FINAL (PART B) 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:	Coronavirus disease 2019 (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.:	147753
EudraCT No.:	2020-000842-32
ClinicalTrials.gov Identifier:	NCT04292730
Study Start Date:	15 March 2020 (First Participant Screened in Part A) 18 April 2020 (First Participant Screened for Part B)
Study End Date:	29 April 2020 (Last Participant Last Observation for the Primary Endpoint) 20 May 2020 (Last Participant Last Observation for Part A) 26 June 2020 (Last Participant Last Observation for Part B)
Principal or Coordinating Investigator:	Name: PPD Affiliation: PPD
Gilead Responsible Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD
Report Date:	28 October 2020
Previous Report Date(s):	05 August 2020 (Interim 2 [Final Part A]) 26 June 2020 (Interim 1 [Part A Day 11])

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: Participants were enrolled across 110 study sites in France, Germany, Hong Kong, Italy, Japan, the Republic of Korea, the Netherlands, Singapore, Spain, Sweden, Switzerland, the United Kingdom, and the United States.

Publications:

Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(11):1048-1057.

Study Period:

15 March 2020 (First Participant Screened for Part A)
18 April 2020 (First Participant Screened for Part B)
29 April 2020 (Last Participant Last Observation for the Primary Endpoint)
20 May 2020 (Last Participant Last Observation for Part A)
26 June 2020 (Last Participant Last Observation for Part B)

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. Part B was a single-group multicenter study of RDV in participants with moderate COVID-19.

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 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

Final results from Part A of the study were described in the Interim 2 (Part A Final) clinical study report (CSR). This final CSR provides efficacy and safety results from Part B of the study.

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 (1000 participants in Part B)
Analyzed (Part B):

- All Enrolled Analysis Set: 517 participants
- Expanded RDV-Treated Analysis Set: 503 participants

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 B was up to 10 days.

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 B, participants received RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5 6, 7, 8, 9, and 10.

The batch numbers of the RDV 100 mg for IV injection were EW1804A1, EW1805A1,

EW2001A1, EW2002A1, and EW2005A1.

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

No study treatment was administered as a reference therapy.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was analyzed in Part A of the study. The efficacy endpoints of interest included endpoints based on clinical status assessed by a 7-point ordinal scale. 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

Efficacy endpoints of interest evaluated in Part B included the following:

- Clinical status on Days 1 to 14, Day 28 and last available assessment
- Change in clinical status on Days 5, 7, 11, 14, 28, and last available assessment
- Time to clinical improvement (days): Clinical improvement is defined as a ≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale
- Percentage of participants with a ≥ 2-point improvement or discharged alive based on the 7-point ordinal scale on Day 5, Day 7, Day 11, Day 14, Day 28, and last available assessment
- Time to ≥ 1-point improvement (days) from baseline clinical status on the 7-point ordinal scale
- Percentage of participants with a ≥ 1-point improvement based on the 7-point ordinal scale on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment
- Time to recovery based on the 7-point ordinal scale, where recovery is defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Percentage of participants with recovery based on the 7-point ordinal scale on Day 5, Day 7, Day 11, Day 14, Day 28, and last available assessment
- Number of days of oxygen support while hospitalized through discharge alive, death or Day 14 based on the 7-point ordinal scale reported values
- Shift in oxygen support status from baseline to Days 5, 7, 11, 14, 28 and last available assessment
- Duration of hospitalization (days) (duration from hospital admission and duration from Day 1)
- All-cause mortality

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

Safety: The other endpoint of interest for Part B was the proportion of participants with treatment-emergent adverse events (TEAEs) in the Extension Treatment Group. 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.

Statistical Methods:

Efficacy: The primary analysis set for efficacy was the Expanded RDV-Treated Analysis Set, which included all participants who were enrolled into Part B of the study and received at least 1 dose of RDV.

The number and percentage of participants in each clinical status category for each day from baseline through Day 14 and at Day 28 and using the last available assessment were summarized by group.

The change from baseline in clinical status category on Days 5, 7, 11, 14, 28 and last available assessment, number of days of oxygen support status modes (invasive mechanical ventilation, high-flow oxygen, low-flow oxygen), and duration of hospitalization were summarized using descriptive statistics.

All-cause mortality was estimated using the Kaplan-Meier product limit method with all available data.

Days to clinical improvement and days to recovery were estimated using a competing risk analysis approach, with death as the competing risk.

The number and percent of participants with ≥ 1-point improvement, ≥ 2-point improvement, and recovery were presented with 95% confidence intervals on Day 5, Day 7, Day 11, Day 14, Day 28 and last available assessment.

Pharmacokinetics: No PK assessments were performed for this report.

Safety: Safety data were summarized for the participants in the Expanded RDV-Treated Analysis Set. All safety data collected on or after the date that study treatment was first dispensed through 30 days after last dose were included in the summaries. All safety data were included in data listings.

Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities, Version 22.1. Toxicity criteria specified in Division of AIDS 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.

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 for each laboratory test for baseline values, values at each postbaseline analysis window, and change from baseline at each postbaseline analysis window.

Descriptive statistics were provided for body weight and vital signs (including heart rate, respiratory rate, and blood pressure) for baseline values, values at each postbaseline visit, and changes from baseline at each postbaseline visit. Concomitant medications were summarized.

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

SUMMARY OF RESULTS:

Participant Disposition: A total of 526 participants were screened, of whom 517 were enrolled, and 503 received at least 1 dose of study treatment in Part B of the study. Fourteen enrolled participants did not receive study treatment.

Of the 503 participants in the Expanded RDV-Treated Analysis Set, 13.1% (66 participants) prematurely discontinued from the study.

The most common reasons for premature discontinuation of study treatment were hospital discharge (57.7%, 290 participants), investigator's discretion (5.6%, 28 participants), AE (2.8%, 14 participants), and participant decision (2.4%, 12 participants).

Participant Demographics and Other Baseline Characteristics: The majority of the participants in the Expanded RDV-Treated Analysis Set were male (56.1%). The median age was 56 years (range: 13 to 93); the majority of the participants were White (60.2%), and the majority were not Hispanic or Latino (67.6%). The median (first quartile [Q1], third quartile [Q3]) body mass index (BMI) was 27.6 (24.0, 33.0) kg/m^2.

The majority of participants had a clinical status of 5 (hospitalized, not requiring supplemental oxygen – requiring ongoing medical care) (88.9%, 447 participants) and the majority of participants were on room air (not requiring oxygen support) (89.7%, 451 participants).

Median (Q1, Q3) baseline ALT and AST were 27 (18, 44) U/L and 30 (21, 45) U/L, respectively. Median (Q1, Q3) baseline serum creatinine and creatinine clearance by Cockcroft-Gault were 0.80 (0.67, 0.97) mg/dL and 104.8 (80.8, 145.2) mL/min, respectively.

Median duration of symptoms prior to first dose of RDV was 8 days and the median duration of hospitalization prior to first dose of RDV was 2 days.

Medical history was reported in 94.4% of participants (475 of 503 participants). The 3 most commonly reported medical history PTs were hypertension (43.5%, 219 participants), hyperlipidemia (24.5%, 123 participants), and cough (18.1%, 91 participants).

The majority of participants were from North America (63.2%, 318 participants); the percentage of participants from Europe was 29.8% (150 participants) and from Asia was 7.0% (35 participants).

Adolescent Participants (12 to < 18 years of age)

There were 4 adolescent participants 12 to < 18 years of age; 3 were female and 1 was male. The median age was 17 years (range: 13 to 17). Three adolescent participants were White, and 1 adolescent participant was Black; 3 adolescent participants were not Hispanic or Latino. The median (Q1, Q3) BMI was 27.2 (23.3, 31.0) kg/m^2.

Three adolescent participants had a clinical status of 5 (hospitalized, not requiring supplemental oxygen – requiring ongoing medical care) and 1 adolescent participant had a clinical status of 4 (hospitalized, requiring low flow supplemental oxygen) at baseline. Median (Q1, Q3) baseline ALT and AST were 21 (11, 30) U/L and 31 (22, 37) U/L, respectively. Median duration of symptoms prior to first dose of RDV was 6 days and the median duration of hospitalization prior to first dose of RDV was 2 days. Adolescent participants were from North America and Europe (2 participants each).

Efficacy Results: Analysis of clinical status on the 7-point ordinal scale demonstrated a majority of participants had been discharged by Day 11 (69.2%, 348 of 503 participants). All adolescent participants were discharged by Day 10. At Day 28, the percentage of participants discharged was 89.3% (449 participants). By Day 11, the percentage of participants with a worsening from baseline in clinical status of at least 1 point was 4.4% (22 participants), and the percentage of

deaths reported was 0.2% (1 participant). The median (Q1, Q3) change from baseline in clinical status on Days 11 and 28 were 2.0 (0.0, 2.0) and 2.0 (2.0, 2.0), respectively.

The majority of participants had a ≥ 2-point or ≥ 1-point clinical improvement by Day 11 (69.4%, 95% CI: 65.2% to 73.4% and 74.4%, 95% CI: 70.3% to 78.1%, respectively). The median time to ≥ 2-point or ≥ 1-point clinical improvement was 7 (5, 13) and 6 (4, 11) days, respectively.

By Day 28, 91.3% (95% CI: 88.4% to 93.6%) of participants recovered and the median (Q1, Q3) time to recovery was 6 (4, 12) days.

Most participants showed an improvement from baseline in oxygen support status at Days 11, 14, and 28. A total of 111 participants were discharged alive on or prior to Day 14 and received low-flow oxygen for a median (Q1, Q3) 3 (1, 5) days. Ten participants were discharged alive on or prior to Day 14 and received high-flow oxygen for a median (Q1, Q3) 2 (2, 4) days. One participant was discharged alive on or prior to Day 14 and received invasive mechanical ventilation for 1 day.

The majority of participants were discharged alive by Day 11 (68.2%, 343 participants). The median (Q1, Q3) duration of hospitalization from Day 1 was 6 (4, 11) days.

A total of 11 participants (2.2%) had died by Day 28.

Analysis of cumulative incidence of recovery at Day 28 for subgroups based on sex at birth, age, baseline oxygen support status, race, and region indicated participants who were < 65 years old, on room air at baseline, or from North America trended towards better outcomes.

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

Safety Results:

Remdesivir administered for 10 days (median [Q1, Q3] exposure, 6 [4, 10] days) was generally well tolerated.

Adverse Events

Overall, 282 participants (56.1%) had at least 1 AE, the most common of which were nausea (8.2%, 41 participants), diarrhea (5.6%, 28 participants), and headache (5.4%, 27 participants). The majority of AEs were Grade 1 or 2 in severity; Grade 3 or higher AEs were reported for 68 participants (13.5%). Adverse events considered related to study treatment were reported in 16.5% of participants (83 of 503 participants).

A total of 13 treatment-emergent deaths were reported during Part B of the study.

Serious adverse events were reported for 40 participants (8.0%). No SAE was reported in > 1% of participants. The only SAE considered related to study treatment was an SAE of hypotension in 1 participant (0.2%).

Adverse events that led to premature discontinuation of study treatment were reported for 15 participants (3.0%). Adverse events that led to premature study treatment discontinuation in > 1 participant were ALT increased (0.6%, 3 participants), AST increased, transaminases increased, and hypotension (each 0.4%, 2 participants).

No pregnancies were reported during the study.

Three adolescent participants had at least 1 AE, none were considered related to study treatment. No AE was reported in > 1 adolescent participant. One adolescent participant had Grade 3 AE (ALT increased), Grade 1 (ALT increased), and Grade 2 (AST increased) AEs that led to premature discontinuation of study treatment. No adolescent participant had an SAE or died.

Higher rates of Grade 3 or higher AEs, and SAEs were reported in older participants (≥ 65 years) compared with younger participants (< 65 years). Higher rates of treatment-emergent death were reported in participants who had low-flow oxygen (5.8%, 3 of 52 participants) in comparison with participants who were on room air (2.2%, 10 of 451 participants). There were no meaningful differences identified in the other subpopulations.

Hepatic Safety

Hepatic AEs were reported in 10.1% of participants (51 of 503 participants). The most commonly reported hepatic AEs reported were ALT increased (3.6%, 18 participants), AST increased, and transaminase increased (each 3.2%, 16 participants). One participant had a nonserious Grade 1 AE of acute hepatitis that was considered related to study treatment and another participant had a nonserious Grade 3 AE of liver toxicity that was related to chemotherapy and not to study treatment.

The combined number of participants with 1 or more transaminase-related AEs (using the PTs ALT increased, AST increased, hepatic enzymes increased, hypertransaminasemia, liver function test increased, and transaminases increased) was 47 participants (9.3%).

No hepatic SAE was reported during Part B of the study. Grade 3 or higher study treatment-related hepatic AEs were reported in 1.4% of participants (7 participants). Hepatic AEs that led to premature study treatment discontinuation were reported in 1.2% of participants (6 participants).

No participant died because of a hepatic event.

Median ALT increased and median AST decreased during Part B of the study; these changes were not clinically meaningful. Grade 3 increases in ALT and AST were reported for 10 participants (2.1%) and 4 participants (0.9%), respectively. No participant had a Grade 4 hepatic-related laboratory abnormality.

Renal Safety

Renal AEs were reported in 1.4% of participants (7 of 503 participants). Renal AEs occurring in more than 1 participant were acute kidney injury (0.8%, 4 participants) and renal failure (0.4%, 2 participants). No renal-related AE was considered related to study treatment.

Between baseline and Day 14, median serum creatinine decreased and median creatinine clearance increased; these changes were not clinically meaningful. Grade 3 or 4 increased creatinine and decreased creatinine clearance were reported for 16 participants (3.3%) and 30 participants (6.4%), respectively.

Laboratory Evaluations

There were no clinically relevant changes from baseline in median values for hematology parameters. Median values for hematology and chemistry parameters were generally within reference ranges.

The majority of participants had at least 1 laboratory abnormality (72.9%, 349 of 479 participants). The majority of the reported laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 or 4 laboratory abnormalities were reported for 83 participants (17.3%). The most common Grade 3 or 4 laboratory abnormality was decreased creatinine clearance (6.4%, 30 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 final analysis of Study GS-US-540-5774 Part B are as follows:

- Participants with moderate COVID-19 who received up to 10 days of RDV had clinical improvement at Day 28 as assessed by a 7-point ordinal scale.
- Remdesivir administered for up to 10 days was generally safe and well tolerated in participants with moderate COVID-19.