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 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.:	147753
EudraCT No.:	2020-000841-15
ClinicalTrials.gov Identifier:	NCT04292899
Study Start Date:	06 March 2020 (First Participant Screened in Part A) 26 March 2020 (First Participant Screened in Part B)
Study End Date:	09 April 2020 (Last Participant Last Observation for the Primary Endpoint) 27 April 2020 (Last Participant Last Observation for Part A) 30 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:	06 November 2020
Previous Report Date(s):	24 June 2020 (Interim [Final Part A] Clinical Study Report)

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: 5 sites in France, 8 sites in Germany, 2 sites in Hong Kong, 12 sites in Italy, 2 sites in Japan, 2 sites in the Republic of Korea, 3 sites in the Netherlands, 3 sites in Singapore, 12 sites in Spain, 3 sites in Sweden, 3 sites in Switzerland, 2 sites in Taiwan, 15 sites in the United Kingdom, and 101 sites in the United States
Publications: There were no publications for Part B of the study at the time of this clinical study report (CSR).
Study Period: 06 March 2020 (First Participant Screened in Part A) 26 March 2020 (First Participant Screened in Part B) 09 April 2020 (Last Participant Last Observation for the Primary Endpoint) 27 April 2020 (Last Participant Last Observation for Part A) 30 June 2020 (Last Participant Last Observation for Part B)
Phase of Development: Phase 3
Objectives: The primary objective of this study was as follows: • To evaluate the efficacy of 2 remdesivir (GS-5734™ [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 treatment in participants with severe COVID-19 was conducted in 2 parts. Part A of this study was a randomized, open-label, multicenter study of RDV in participants with severe COVID-19. Final results from Part A were described in the Study GS-US-540-5773 interim clinical study report (GS-US-540-5773 Interim [Final Part A] CSR).

Part B of this study was a multicenter study of RDV in participants with severe COVID-19. For Part B, up to approximately 5600 additional eligible participants were to be enrolled. Participants were assigned to one of the following 2 groups based on whether or not they were mechanically ventilated at enrollment:

Mechanically Ventilated Treatment Group: continued standard of care therapy together with IV RDV 200 mg on Day 1 followed by intravenous (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

Data are reported descriptively for participants enrolled in Part B. 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) 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), aspartate aminotransferase (AST), creatinine, and creatinine clearance, was performed according to local practice.

The date of enrollment was considered Day 1, and it was expected that all enrolled 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 enrollment, 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 5600 participants in Part B)

Analyzed (Part B):

- All Enrolled Analysis Set: 4490
- Expanded RDV-Treated Analysis Set: 4441 participants (844 in the Mechanically Ventilated group and 3597 in the Extension 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, who had radiographic evidence of pulmonary infiltrates, and who were willing and able to provide written informed consent, or were 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.

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 for injection, 100 mg, 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 in both the Mechanically Ventilated and Extension groups received 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. If the participant was discharged, RDV treatment was stopped at that time.

The batch numbers of the RDV 100 mg for IV injection were EW1802A1, EW1803A1, EW1804A1, EW1805A1, EW2001A1, EW2002A1, and EW2005A1.

Reference Therapy, Dose, Mode of Administration, and Batch No.: None.

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was evaluated 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 endpoint was derived by combining the available death, hospital discharge alive, and ordinal scale assessment reported by the site, where death superseded discharge alive and discharge alive superseded the ordinal scale score reported by the site. 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 requiring ongoing medical care (other than per protocol RDV administration)
7. Not hospitalized

The 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 was 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 Days 5, 7, 11, 14, 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 Days 5, 7, 11, 14, 28, and last available assessment
- Time to recovery based on the 7-point ordinal scale, where recovery was defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Percentage of participants with recovery based on the 7-point ordinal on Days 5, 7, 11, 14, 28, and last available assessment
- Number of days of oxygen support (invasive mechanical ventilation, high-flow oxygen device, low-flow supplemental oxygen) 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: Collection of pharmacokinetic (PK) samples was optional for participants/sites in Part B of the study. Sparse PK assessment were to be performed on Days 2, 4, and 7, and intensive PK assessments on Day 1 and either Day 5 or 10.

Safety: Treatment-emergent adverse events (AEs) were a safety endpoint of interest. 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 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. Part B participants were grouped according to their baseline ordinal scale (Mechanically Ventilated group [baseline ordinal scale 2] or Extension group [baseline ordinal scale > 2]).

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.

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

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.

Pharmacokinetics: Individual PK concentration data and sampling details were listed.

Safety: Safety data was 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 (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, were 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 treatment-emergent AEs was summarized for the subgroups age, sex at birth, race, baseline oxygen support status, and region.

SUMMARY OF RESULTS:

Participant Disposition: A total of 4551 participants were screened, of whom 4490 were enrolled, and 4441 received at least 1 dose of study treatment in Part B of the study. Twenty-four participants met all eligibility criteria and were not enrolled due to withdrawal of consent (11), study enrollment closed (3), investigator's discretion (2), AE (1), and other reasons (7). Forty-nine enrolled participants did not receive any study treatment.

Of the 4441 participants treated, 54.6% (2425 participants) prematurely discontinued study treatment (Mechanically Ventilated group 30.3%, 256 participants; Extension group 60.3%, 2169 participants), and 19.5% (868 participants) prematurely discontinued from the study (Mechanically Ventilated group 26.4%, 223 participants; Extension group 17.9%, 645 participants).

The most common reasons for premature discontinuation of study treatment were hospital discharge (Mechanically Ventilated group 4.6%, 39 participants; Extension group 44.9%, 1614 participants), AE (Mechanically Ventilated group 16.0%, 135 participants; Extension group 7.7%, 277 participants), and death (Mechanically Ventilated group 5.0%, 42 participants; Extension group 3.3%, 118 participants).

Participant Demographics and Other Baseline Characteristics: The majority of the participants in the Expanded RDV-Treated Analysis Set were male (62.6%). The median age was 59 years (range 14 to 96 years); the majority of participants were white (64.8%) and were not Hispanic/Latino (60.9%). The median (first quartile [Q1], third quartile [Q3]) body mass index (BMI) was 30.1 (26.3, 35.5) kg/m^2.

In the Extension group (participants not on mechanical ventilation at baseline), the majority of the participants (61.6%, 2214 of 3597 participants) had a baseline clinical status of 4 (hospitalized, requiring low-flow supplemental oxygen) on the 7-point ordinal scale.

Median (Q1, Q3) baseline ALT was 38 (24, 57) U/L in the Mechanically Ventilated group and 37 (23, 60) U/L in the Extension group, and median (Q1, Q3) baseline AST was 48 (33, 70) U/L in the Mechanically Ventilated group and 43 (30, 63) U/L in the Extension group.

Median (Q1, Q3) baseline serum creatinine was 0.85 (0.68, 1.10) mg/dL in the Mechanically Ventilated group and 0.80 (0.66, 0.97) mg/dL in the Extension group, and median (Q1, Q3) baseline creatinine clearance by Cockcroft-Gault was 112.4 (81.3, 150.6) mL/min in the Mechanically Ventilated group and 114.8 (86.2, 151.4) mL/min in the Extension group.

Median duration of symptoms prior to first dose of RDV was 9 days in the Mechanically Ventilated group and 8 days in the Extension group. Median duration of hospitalization prior to first dose of RDV was 2 days in each group.

The majority of participants in each group were in North America (85.5%, 722 participants in the Mechanically Ventilated group and 81.4%, 2927 participants in the Extension group).

Medical history was reported in 97.3% (821 participants) in the Mechanically Ventilated group and 95.8% (3445 participants) in the Extension group. The most commonly reported medical history preferred term (PT) in both groups was hypertension (49.2%, 415 participants and 46.7%, 1679 participants in the Mechanically Ventilated group and Extension group, respectively).

Adolescent Participants (12 to < 18 years of age)

Of the 12 adolescent participants 12 to < 18 years of age in the study, 7 were male and 5 were female. The median age was 16 years (range: 14 to 17). Seven of the participants were white, 2 were black, and 1 each were Asian, Other, and race not permitted. Six of the participants were not Hispanic/Latino and 5 were Hispanic/Latino (1 not permitted). The median (Q1, Q3) BMI was 30.6 (26.5, 39.0) kg/m^2.

Four of the adolescent participants were in the Mechanically Ventilated group. Of the 8 adolescent participants in the Extension group, 6 had a baseline clinical status of 3 (hospitalized, on noninvasive ventilation or high-flow oxygen devices) and 2 had a baseline clinical status of 4 (hospitalized, requiring low-flow supplemental oxygen). Median (Q1, Q3) baseline ALT and AST were 39 (17, 50) U/L and 40 (27, 64) U/L for the adolescent participants in the Mechanically Ventilated and Extension groups, respectively. Median duration of symptoms prior to first dose of RDV was 7 days and the median duration of hospitalization prior to first dose of RDV was 2 days. Eleven of the 12 adolescent participants were enrolled in North America.

Efficacy Results: Analysis of clinical status as assessed by a 7-point ordinal scale demonstrated that by Day 14, 15.0% (127 of 844 participants) in the Mechanically Ventilated group and 64.9% (2333 of 3597 participants) in the Extension group had been discharged from the hospital. By Day 28, 37.7% (318 participants) in the Mechanically Ventilated group and 76.9% (2754 participants) in the Extension group had been discharged. By Day 14, 12.9% (109 participants) in the Mechanically Ventilated group and 6.8% (245 participants) in the Extension group had died. By Day 28, 23.0% (194 participants) in the Mechanically Ventilated group and 10.5% (377 participants) in the Extension group had died.

By Day 14, none of the 4 adolescent participants in the Mechanically Ventilated group had been discharged from the hospital and none had died, and 5 of the 8 adolescent participants in the Extension group had been discharged and 1 had died. By Day 28, 2 adolescent participants in the Mechanically Ventilated group had been discharged from the hospital and none had died, and in the Extension group, 5 adolescent participants had been discharged and 1 had died (no change from Day 14).

The median (Q1, Q3) change from baseline in clinical status on Day 14 was 0.0 (0.0, 2.0) and 3.0 (0.0, 3.0) in the Mechanically Ventilated and Extension groups, respectively, and on Day 28 was 2.0 (0.0, 5.0) and 3.0 (2.0, 3.0), respectively. Analysis of change from baseline in clinical status by baseline oxygen support showed that by Day 14, the highest percentage of participants discharged from the hospital and the lowest percentage who died were those on room air at baseline (85.4% [268 participants] and 1.6% [5 participants], respectively).

Fewer participants in the Mechanically Ventilated group had ≥ 2-point or ≥ 1-point clinical improvement from baseline at all timepoints compared with participants in the Extension group. The median time to a ≥ 2-point or ≥ 1-point clinical improvement from baseline clinical improvement was longer in the Mechanically Ventilated group compared with the Extension group. Fewer participants in the Mechanically Ventilated group achieved recovery at all timepoints compared with participants in the Extension group. The median time to recovery was longer in the Mechanically Ventilated group compared with the Extension group.

Of the 3 levels of oxygen support (invasive mechanical ventilation, high-flow oxygen, or low-flow oxygen), participants on invasive mechanical ventilation during the study were on oxygen support the longest. At Days 14 and 28, fewer participants in the Mechanically Ventilated group showed an improvement from baseline in oxygen support status compared with those in the Extension group.

Fewer participants in the Mechanically Ventilated group than the Extension group were discharged from the hospital alive by Day 14 (15.0%, 127 of 844 participants vs 64.9%, 2333 of 3597 participants, respectively) and Day 28 (37.7%, 318 participants vs 76.6%, 2754 participants, respectively).

The median (Q1, Q3) duration of hospitalization from Day 1 of the study was longer for the Mechanically Ventilated group than for the Extension group (16 [11, 21] days vs 8 [5, 11] days, respectively).

By Day 28, 23.0% (194 of 844 participants) in the Mechanically Ventilated group had died compared with 10.5% (377 of 3597 participants) in the Extension group.

Analyses of subgroups based on sex at birth, age, race, baseline oxygen support status, and region demonstrated higher cumulative incidences of recovery in younger participants (< 65 years old) in both the Mechanically Ventilated and Extension groups, and in participants with less severe disease in the Extension group. The time to recovery for participants was longer and the mortality rate by Day 28 was higher in the Mechanically Ventilated group across the majority of subgroups analyzed, which is consistent with analyses for the overall study population.

Pharmacokinetics Results: Plasma pharmacokinetic samples were collected preinfusion on Days 4 and 7, and at the end of infusion on Days 2, 4, and 7 for 1 participant in the study. The plasma samples were analyzed for concentrations of RDV, GS-441524 (nucleoside analog of RDV), and GS-704277 (metabolite of RDV) using validated bioanalytical methods. Due to the limited number of samples, no further PK or statistical analyses were conducted.

Safety Results: Remdesivir was administered for a median (Q1, Q3) exposure of 10 (8, 10) days in the Mechanically Ventilated group and 7 (5, 10) days in the Extension group.

Adverse Events

Adverse events were reported in 84.7% (715 of 844 participants) and 61.7% (2219 of 3597 participants) in the Mechanically Ventilated group and Extension group, respectively, during the study.

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

- Mechanically Ventilated group acute kidney injury (18.4%, 155 of 844 participants), hypotension (14.3%, 121 participants), and hypertension and hypernatremia (11.0%, 93 participants each)
- Extension group respiratory failure (8.2%, 296 of 3597 participants), constipation (6.6%, 237 participants), and nausea (6.1%, 220 participants)

With the exception of nausea (Mechanically Ventilated group 3.3%, 28 participants; Extension group 6.1%, 220 participants), participants in the Mechanically Ventilated group had higher

Serious adverse events (SAEs) were reported in a higher percentage of participants in the Mechanically Ventilated group compared with the Extension group (42.9%, 362 participants vs 23.7%, 851 participants, respectively). The most commonly reported SAE in each treatment group was respiratory failure (7.0%, 59 participants and 7.1%, 254 participants in the Mechanically Ventilated group and Extension group, respectively).

The incidence of Grade 3 or higher AEs was higher in the Mechanically Ventilated group than the Extension group (64.3%, 543 participants and 30.9%, 1113 participants respectively). Adverse events considered related to study treatment were reported in a similar percentage of participants in each group (Mechanically Ventilated group 15.0%, 127 participants; Extension group 12.1%, 437 participants).

Adverse events that led to premature discontinuation of study treatment were reported in a higher percentage of participants in the Mechanically Ventilated group compared with the Extension group (16.0%, 135 participants and 7.7%, 277 participants, respectively). The most common AE that led to premature study treatment discontinuation in both groups was acute kidney injury, reported in 6.9% (58 participants) in the Mechanically Ventilated group and 1.9% (67 participants) in the Extension group.

More participants in the Mechanically Ventilated group died during the study compared with participants in the Extension group (Mechanically Ventilated group 25.2%, 213 participants; Extension group 11.7%, 422 participants).

The majority of 12 adolescent participants had at least 1 AE during the study (all 4 participants in the Mechanically Ventilated group and 7 of 8 participants in the Extension group). The 3 most common AEs overall in the 12 adolescent participants were agitation (2 participants in the Mechanically Ventilated group and 1 participant in the Extension group) and constipation and liver function test increased (each 1 participant in the Mechanically Ventilated group and 2 participants in the Extension group). Serious AEs were reported in 1 participant in the Mechanically Ventilated group and 2 participants in the Extension group. One participant in each group prematurely discontinued study treatment because of an AE. One adolescent participant, in the Extension group, died.

In general, higher percentages of AEs were reported in participants aged ≥ 65 years versus those aged < 65 years, in men versus women, and with increasing oxygen support requirement at baseline.

Hepatic Safety

Hepatic AEs were reported in 20.6% (174 of 844 participants) in the Mechanically Ventilated group and 11.4% (410 of 3597 participants) in the Extension group. The overall pattern and types of hepatic AEs were similar in the 2 groups. The 3 most commonly reported hepatic AEs in the Mechanically Ventilated group were AST increased (7.9%, 67 participants), ALT increased (6.4%, 54 participants), and transaminases increased (5.5%, 46 participants), and in the Extension group were ALT increased (4.6%, 167 participants), AST increased (3.6%, 128 participants), and transaminases increased (2.7%, 96 participants).

The combined numbers of participants in each treatment group with 1 or more transaminase-related AEs (using the PTs ALT increased, AST increased, hepatic enzyme increased, hypertransaminasemia, liver function test increased, and transaminases increased)

were 17.3% (146 participants) in the Mechanically Ventilated group and 10.1% (364 participants) in the Extension group.

Hepatic SAEs were reported in a similar percentage of participants in each treatment group, and Grade 3 or higher hepatic AEs were reported in a higher percentage of participants in the Mechanically Ventilated group than the Extension group. Hepatic AEs leading to study treatment discontinuation were reported in 4.7% (40 participants) and 2.7% (96 participants) in the Mechanically Ventilated group and Extension group, respectively.

Median ALT increased in the Mechanically Ventilated group and median AST decreased in both groups during the study; the changes were not clinically relevant. Grade 3 or 4 increased ALT, Grade 3 or 4 increased AST, and Grade 3 or 4 total bilirubin were each reported in higher percentages of participants in the Mechanically Ventilated group versus the Extension group.

Renal Safety

Renal AEs occurred more frequently in the Mechanically Ventilated group (24.8%, 209 of 844 participants) compared with the Extension group (7.1%, 257 of 3597 participants). The overall pattern and types of renal AEs were generally similar in the 2 groups with the exception of acute kidney injury, reported in 18.4% (155 participants) in the Mechanically Ventilated group and 4.9% (177 participants) in the Extension group. The 3 most common renal AEs in the Mechanically Ventilated group were acute kidney injury, blood creatinine increased (2.7%, 23 participants), and renal failure (2.6%, 22 participants), and in the Extension group were acute kidney injury, renal failure (0.8%, 30 participants), and blood creatinine increased (0.8%, 27 participants).

Median serum creatinine decreased and median creatinine clearance increased in both groups during the study; the changes were not clinically relevant.

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 chemistry parameters were generally within reference ranges.

The majority of participants in each treatment group had at least 1 laboratory abnormality (97.5%, 819 of 840 participants and 77.4%, 2725 of 3521 participants in the Mechanically Ventilated group and Extension group, respectively). Grade 3 or 4 laboratory abnormalities were reported in more participants in the Mechanically Ventilated group (67.3%, 565 of 840 participants) compared with the Extension group (27.0%, 950 of 3521 participants). Excluding the 12 participants < 18 years of age who had estimated glomerular filtration rate calculated using the Schwartz formula, the most common Grade 3 or 4 laboratory abnormality in both groups was creatinine clearance decreased (33.5%, 277 of 828 participants and 13.4%, 468 of 3500 participants in the Mechanically Ventilated group and Extension group, respectively). Grade 4 creatinine clearance decreased was more common in the Mechanically Ventilated group than the Extension group (20.3%, 168 participants vs 6.3%, 220 participants, respectively).

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

CONCLUSIONS:

- Most participants with severe COVID-19, including those on invasive mechanical ventilation, had clinical improvement at Days 14 and 28 as assessed by a 7-point ordinal scale.
- The magnitude of clinical improvement was greater in those not on invasive mechanical ventilation, reflecting the impact of COVID-19 disease severity at the time of treatment initiation.
- Remdesivir administered for up to 10 days was generally safe and well tolerated in participants with severe COVID-19, including those on invasive mechanical ventilation.
- Remdesivir administered for up to 10 days in this patient population was not associated with new or unexpected clinical or laboratory safety findings.