020
Amendment 1.1 (United Kingdom):	07 October 2020
Amendment 1.1 (Germany):	14 October 2020
Amendment 2 Date:	06 November 2020
Amendment 3 Date:	12 November 2020

Rationale:	Herein is a summary of the changes made to the protocol amendment #2 dated 06 November 2020 and reflected in Amendment #3 dated 12 November 2020. Specific changes contained in Amendment #3 are presented herein as ***bold and italicized*** or ~~strikethrough~~. The protocol synopsis, study procedures table, and all applicable sections were updated to align with above-mentioned changes in the protocol. In addition, the opportunity was taken to correct typographical or grammatical errors.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

PROTOCOL AMENDMENT #4

STUDY GS-US-540-9012

A Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting

Original Protocol Date:	21 July 2020
Amendment 1 Date:	11 August 2020
Amendment 1.1 (United Kingdom):	07 October 2020
Amendment 1.1 (Germany):	14 October 2020
Amendment 2 Date:	06 November 2020
Amendment 3 Date:	12 November 2020
Amendment 4 Date:	14 January 2021

Rationale:	Herein is a summary of the changes made to the protocol amendment #3 dated 12 November 2020 and reflected in amendment #4 dated 14 January 2021: • Update to primary and secondary study objectives • Update to primary and secondary study endpoints • Update to exclusion criterion #3 • Update to study drugs' storage and handling requirements • Update to statistical methods Specific changes contained in Amendment #4 are presented herein as ***bold and italicized*** or ~~strikethrough~~. The protocol synopsis and all applicable sections were updated to align with above-mentioned changes in the protocol. In addition, the opportunity was taken to correct typographical or grammatical errors.

6.1. GS-US-540-9012: List of Principal Investigators

Geographic Region/ Country Principal Investigator	Study Site
Europe / Denmark	Hvidovre Hospital Kettegard Alle 30 2650 Hvidovre
Europe / Denmark	Rigshospitalet Blegdamsvej 9 2100 Copenhagen
Europe / Denmark	Odense University Hospital J.B. Winsløws Vej 4 5000 Odensa C
Europe / Denmark	Aalborg University Hospital Hobrovej 18-22 9000 Aalborg
Europe / Denmark	Aarhus Universitetshospital Palle Juul-Jensens Boulevard 99 8200 Aarhus Aarhus University Hospital Palle Juul-Jensens Boulevard 99 8200 Aarhus
Europe / Spain	Hospital Universitario Germans Trias i Pujol Ctra. de Canyet s/n 08916 Badalona
Europe / Spain	Hospital Universitario Infanta Leonor Avda. Gran Via del Este 80 28031 Madrid
Europe / United Kingdom	University College London Hospitals NHS Foundation Trust 235 Euston Road NW1 2BU London
Europe / United Kingdom	NIHR Bradford Patient Recruitment Centre, Bradford Teaching Hospitals NHS Foundation Trust Duckworth Lane BD9 6RJ Bradford

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	Ascada Research 301 Bastanchury Rd 175 Fullerton, California 92835
North America / United States	St Joseph Hospital Eureka 2700 Dolbeer St. Eureka, California 95501
North America / United States Adams, Atoya, MD	AB Clinical Trials 2110 East Flamingo Road, Suite 103 Las Vegas, Nevada 89119
North America / United States	Be Well Medical Center 1964 11 Mile Rd Berkley, Michigan 48072
North America / United States	Northstar Healthcare 2835 N Sheffield Ave, Suite 500 Chicago, Illinois 60657
North America / United States	Central Texas Clinical Research 900 East 30th Street, Suite 302 Austin, Texas 78705
North America / United States	The Lindner Center for Research and Education at the Christ Hospital 2123 Auburn Avenue, Suite 424 Cincinnati, Ohio 45219

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	Agile Clinical Research Trials, LLC 750 Hammond Dr, Building 2, Suite 100 Atlanta, Georgia 30328
North America / United States	Brody School of Medicine at East Carolina University, Adult Specialty Care 2390 Hemby Lane Greenville, North Carolina 27834
North America / United States	The Crofoot Research Center, INC. 3701 Kirby Drive , Suite 1230 Houston, Texas 77098
North America / United States	Rosedale Infectious Diseases 103 Commerce Centre Dr., Suite 103 Huntersville, North Carolina 28078
North America / United States	North Shore University Hospital/ Division of Infectious Diseases 400 Community Drive Manhasset, New York 11030
North America / United States	Focilmed 300 South A Street, Suite 105, Suite 100, and Parking Lot Oxnard, California 93030

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	Sound Medical Research 463 Tremont St W Port Orchard, Washington 98366
North America / United States	Invesclinic US LLC 4800 N Federal Highway, Suite 202 Fort Lauderdale, Florida 33308
North America / United States	VIP Trials 12103 Huebner Rd San Antonio, Texas 78230
North America / United States	STAAMP Research, LLC 7711 Louis Pasteur Dr., Suite 406 San Antonio, Texas 78229
North America / United States	AXCES Research Group 531 Harkle Road Ste B Santa Fe, New Mexico 87505
North America / United States	Baylor University Medical Center at Dallas 3600 Gaston Avenue, Suite 1202 Dallas, Texas 75246
North America / United States	BSWH Waco 2201 MacArthur Dr., Suite 100 Waco, Texas 76708

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	L&C Professional Medical Research Institute 5965-5975 SW 8 Street, Suite B Miami, Florida 33144
North America / United States	Luminous Clinical Research - South Florida Urgent Care 302 NW 179th Ave., Suite 103 Pembroke Pines, Florida 33029
North America / United States	COVID-19 Clinical Research Center 820 Minor Ave North Seattle, Washington 98109-1024
North America / United States	Quality Clinical Research, Inc 10040 Regency Cr, Suite 375 Omaha, Nebraska 68114
North America / United States	South Shore Hospital 55 Fogg Rd Weymouth, Massachusetts 02190
North America / United States	ClinPoint Trials 100 Professional Place Waxahachie, Texas 75165
North America / United States	IMIC Inc 18320 Franjo Rd Palmetto Bay, Florida 33157
North America / United States	Med Partners, Inc. dba Premiere Medical Center of Burbank. Inc. 4418 Vineland Avenue, Suite 102 & 116 Toluca Lake, California 91602

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	Onyx Clinical Research 2241 S Linden Rd, Suite D Flint, Michigan 48532
North America / United States	Cherokee Nation Outpatient Health Center 19600 E Ross St Tahlequah, Oklahoma 74464
North America / United States	Mills Clinical Research at Men's Health Foundation 9201 W Sunset Blvd, Suite 812 Los Angeles, California 90069
North America / United States	Care United Research, LLC 375 N. Farm to Market 548, Suite 100 Forney, Texas 75126
North America / United States	Midland Florida Clinical Research Center, LLC 665 Peachwood Drive Deland, Florida 32720
North America / United States	Triple O Research Institute, P.A. 2580 Metrocentre Blvd, Suite 4 West Palm Beach, Florida 33407
North America / United States	St. Joseph Heritage Healthcare 2151 N. Harbor Blvd, Suite 3200 Fullerton, California 92835
North America / United States	Memorial Hospital at Gulfport 4500 13th Street Gulfport, Mississippi 39501

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	Evolution Clinical Trials, Inc. 8302 NW 103rd St, Suites 106 and 201 Hialeah Gardens, Florida 33016
North America / United States	Encore Medical Research 5555 Hollywood Blvd, Suite 101 Hollywood, Florida 33021
North America / United States	AIDS Research and Treatment Center of the Treasure Coast 981 37th Place Vero Beach, Florida 32960
North America / United States	Atrium Health ID Consultants 4539 Hedgemore Drive, Suite 110 Charlotte, North Carolina 28209
North America / United States	Midway Immunology and Research Center 360 East Midway Road Fort Pierce, Florida 34982
North America / United States	The Institute of Liver Health 2152 S. Vineyard, Bldg. 8 Suite 123 Mesa, Arizona 85210
North America / United States	VCU Health Medical Center 1250 East Marshall Street Richmond, Virginia 23298
North America / United States	New York-Presbyterian-Queens Hospital 56-45 Main Street Flushing, New York 11355

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	NorthShore University HealthSystem Immediate Care Center - Gurnee 7900 Rollins Rd. Gurnee, Illinois 60031
North America / United States	St. Hope Foundation, Inc, 6800 W Loop South, Ste 500, 560, 580 Bellaire, Texas 77401
North America / United States	Kaiser Permanente San Jose 250 Hospital Parkway Suite 850 San Jose, CA 95119
North America / United States	Kaiser Permanente South San Francisco Medical Center 1200 El Camino Real South San Francisco, California 94080
North America / United States	Kaiser Permanente San Leandro Medical Centre 2500 Merced Street, Rooms 1690 and 1691 San Leandro, California 94577
North America / United States	Kaiser Permanente Sacramento Medical Center 2025 Morse Avenue Sacramento, California 95825
North America / United States	Kaiser Permanente South Sacramento Medical Center 6600 Bruceville Road, Medical Office Building IV Sacramento, California 95823
North America / United States	Kaiser Permanente Vallejo Medical Center 975 Sereno Drive Vallejo, California 94589

Geographic Region/ Country Principal Investigator	Study Site
North America / United States	Porter Adventist Hospital 2525 South Downing Street Denver, Colorado 80210
North America / United States	Center for Pediatric and Community Research (CPCR) 6001 S Sharon Avenue, Suite 2 Sioux Falls, South Dakota 57108
North America / United States	L.A. Universal Research Center, Inc. 820A-822 South Alvarado Street, Clinica Fatima Los Angeles, California 90057
North America / United States	Nuren Medical & Research Center 8260 W Flagler St, Suite 2N Miami, Florida 33144
North America / United States	Intermountain Healthcare 5121 South Cottonwood Street Murray, Utah 84107