CADTH COVID-19 PANDEMIC

COVID-19 CADTH Health Technology Review

Remdesivir: Evidence Review and Appraisal

To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

This report reviews the current scientific evidence on the potential benefits and harms of remdesivir.

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Version	Date	Summary of revisions
1.0	May 14, 2020	First report.
2.0	May 26, 2020	Addition of preliminary results of ACTT from the publication by Beigel et al.[1]
3.0	June 15, 2020	Addition of new data on the GS-US-540-5773 study from the publication by Goldman et al.[2] Review of protocol by Wang et al.[3]
4.0	September 11, 2020	Addition of new data on the GS-US-540-5774 study by Spinner et al.[4] Updates to regulatory status in Canada and in other countries.
5.0	October 22, 2020	Addition of final results of ACTT-1 from the publication by Beigel et al.[5] Update to regulatory status in the US.
6.0	December 2, 2020	Addition of interim study results of WHO Solidarity trial from the publication by the WHO Solidarity Trial Consortium[6]

ACTT = Adaptive COVID-19 Treatment Trial.

Key Findings

Remdesivir (development name GS-5734) by Gilead Sciences Inc. is an antiviral medication that works by stopping the production of viral genetic material, thus preventing viral replication. It was initially developed as a treatment for Ebola but has been fully or conditionally accepted to treat COVID-19 in at least seven jurisdictions around the world, including Canada. This report reviews the currently available scientific evidence on the potential benefits and harms of using remdesivir to treat COVID-19.

Five key studies of remdesivir for the treatment of COVID-19 were the focus of this evidence review. Only one of the trials was completed with all results being published in full (ACTT-1[1,5,7]). Wang et al published results for a trial that was terminated before completion due to recruitment issues. The WHO Solidarity[6] trial is ongoing but has published interim results. Two manufacturer-sponsored trials (GS-US-540-5773, and GS-US540-5774), have each published trial results for the first part of their two-part design.[2,4,8,9] More than 10 other trials of remdesivir for the treatment of COVID-19 have been registered and are ongoing.

While all five of the reviewed studies were phase III, randomized trials, they have important methodological differences. For example, only ACTT-1 and Wang et al. were double-blinded, placebo-controlled trials. The WHO Solidarity trial and Part A of each of the two manufacturer-conducted trials were open label. The WHO Solidarity trial included remdesivir as one of multiple treatment arms with the comparator being standard of care. Part A of GS-US-540-5774) compared two remdesivir treatment regimens of five or ten days with standard of care while Part A of GS-US540-5773 compared a five- and ten-day remdesivir treatment regimen but had no other comparator group.

All participating patients in these studies were hospitalized but the severity of COVID-19 varied. In ACTT-1, 90% of patients were classified as severe with the remaining 10% being considered to have moderate disease. In the trial by Wang et al., all patients were considered as having severe COVID-19. In the WHO Solidarity trial, there were no eligibility criteria related to severity of disease. In Part A of GS-US-540-5774 all patients had moderate COVID-19 while those in Part A of GS-US-540-5773 had severe COVID-19 but were not mechanically ventilated.

The outcomes measured in these studies also varied. While all five trials assessed some form of clinical improvement or recovery, measurement was done in different ways and only Wang et al. (28 days), ACTT-1 (29 days) and WHO Solidarity (in-hospital) measured mortality albeit at slightly different time points. While there was some evidence that time to recovery from COVID-19 may be shorter in patients treated with remdesivir, none of the three trials that examined mortality reported a statistically significant protective effect.

However, important variations in study design, characteristics of the patient population and measured outcomes as well as the methodological limitations of each trial makes synthesis and interpretation of their results very challenging. Until further evidence becomes available for patients with moderate or severe COVID-19, decision-makers and healthcare providers must consider: the value of potential but still uncertain benefits of treatment with remdesivir; the potential risks; and the financial and other implications of access to a therapy that may or may not prove to be effective when additional evidence becomes available.

Introduction

Remdesivir (development name GS-5734, brand name Veklury) by Gilead Sciences Inc. is an antiviral medication with activity against ribonucleic acid (RNA) viruses such as Coronaviridae.[10] It works by stopping the production of viral genetic material, thus preventing viral replication. Initially developed as a treatment for Ebola,[11] remdesivir is currently being used to treat acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Remdesivir is administered by intravenous (IV) infusion;[12] however, the manufacturer has announced that it is investigating an inhaled formulation that would be administered with a nebulizer.[13,14]

Remdesivir received a notice of compliance with conditions in Canada on July 27, 2020.[12] The regulatory status in various jurisdictions is shown in Table 1. In the US, the price of remdesivir is US$520 per vial (US$3,120 for a five-day treatment course).[15]

Table 1: Regulatory Status

Regulatory body	Jurisdiction	Status	Indication
Health Canada[12]	Canada	Notice of Compliance with Conditions (July 27, 2020)	To treat adults and adolescents (aged 12 years and older with a body weight of at least 40 kg) with severe symptoms of COVID-19 who have pneumonia and require extra oxygen.
FDA[16]	US	Full approval (October 22, 2020)	For the treatment of COVID-19 in adult and pediatric patients (aged 12 years and older weighing at least 40 kg) who require hospitalization. Remdesivir should only be administered in a hospital or health care setting capable of providing acute care comparable to inpatient hospital care.
European Medicines Agency[17]	European Union	Conditional marketing authorization (June 25, 2020)	For the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen.
NHS[18,19]	UK	Available under the Early Access to Medicines Scheme (May 26, 2020)	For the treatment of adults and adolescent patients aged ≥ 12 years and weighing at

Regulatory body	Jurisdiction	Status	Indication
			least 40 kg hospitalized with suspected or laboratory-confirmed SARS-CoV-2 infection and severe disease. Patients with severe disease are those with an SpO2 ≤ 94% on room air or requiring supplemental oxygen or requiring non-invasive or invasive ventilation or ECMO.
Therapeutics Good Administration[20]	Australia	Approved for provisional registration (July 20, 2020)	For the treatment of COVID-19 in adults and adolescents (aged 12 years and older weighing at least 40 kg) with pneumonia, requiring supplemental oxygen.
Medsafe[21]	New Zealand	Not approved	NA
Ministry of Health, Labour and Welfare[22]	Japan	Approved (May 7, 2020)	Patients with severe COVID-19 symptoms
Health Sciences Authority [23]	Singapore	Conditional approval (June 10, 2020)	For the treatment of COVID-19 patients; restricted to Infectious Diseases physicians.

ECMO = extracorporeal membrane oxygenation; NA = not applicable; NHS = National Health Service; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SpO2 = peripheral capillary oxygen saturation.

This report reviews the current scientific evidence on the potential benefits and harms of remdesivir.

Clinical Evidence

Literature Search Methods

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[24]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was remdesivir. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's Organization's International Clinical Trials Registry Platform (ICTRP) via ClinicalTrials.gov, the European Union Clinical Trials Register, and Health Canada's Clinical Trials Database.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Where possible, retrieval was limited to the human population.

The initial search was completed on May 5, 2020. Regular alerts updated the search until December 2, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature checklist:[25] Health Technology Assessment

(HTA) Agencies, Drug and Device Regulatory Approvals, Advisories and Warnings, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. Preprints (unpublished manuscripts) were also searched.

Selection Criteria

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. Studies of interest were selected for review according to the criteria outlined in Table 2.

Non-randomized studies, single-arm trials, case series, case reports, conference reports, editorials, letters to editor, and press releases were excluded from the evidence review.

Table 2: Selection Criteria

Population	Patients who are hospitalized with a proven or suspected diagnosis of COVID-19
Intervention	Remdesivir as monotherapy or in combination with standard of care
Comparators	Placebo Standard of care Other pharmacotherapies Other dose or duration of remdesivir
Outcomes	Efficacy; safety
Study design	Randomized controlled trials published in full (excluding preprints)

Literature Search Results

The initial literature search identified one RCT that met the inclusion criteria.[7] Three other unpublished RCTs identified in the initial literature search were considered of interest: one RCT had ended recruitment but was not yet published in full[26] and two RCTs that were ongoing with trial completion dates in May 2020.[8,9] Data from two of the unpublished RCTs[8,26] provided evidence for the US FDA in its initial Emergency Use Authorization of remdesivir.[27]

On May 22, 2020, preliminary trial results were published for ACTT-1.[1] On May 27, 2020 and on August 21, 2020, the Part A trial results were published for GS-US-540-5773 and GS-US-540-5774, respectively.[2,4] On October 9, 2020, the final results for ACTT-1 were published.[5] On December 2, 2020, the interim results of the WHO Solidarity trial were published.[6] CATCO, the Canadian arm of the WHO Solidarity trial is still recruiting patients.[28]

The list of excluded studies are provided in Appendix 1. The details of other ongoing trials are listed in Appendix 2.

Study Characteristics

The characteristics of the studies of interest to this report are summarized in Table 3.

Table 3: Characteristics of the Included RCTs

		Wang et al.	ACTT-1	GS-US-540-5773	GS-US-540-5774	WHO Solidarity
DESIGNS AND POPULATIONS	**Clinical trial number**	NCT04257656	NCT04280705	NCT04292899	NCT04292730	ISRCTN83971151
	Status	Terminated	Completed	Completed (Part A)	Completed (Part A)	Ongoing CATCO, the Canadian Arm of the WHO Solidarity trial is still recruiting patients.
	Actual study completion Date	April 10, 2020	May 21, 2020	June 30, 2020	June 26, 2020	March 3, 2021
	Funding	National Key Research and Development Program of China	National Institute of Allergy and Infectious Diseases	Gilead Sciences, Inc.	Gilead Sciences, Inc.	WHO
	Study design	Phase III, DB, PC, multi-centre RCT 2:1 randomization	Adaptive phase III, DB, PC, multi-centre RCT 1:1 randomization	Phase III, OL, multi-centre RCT 1:1 randomization	Phase III OL, multi-centre, RCT 1:1:1 randomization	Phase III OL, multi-centre, RCT 1:1 randomization
	Locations	10 hospitals in Hubei, China	73 study locations (10 countries, excluding Canada)	Part A: 55 study locations (8 countries, excluding Canada) Part B: 183 study locations (14 countries, excluding Canada)	105 hospitals (15 countries, excluding Canada)	405 hospitals (30 countries including Canada)
	Randomized, N	237	1,062	402	596	5,475
	Part B, N	NA	NA	4,489 (total # of patients in trial was 4,891)	517 (total # of patients in trial was 1,113)	
	Inclusion criteria	• ≥ 18 years old • RT-PCR positive for SARS-CoV-2 infection Pneumonia confirmed by chest	• ≥ 18 years old • Laboratory-confirmed SARS-CoV-2 infection by RT-PCR < 72 hours prior to randomization or ≥ 72 hours prior to	• ≥ 12 years old • SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization	• ≥ 12 years old • Weight ≥ 40 kg for patients 12 to < 18 years old	• ≥ 18 years old • Hospitalized • With a definite diagnosis of COVID-19 • Not already receiving any of the study drugs

	Wang et al.	ACTT-1	GS-US-540-5773	GS-US-540-5774	WHO Solidarity
	imaging, O_2 saturation ≤ 94% on room air or arterial O_2 partial pressure to fractional inspired O_2 ≤ 300 mm Hg • Within 12 days of symptom onset	randomization if unable to obtain sample or if patient had progressive disease consistent with SARS-CoV-2 • Agreement to not participate in another COVID-19 clinical trial through day 29 • Symptoms of any duration and at least one of the following (suggestive of lower respiratory tract infection): ○ Radiographic infiltrates by imaging ○ O_2 saturation ≤ 94% on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO	• Hospitalized • O_2 saturation ≤ 94% or requiring supplemental oxygen at screening • Radiographic evidence of pulmonary infiltrates	• SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization • Moderate COVID-19 defined as any radiographic evidence of pulmonary infiltrates and O_2 saturation > 94% on room air	
Exclusion criteria	• Pregnant or breastfeeding • Hepatic cirrhosis • AST or ALT > 5 times ULN • eGFR < 30 mL/min/ 1.73 m^2 or receiving renal replacement therapy, hemodialysis or peritoneal dialysis • Enrolment in an investigational treatment for	• Pregnant or breastfeeding • AST or ALT > 5 times ULN • eGFR < 30 mL/min (including patients receiving hemodialysis or hemofiltration) • Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 hours • Allergy to study medication	• Pregnant or breastfeeding • Participation in any other clinical trial of an experimental treatment for COVID-19 • Concurrent treatment with other drugs with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours before study drug dosing	• Pregnant or breastfeeding • Participation in any other clinical trial of an experimental treatment for COVID-19 • Concurrent treatment with other drugs with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours before study drug dosing • Requiring mechanical ventilation at screening • ALT or AST > 5 times ULN • Creatinine clearance < 50 mL/min	• Known allergy to any of study drugs • Contraindications to study drugs (e.g., chronic liver disease, heart disease or pregnancy) • Anticipated transfer within 72 hours to a non-study hospital

		Wang et al.	ACTT-1	GS-US-540-5773	GS-US-540-5774	WHO Solidarity
		COVID-19 30 days before screening • Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 hours		• Evidence of multiorgan failure • Mechanically ventilated or receiving ECMO • AST or ALT > 5 times ULN • Creatinine clearance < 50 mL/min		
Drugs	**Intervention(s)**	Remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 10. Use of other treatments such as lopinavir-ritonavir was permitted.	Remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 10 or until hospital discharge or death. Supportive care according to the standard of care for the trial site hospital.	**PART A** **Treatment group 1:** (Remdesivir, 5 days, not mechanically ventilated): Standard of care together with remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 5. **Treatment group 2:** (Remdesivir, 10 days, not mechanically ventilated): Standard of care together with remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 10.	**PART A** **Treatment group 1:** Standard of care together with remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 5. **Treatment group 2:** Standard of care together with remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 10. **Standard of care** No description provided **PART B:** **(Extension treatment** (Remdesivir 5 or 10 days): Continued standard of care therapy together with IV remdesivir 200 mg on day 1 followed by IV remdesivir	Remdesivir 200 mg on day 0 given as an IV infusion and 100 mg given as an IV infusion on days 1 through 9. Other treatment groups of WHO Solidarity: Hydroxychloroquine 800 mg orally at hour 0 and hour 6; then 400 mg twice daily orally staring at hour 12 for 10 days. Lopinavir 400 mg (combined with ritonavir 100 mg) orally twice daily for 14 days Interferon beta-1a 44 mcg subcutaneously at randomization, at day 3 and at day 6. Where available, patients receiving high-flow oxygen, ventilation, or ECMO were given interferon beta-1a 10 mcg IV daily for 6 days. (Interferon was administered with lopinavir-ritonavir until July 4, 2020).

		Wang et al.	ACTT-1	GS-US-540-5773	GS-US-540-5774	WHO Solidarity
				PART B: Extension Treatment Group (Remdesivir, 5 or 10 days): Standard of care together with remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 10. If the five-day dosing regimen used in treatment group 1 of Part A is selected for Part B, all participants in the extension treatment group and all new participants will be reassigned to receive treatment for a total of five days. **Mechanically Ventilated Treatment Group** (Remdesivir, 10 days): Standard of care together with remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 10. Remdesivir treatment will be stopped at discharge regardless	100 mg on days 2 to 10, unless treatment group 1 of Part A is selected. If treatment for 5 days is selected, all participants in the Extension Treatment Group and all new patients will be reassigned to receive treatment for a total of 5 days.	The hydroxychloroquine, lopinavir-ritonavir, and interferon regimens were discontinued for futility on, June 19, 2020, July 4, 2020, and October 16, 2020, respectively.

		Wang et al.	ACTT-1	GS-US-540-5773	GS-US-540-5774	WHO Solidarity
				of the scheduled duration of therapy.		
	Comparator(s)	Same volume of placebo infusions for a total of 10 days (provided by Gilead Sciences, Inc.)	Matching placebo given as an IV infusion on day 1 then as an IV infusion on days 2 to 10. A placebo of normal saline of equal volume was given at the European sites and some non-European sites due to a shortage of matching placebo supplies. At these sites, IV treatment and control bags and tubing were covered with opaque wrapping to maintain blinding. Supportive care according to the standard of care for the trial site hospital.	None	**PART A:** Standard of care treatment for COVID-19 infection (not described)	Each treatment group was compared to no treatment (local standard of care)
DURATION	**Phase**					
	Treatment duration	10 days	10 days	Up to 10 days (Part A)	Up to 10 days (Part A)	6 days to 14 days (10 days for remdesivir)
	Follow-up	28 days from randomization	28 days from randomization	28 days from first dose	28 days from first dose	28 days
OUTCOMES	**Primary end point**	Time to clinical improvement within 28 days after randomization[a]	Time to recovery[b]	Clinical status assessed by a seven-point ordinal scale[e] on day 14	The odds of clinical improvement on a seven-point ordinal scale[e] on day 11	In-hospital mortality
	Secondary end points	• Proportions of patients in each category of a six-point clinical improvement scale[a] at day 7,	Key secondary end point • Clinical status on an eight-point ordinal scale[c] on day 15 Other secondary end points	Secondary end point: • Proportion of patients experiencing TEAEs for up to 30 days after last dose	Proportion of patients experiencing TEAEs Pre-specified exploratory end points:	• Initiation of mechanical ventilation • Duration of hospitalization (time to discharge alive)

		Wang et al.	ACTT-1	GS-US-540-5773	GS-US-540-5774	WHO Solidarity
		14, and 28 after randomization • All-cause mortality at day 28 • Frequency of invasive mechanical ventilation • Duration of oxygen therapy • Duration of hospital admission • Proportion of patients with nosocomial infection • Proportion of patients with viral RNA detected and viral RNA load measured by quantitative RT-PCR • TEAEs • SAEs • AEs • Premature discontinuation of study drug	• Time to improvement of one or two categories from the baseline clinical status ordinal scale • Clinical status as assessed on the ordinal scale at days 3, 5, 8, 11, 15, 22, and 29 • Mean change in status on the ordinal scale from day 1 to days 3, 5, 8, 11, 15, 22, and 29 • Time to discharge or NEWS[d] of ≤ 2 (maintained for 24 hours), whichever occurred first • Change in NEWS from day 1 to days 3, 5, 8, 11, 15, 22, and 29 • Days of supplemental oxygen, with non-invasive ventilation or high-flow oxygen, and with invasive ventilation of ECMO up to day 29 • Incidence and duration of new oxygen use, of non-invasive ventilation or high-flow oxygen, and of invasive ventilation or ECMO up to day 29 • Number of days of hospitalization up to day 29 • Mortality at 14 and 28 days after enrollment • Grade 3 and 4 adverse events and serious adverse events	Pre-specified exploratory end points: • Time to clinical improvement[f] • Time to recovery[g] • Time to modified recovery[h] • All-cause mortality Other protocol specified end points for Part A, not reported in the publication: • Patients with negative PCR on days 5 and 10 • Days on oxygen support • Days on invasive mechanical ventilation • Days on high-flow oxygen devices • Days on low-flow supplemental oxygen • Duration of hospitalization • Time to room air based on seven-point ordinal scale	• Proportion of patients with negative SARS-CoV-2 PCR • Time to clinical improvement defined as ≥ 2-point improvement in clinical status (7-point ordinal scale) from day 1 • Time to ≥ 1-point improvement from baseline clinical status • Time to recovery[i] • Time to modified recovery[j] • Time to room air[k] • Duration of oxygen therapy • Shift in oxygen support status from baseline • Duration of hospitalization • All-cause mortality at day 28	

		Wang et al.	ACTT-1	GS-US-540-5773	GS-US-540-5774	WHO Solidarity
			• Discontinuation or temporary suspension of infusions • Changes in assessed laboratory values over time.			
NOTES	**Publications**	Wang et al.[7]	Beigel et al.,[1] Beigel et al.,[5] ClinicalTrials.gov,[26] FDA EUA[27]	Goldman et al.,[2] ClinicalTrials.gov,[8] FDA EUA[27]	Spinner et al.[4] ClinicalTrials.gov[9]	WHO Solidarity Trial Consortium[6]

ACTT = Adaptive COVID-19 Treatment Trial; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DB = double blind; CR = creatinine; EAU = Emergency Use Authorization; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; Hg = hemoglobin; O2 = oxygen; min = minute; NA = not applicable; NEWS = National Early Warning Score; OL = open label; PC = placebo controlled; PCR = polymerase chain reaction; PT = prothrombin time; RNA = ribonucleic acid; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; TEAE = treatment-emergent adverse event; ULN = upper limit of normal; WBC = white blood cell; WHO = World Health Organization.

[a] Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or live discharge from the hospital, whichever came first. The six-point scale was as follows: 6 = death; 5 = hospital admission for extracorporeal membrane oxygenation or mechanical ventilation; 4 = hospital admission for non-invasive ventilation or high-flow oxygen therapy; 3 = hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation); 2 = hospital admission but not requiring oxygen therapy; and 1 = discharged or having reached discharge criteria (defined as clinical recovery; i.e., normalization of pyrexia, respiratory rate lower than 24 breaths per minute, saturation of peripheral oxygen greater than 94% on room air, and relief of cough, all maintained for at least 72 hours).

[b] day of recovery is defined as the first day on which the patient satisfies one of the following three categories from the ordinal scale: 1 = Not hospitalized, no limitations on activities; 2 = Not hospitalized, limitations of activities, home oxygen requirement, or both; 3 = Hospitalized, not requiring supplemental oxygen and no longer require ongoing medical care (used if hospitalization was extended for infection-control reasons).

[c] The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The eight-point scale is as follows: 1 = Not hospitalized, no limitations of activities; 2 = Not hospitalized, limitation of activities, home oxygen requirement, or both; 3 = Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4 = Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions); 5 = Hospitalized, requiring any supplemental oxygen; 6 = Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices; 7 = Hospitalized, receiving invasive mechanical ventilation or ECMO; and 8 = Death.

[d] The NEWS has demonstrated an ability to discriminate patients at risk of poor outcomes. This score is based on seven clinical parameters:(respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, and level of consciousness).

[e] The ordinal scale is an assessment of the clinical status at a given day. Each day, the worst score from the previous day will be recorded. The scale is as follows: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on non-invasive ventilation or high-flow oxygen devices; 4 = Hospitalized, requiring low-flow supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise); 6 = Hospitalized, not requiring supplemental oxygen; no longer required ongoing medical care (other than per-protocol remdesivir administration); 7 = Not hospitalized.

[f] Clinical improvement was defined as an improvement of at least two points from baseline on the seven-point ordinal scale.

[g] Recovery was defined as an improvement from a score of 2 to 5 at baseline on the ordinal scale to a score of 6 or 7.

[h] Modified recovery was defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7.

[i] improvement in baseline score from 2-5 to 6 or 7, or from a baseline score of 6 to a score of 7.

[j] improvement in baseline score of 2-4 to a score of 5-7, or baseline score of 5 to a score of 6-7, or baseline score of 6 to 7.

[k] improvement in baseline score from 2-4 to a score of 5-7.

Study Design Characteristics

Wang et al.

Wang et al. reported the findings of a randomized, double-blind, placebo-controlled trial of remdesivir in patients with severe COVID-19.[7] The study was conducted in 10 hospitals in the city of Wuhan (Hubei, China).

Non-pregnant women and men 18 years and older with laboratory-confirmed SARS-CoV-2 infection and radiologically confirmed pneumonia, with an oxygen saturation of 94% or less on room air, or an arterial O2 partial pressure to fractional inspired O2 of 300 mm Hg or less were eligible for enrolment. As well, patients were required to be within 12 days of symptom onset to be eligible. Patients with hepatic cirrhosis, elevated liver enzymes, or severe renal impairment were excluded.[7] The details of the inclusion and exclusion criteria are provided in Table 3.

Originally, the trial was to enrol a total of 457 patients and had allowed for an interim analysis after 240 patients had been enrolled. However, the trial was terminated early when the epidemic of COVID-19 was brought under control in China and no additional patients could be enrolled. Consequently, the trial data were analyzed when 237 patients had been randomized into the study. Patients were randomly assigned in a 2:1 ratio to remdesivir 200 mg administered by IV infusion on the first day of treatment followed by 100 mg remdesivir administered daily by IV infusion for nine days, or to placebo administered by daily IV infusions for 10 days using the same infusion volume as in the remdesivir group. Randomization was stratified according to the level of respiratory support at the time of randomization as follows: no oxygen support or oxygen support with nasal duct or mask; or high-flow oxygen, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation (ECMO). The use of other treatments, including lopinavir-ritonavir, was permitted.[7]

The primary end point was the time to clinical improvement within 28 days after randomization. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or live discharge from the hospital, whichever came first. The six-point scale was defined as follows: 6 = Death; 5 = Hospital admission for ECMO or mechanical ventilation; 4 = Hospital admission for non-invasive ventilation or high-flow oxygen therapy; 3 = Hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation); 2 = Hospital admission but not requiring oxygen therapy; 1 = Discharged or having reached discharge criteria (defined as clinical recovery; i.e., normalization of pyrexia, respiratory rate of less than 24 breaths per minute, saturation of peripheral oxygen of more than 94% on room air, and relief of cough, all maintained for at least 72 hours). Data were captured daily by trained nurses from day 0 to day 28 or until death.[7] Details of the statistical analysis are provided in Appendix 3.

Adaptive COVID-19 Treatment Trial (ACTT-1)

The National Institute of Allergy and Infectious Diseases conducted a phase III, adaptive, double-blind, placebo-controlled trial of remdesivir compared with placebo in adults who were hospitalized as a result of diagnosed COVID-19 and had evidence of a lower respiratory track infection (ACTT-1).[1,5] The study was conducted at 73 study sites and subsites globally and across 10 countries (with no study locations in Canada) (Table 3). Under its adaptive design, ACTT-1 included interim monitoring that would allow for the introduction of new arms and allow early termination for reasons of futility, efficacy, or

safety, as well as updates to sample size.[27] As an adaptive design feature of ACTT-1, if a treatment was found to be efficacious, it could become the control arm for comparisons to other drugs under study.[27] A total of 1,062 patients were randomized into the trial; recruitment ended on April 19, 2020. A preliminary report of results by day 14 was published on May 22, 2020.[1] When these results were made public, physicians could request to be made aware of the treatment assignment of patients who had not completed the trial to day 29 if clinically indicated (for example, for those with worsening clinical status). Hence, patients assigned to placebo could be crossed over to the remdesivir group. The final results of ACTT-1 were published on October 9, 2020.[5]

Patients age 18 years and older with laboratory-confirmed SARS-CoV-2 infection and who had at least one of the following were eligible for enrolment: radiographic infiltrates on imaging, an oxygen saturation of 94% or less on room air, or a requirement of supplemental oxygen, mechanical ventilation, or ECMO. Patients who were pregnant and breast feeding were excluded, as were those with allergy to study product, hepatic impairment (defined as an alanine aminotransferase or aspartate aminotransferase > five times the upper limit of normal) or severe renal impairment (defined as stage 4 severe chronic kidney disease or requiring dialysis). Patients were not permitted to participate in other COVID-19 trials during the 29-day trial duration. Patients with anticipated discharge from the hospital or transfer to another hospital within 72 hours of enrollment were excluded. There were no restrictions on symptom duration prior to enrollment.[5] Inclusion and exclusion criteria details are provided in Table 3.

In ACTT-1, patients were randomly assigned in a 1:1 ratio (stratified by study site and disease severity at enrollment) to remdesivir or placebo. Severe disease was defined as patients meeting one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an oxygen saturation of 94% or less on room air, or tachypnea (respiratory rate of 24 breaths or more per minute). Mild-to-moderate disease was defined by an oxygen saturation of more than 94% and respiratory rate less than 24 breaths per minute without requiring supplemental oxygen. Remdesivir 200 mg was administered by IV infusion on the first day of treatment followed by remdesivir 100 mg administered daily by IV infusion on days 2 to 10, or until discharge or death; patients randomized to placebo received matching placebo IV infusions for 10 days, or until discharge or death. An equal volume of normal saline was used at the European sites and some non-European sites due to a shortage of matching placebo. Blinding was maintained for remdesivir and placebo infusions by using opaque bag and tubing covers if matching placebo was unavailable. Patients were permitted to receive other treatments for COVID-19 if the study site had a written policy or guideline for the use of those treatments. However, other experimental treatment or off-label medications for COVID-19 were not permitted if the study site did not have a policy or guideline for their use.[5]

Clinical status was assessed throughout the trial using an eight-point ordinal scale defined as follows: 1 = Not hospitalized, no limitations of activities; 2 = Not hospitalized, limitation of activities, home oxygen requirement, or both; 3 = Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4 = Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions); 5 = Hospitalized, requiring any supplemental oxygen; 6 = Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices; 7 = Hospitalized, receiving invasive mechanical ventilation or ECMO; and 8 = Death. Clinical status was also assessed daily using the National Early Warning Score (NEWS). Patients were assessed daily from days 1

to 29 while hospitalized. The primary end point of the trial was time to recovery, which was defined as the first day on which a patient satisfied categories one, two, or three of the eight-point ordinal scale during the 28-day period following enrolment. The key secondary end point of the study was clinical status assessed on day 15 of the trial, measured on the eight-point ordinal clinical status scale.[5] Other secondary outcomes are listed in Table 3. Details of the statistical analysis of ACTT-1 are described in Appendix 3.

Subgroup analyses were pre-specified according to disease severity at baseline, sex, age, race, ethnic group, comorbidities, duration of symptoms before randomization (less than or equal to 10 days or greater than 10 days, in quartiles, and as the median) and site location.

GS-US-540-5773

GS-US-540-5773 was a manufacturer-conducted, open-label, randomized trial that compared remdesivir treatment regimens of different duration in patients diagnosed with severe COVID-19.[2] Initially, only adult patients (≥ 18 years) were eligible for inclusion, but the original trial protocol was revised to include patients aged 12 and older.[8] The multi-centre study included 55 sites across eight countries (with no study locations in Canada) (Table 3). Part A of the trial included a total of 397 patients across treatment groups.

Patients with laboratory-confirmed SARS-CoV-2 infection up to four days before randomization and who were hospitalized with radiographic evidence of pulmonary infiltrates and either oxygen saturation of 94% or less on room air or who were on supplemental oxygen were eligible for inclusion. Patients on ECMO or mechanical ventilation at screening were excluded, as were patients with signs of multiorgan failure. Patients who received an antiviral with activity against SARS-CoV-2 less than 24 hours before screening were not eligible for inclusion, nor were those participating in another clinical trial for a COVID-19 treatment. Hepatic impairment or severe renal impairment before screening were other key exclusion criteria.[2] The details of the inclusion and exclusion criteria are provided in Table 3.

In Part A of GS-US-540-5773, which included only patients who were not mechanically ventilated, patients were randomly assigned in a 1:1 ratio to remdesivir plus standard of care for either a five-day or a 10-day treatment regimen. Randomization was not stratified. For both groups, the remdesivir dose was 200 mg administered by IV infusion on the first day of treatment followed by 100 mg remdesivir administered daily by IV infusion for the remainder of the regimen (Table 3).[2] Patients whose condition improved and were discharged from the hospital were not required to complete the full course of treatment. In a revision to the initial trial protocol, a second phase of the trial, Part B, was added and results have not yet been published.[8]

The primary end point of the trial was the clinical status measured on day 14 on a seven-point ordinal scale (Table 3). Each day, the worst score from the previous day was recorded. The scale was as follows: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on non-invasive ventilation or high-flow oxygen devices; 4 = Hospitalized, requiring low-flow supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise); 6 = Hospitalized, not requiring supplemental oxygen; no longer required ongoing medical care (other than per-protocol remdesivir administration); 7 = Not hospitalized. The proportion of patients experiencing treatment-emergent adverse events was a secondary outcome in the trial. Additional study outcomes are described in Table 3, but not all outcomes specified in the study protocol were reported in the publication.

Patients were followed for 28 days after their first dose.[2] Details of the statistical analysis are described in Appendix 3.

Part B of GS-US-540-5773 included a treatment group of mechanically ventilated patients who received a 10-day treatment course of remdesivir.[8] It also included an extension treatment group of patients who received a five-day or 10-day treatment course of remdesivir. If the five-day dosing regimen used in Part A was selected for Part B, all participants in the extension treatment group and all new participants were reassigned to receive treatment for a total of five days. Initially, a sample size of 5,600 patients was planned for Part B and the actual number of patients was 4,489 (Table 3).[8] No data have been reported for Part B of GS-US-540-5773. Part B data will be reported descriptively.

GS-US-540-5774

GS-US-540-5774 was a manufacturer-conducted, open-label, randomized trial in patients diagnosed with moderate COVID-19. The multi-centre study included 105 hospitals across 15 countries (with no study locations in Canada) (Table 3). Part A of the trial included a total of 584 patients across treatment groups.[4]

Patients with SARS-CoV-2 infection that was confirmed by PCR four days or less before randomization and moderate COVID-19 pneumonia defined as radiographic evidence of pulmonary infiltrates and oxygen saturation greater than 94% on room air were eligible for inclusion. Patients on mechanical ventilation at screening were excluded. Initially, only adult patients (18 years or older) were eligible for inclusion, but the original trial protocol was revised to include patients 12 years and older. Patients on concurrent treatment or planned concurrent treatment with a drug active against SARS-CoV-2 were not eligible for inclusion, and neither were those participating in another clinical trial for a COVID-19 treatment. Severe renal impairment before screening was another key exclusion criterion. The details of the inclusion and exclusion criteria are provided in Table 3.[4]

In Part A of GS-US-540-5774, patients were randomly assigned in a 1:1:1 ratio to receive remdesivir plus standard of care for five days, remdesivir plus standard of care for 10 days, or standard of care alone. Randomization was not stratified. The study was open-label and study follow-up was 28 days. In patients that received continued standard of care with remdesivir for five days or 10 days, the remdesivir dose was 200 mg administered by IV infusion on day one followed by 100 mg remdesivir administered daily by IV infusion for four or nine days, respectively (Table 3). Standard of care was not described. Treatment with remdesivir was discontinued in patients that experienced severe hepatic or renal impairment, a serious adverse event, or an adverse event of grade 3 or 4 severity. Patients whose condition improved and were discharged from the hospital were not required to complete the full course of treatment.[4] In a revision to the initial trial protocol, a nonrandomized extension phase of the trial, Part B, was added and results have not yet been published.

The original primary end point of the trial was the proportion of patients discharged by day 14. It was subsequently amended to the odds of clinical improvement on a seven-point ordinal scale on day 11. (Table 3). Each day, the worst score from the previous day was recorded. The scale was as follows: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on non-invasive ventilation or high-flow oxygen devices; 4 = Hospitalized, requiring low-flow supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise); 6 = Hospitalized, not requiring supplemental oxygen; no longer required

ongoing medical care (other than per-protocol remdesivir administration); 7 = Not hospitalized. The proportion of patients experiencing treatment-emergent adverse events was a secondary outcome in the trial. Additional pre-specified exploratory end points are described in Table 3, but not all outcomes specified in the study protocol were reported in the publication. In an amendment to the statistical analysis plan, analysis on clinical status up to 28 days was performed.[4]

The details of the inclusion and exclusion criteria are provided in Table 3.

Part B of GS-US-540-5774 is an extension, manufacturer-conducted, nonrandomized, single group, multicenter study of patients with moderate COVID-19. The study protocol dated April 29, 2020 specified a target sample size of approximately 1,000 patients who were enrolled following completion of enrollment in Part A. The actual number of patients completing Part B was 517.[9] Patients continued standard of care therapy and remdesivir 200 mg on day 1, followed by remdesivir 100 mg on days 2 to 10, unless patients were assigned to the five-day treatment regimen in Part A. If the five-day dosing regimen was selected, all patients in the extension treatment group and all new patients were reassigned to receive treatment for a total of five days. No data have been reported for Part B of GS-US-540-5774. Part B data will be reported descriptively.[9]

WHO Solidarity

WHO Solidarity conducted by the World Health Organization (WHO) was a multi-centre, open-label, adaptive, randomized trial that compared remdesivir, hydroxychloroquine, lopinavir-ritonavir, or interferon beta-1a (combined with lopinavir-ritonavir until July 4, 2020) against their own control group in hospitalized patients with a confirmed diagnosis of COVID-19.[6] While there were four treatment groups, only the results of the remdesivir group are pertinent to this report. Since the trial was adaptive, treatment arms could be dropped and added accordingly. This trial included 405 hospitals across 30 countries. A total of 11,330 patients were included in the trial, with 5,475 patients assigned to remdesivir or its control group.

The following treatment groups including hydroxychloroquine, lopinavir-ritonavir, and interferon beta-1a were discontinued due to futility on June 19, 2020, July 4, 2020 and October 16, 2020, respectively.

Patients 18 years and older, hospitalized with definite COVID-19 and not already receiving any of the study drugs, without known allergy or contraindications to any of the study drugs, and without anticipated transfer within 72 hours to a non-study hospital were eligible for inclusion. Patients were excluded if any of the treatment drugs were contraindicated. The details of the inclusion and exclusion criteria are provided in Table 3.

Patients were randomly assigned to one of the treatment regimens or to no experimental treatment in a 1:1 ratio. All patients received the local standard of care. Remdesivir was administered intravenously at a dose of 200 mg on day 0 and 100 mg on day one to nine for a total of 10 days of treatment. The study drug was given until the treatment course was completed or until the treating physician decided to stop the drug or any serious adverse reactions were identified.

The primary outcome was in-hospital mortality at day 28. The secondary outcomes included initiation of mechanical ventilation and length of hospital stay (time to discharge).[6] Details of the statistical analysis are described in Appendix 3.

Evidence Results

Patient Disposition

Wang et al.

The patient disposition for the study by Wang et al. is shown in Appendix 4. Of 255 patients who were screened for trial inclusion, 237 patients were randomized to remdesivir (158 patients) or to placebo (79 patients). One patient (1.3%) in the placebo group withdrew their consent. The per-protocol population excluded three (1.9%) patients receiving remdesivir who did not start the trial and five patients (3.2%) who received treatment for less than five days. The placebo arm had two patients (2.2%) who received placebo for less than five days.[7]

Adaptive COVID-19 Treatment Trial (ACTT-1)

The patient disposition of ACTT-1 is summarized in Appendix 4. Of 1,114 patients who were screened, 1,062 were eligible for inclusion and randomized into the trial: 541 to remdesivir and 521 to placebo (intention-to-treat population). A total of 1,025 patients (517 patients in the remdesivir group and 508 patients in the placebo group) completed the trial through day 29, recovered, or died. In the remdesivir and placebo groups, 14 patients and nine patients, respectively, terminated the trial before day 29. The as-treated population included 1,048 patients (532 in the remdesivir group and 516 in the placebo group). A total of 14 patients who were randomized did not receive any dose of their assigned treatment and two patients received the wrong treatment (one patient was randomized to remdesivir but received placebo and one patient was randomized to placebo but received remdesivir).[5]

At the preliminary primary analysis, 16 (3.0%) patients in the remdesivir group and 35 (6.7%) patients in the placebo group were unblinded. A total of 26 patients originally in the placebo group who were unblinded were given remdesivir.[5]

GS-US-540-5773 — Part A

The patient disposition of GS-US-540-5773 is presented in Appendix 4. Of the 408 patients who were screened, 402 were eligible for inclusion and were randomized into the trial. Of those 402 patients, 202 patients were randomized to the remdesivir five-day regimen and 200 patients were randomized to the remdesivir 10-day regimen. Of the randomized patients, two patients assigned to the five-day regimen and three patients assigned to the 10-day regimen were not treated with remdesivir and were excluded from the full analysis set. The full analysis set, and the safety set included 200 patients and 197 patients in the five-day and 10-day treatment regimens, respectively. In the five-day group, 85.1% (172 out of 202) of randomized patients completed the course of treatment (median duration of five days) and in the 10-day group, 43.0% (86 out of 200) of randomized patients completed the course of treatment (median duration of nine days).[2]

GS-US-540-5774 — Part A

The patient disposition of GS-US-540-5774 is presented in Appendix 4. Of the 612 patients who were screened, 596 met the inclusion criteria and were randomized into the trial. A total of 384 patients started remdesivir treatment (191 patients started the remdesivir five-day regimen as randomized and 193 patients started the remdesivir 10-day regimen as randomized) and 200 patients received standard of care alone. Of the 12 patients who were randomized but did not receive remdesivir treatment, eight patients withdrew consent, three patients had protocol violations and one patient was withdrawn at the discretion of the

investigator. The full analysis set, and the safety set included patients receiving at least one dose of remdesivir. The full analysis set was used as the primary analysis set for the efficacy analysis. In the five-day group, 75.9% (145 of 191) of randomized patients completed the course of treatment (median five doses received) and in the 10-day group, 37.8% (73 of 193) of randomized patients completed the course of treatment (median six doses received). There were 533 patients (91.3%) who were followed up to day 28 in the study.[4]

WHO Solidarity

The patient disposition of WHO Solidarity is presented in Appendix 4. Of the 11,330 patients who underwent randomization, 5,475 patients were randomized to the remdesivir or its control group.[6]

A total of 2,750 patients were assigned to receive remdesivir treatment of which, seven patients had no or unknown consent to follow-up. This resulted in 2,743 patients in the intention-to-treat analysis. Of these 2,743 patients, 2,260 died in the hospital or were discharged: 88 patients who entered the trial before September 2020 were still inpatients in late September; 67 patients who entered the trial before September were not yet reported on in late September; and 328 patients who entered the trial in or after September were not reported on in late September.

There were 2,725 patients assigned to receive standard of care according to local practices, of which 17 patients had no or unknown consent to follow-up. This resulted in 2,708 patients in the intention-to-treat analysis. Of these 2,708 patients, 2,252 died or left the hospital: 72 patients who entered the trial before September 2020 were still inpatients in late September; 76 patients who entered the trial before September were not yet reported on in late September; and 308 who patients entered the trial in or after September were not reported on in late September.[6]

Baseline Characteristics

Wang et al.

The patient baseline demographic and clinical characteristics are presented in Appendix 5. The median age of patients was 66.0 years (interquartile range [IQR] = 57.0 to 73.0 years) in the remdesivir group and 64.0 years (IQR = 53.0 to 70.0 years) in the placebo group.[7] The percentage of males in the placebo group (65%) was higher than in the remdesivir group (56%). Although 71% of patients in each group had comorbidities, the percentage of patients with hypertension, diabetes, and coronary heart disease was higher in the remdesivir group compared with the placebo group. A respiratory rate greater than 24 breaths per minute was reported in 23% of the remdesivir patients compared with 14% of the placebo patients. The oxygen saturation at room air or the arterial blood gas at room air was not reported at baseline. More than 80% of patients in each group required supplemental oxygen at baseline. The mean viral load of nasopharyngeal and oropharyngeal swabs at baseline appeared to be balanced between groups. The time from symptom onset to starting remdesivir and placebo treatment was 11 days (IQR = 9 to 12 days) and 10 days (IQR = 9 to 12 days), respectively. A higher proportion of patients receiving remdesivir (54%) started treatment more than 10 days after symptom onset compared with patients receiving placebo (40%). The use of interferon alfa-2b, lopinavir-ritonavir, and corticosteroids at baseline appeared to be balanced between groups. A

higher percentage of patients receiving placebo received antibiotics at baseline compared with patients receiving remdesivir (81% and 77%, respectively).[7]

Adaptive COVID-19 Treatment Trial (ACTT-1)

The baseline demographic and clinical characteristics of patients included in ACTT-1 are presented in Appendix 5. The mean age of patients in the remdesivir group was 58.6 years (standard deviation [SD] = 14.6) and 59.2 years (SD = 15.4) in the placebo group. The percentage of males was similar in the remdesivir and placebo groups (65.1% and 63.7%, respectively). Patients were mainly enrolled at sites in North America (79.8%), with no Canadian sites. The majority of patients in both groups had two or more pre-specified coexisting conditions at enrollment (55.7% of patients in the remdesivir group and 54.7% of patients in the placebo group). Hypertension was the most prevalent comorbidity, affecting 50.6% of those in the remdesivir group and 50.9% of those in the placebo group. Information on comorbidities was missing or incomplete for 14 patients at baseline. The median time from symptom onset to starting remdesivir and placebo treatment was nine days in both groups.

At randomization, there were 903 (85.0%) patients classified as having severe disease and 159 (15.0%) patients with mild-to-moderate disease. Subsequently 54 patients in the mild-to-moderate category were determined to meet the criteria for severe disease which meant that 105 (9.9%) patients had mild-to-moderate disease and 957 (90.1%) patients had severe disease.[5]

The distribution of baseline score on the eight-point ordinal clinical status scale was similar, with the largest percentage of patients falling into category 5 (defined as hospitalized, requiring any supplemental oxygen; 42.9% of patients in the remdesivir group and 39.0% of patients in the placebo group). In the as-treated population, the most common concomitant treatments during the trial in the remdesivir and placebo groups, respectively, were antibiotics (78.9% and 85.9%), hydroxychloroquine (34.6% and 36.6%), vasopressors (27.6% and 37.8%), and corticosteroids (21.6% and 24.4%).[5]

GS-US-540-5773 — Part A

The baseline demographic and clinical characteristics of patients included in Part A of GS-US-540-5773 are presented in Appendix 5. The median age in the five-day remdesivir group was 61 years (IQR = 50 to 69) and was 62 years (IQR = 50 to 71) in the 10-day remdesivir group.[2] The percentage of males was lower in the five-day remdesivir group than in the 10-day remdesivir group (60% versus 68%, respectively). Hypertension was the most prevalent comorbidity, affecting 50% of patients in each group. The 10-day patient group had worse clinical status at baseline, with a higher percentage of patients requiring invasive mechanical ventilation and high-flow oxygen support. More than half of patients in each group received low-flow supplemental oxygen at baseline. The median duration of hospitalization before the first dose of remdesivir was two days (IQR = 1 to 3) for both groups. The median duration of symptoms before the first dose of remdesivir was eight days (IQR = 5 to 11) and nine days (IQR = 6 to 12) for the five-day and 10-day regimens, respectively. No information was provided on prior or baseline use of other treatments for COVID-19 or supportive pharmacotherapies.[2]

GS-US-540-5774 — Part A

The baseline demographic and clinical characteristics of patients included in Part A of GS-US-540-5774 are presented in Appendix 5. The mean age of patients in the five-day

remdesivir group was 58 years (IQR = 48 to 66), 56 years (IQR = 45 to 66) in the 10-day remdesivir group, and 57 years (IQR = 45 to 66) in the standard of care group.[4] The percentage of males was balanced across the treatment groups: five-day remdesivir (60%), 10-day remdesivir group (61%) and standard of care group (63%). Cardiovascular disease was the most prevalent coexisting condition affecting 58% each in the five-day and 10-day remdesivir group compared to 54% of patients in the standard of care group. Based on the 7-point ordinal scale baseline assessment, there were 84% of patients each in the five-day and 10-day remdesivir group that did not require supplemental oxygen but required ongoing medical care compared to 80% of patients in the standard of care group. At baseline in the 10-day remdesivir group, six patients (3%) were hospitalized and did not require supplemental oxygen or ongoing medical care compared to no patients (0%) in the five-day remdesivir group and two patients (1%) in the standard of care group. Azithromycin was the most common concomitant medication used by patients in the five-day and 10-day remdesivir group (18% and 21% each, respectively), although use of azithromycin was 31% in the standard of care group. Hydroxychloroquine or chloroquine was the most commonly used medication in the standard of care group (45%); use was less frequent in the five-day and 10-day remdesivir groups (8% and 11%, respectively). The mean duration of hospitalization before the first dose of remdesivir was two days (IQR = 1 to 3) for all three treatment groups. The mean duration of symptoms before the first dose of remdesivir was eight days each (IQR = 5 to 11) in the five-day and 10-day remdesivir group compared to nine days (IQR = 6 to 11) in the standard of care group.[4]

WHO Solidarity

The baseline demographic and clinical characteristics of patients included in WHO Solidarity are presented in Appendix 5. The mean age of patients was not reported. Patients were categorized according to age groups, with 35.0% and 35.2% of patients younger than 50 years old in the remdesivir and standard of care group, respectively; 46.7% and 47.5% of patients 50 years to 69 years old in the remdesivir and standard of care group, respectively; and 18.2% and 17.3% of patients being 70 years or older in the remdesivir and standard of care group, respectively. The proportion of males was 62.2% and 63.7% in the remdesivir and standard of care groups, respectively. Approximately 25% of patients were located in Europe or Canada and more than half of the patients were in Asia and Africa. Very few patients were smokers (approximately 6%). The most common coexisting conditions at baseline were diabetes (25.8% and 24.6% for remdesivir and standard of care, respectively) and heart disease (20.8% and 20.9% for remdesivir and standard of care, respectively). Most patients were receiving supplemental oxygen at baseline (66.6% and 66.9% for remdesivir and standard of care, respectively) or ventilation (9.3% and 8.6% for remdesivir and standard of care, respectively). At baseline, 40.2% and 39.1% of patients in the remdesivir and standard of care group, respectively, had been hospitalized for two days or more.[6]

Efficacy

Wang et al.

The clinical efficacy results for Wang et al.[7] are reported in Table 4.

- Clinical improvement
  - The median time to clinical improvement (with clinical improvement defined as a two-point improvement on the six-point ordinal scale) was 21 days (IQR = 13.0 to

28.0) with remdesivir and 23 days (IQR = 15.0 to 28.0) with placebo (hazard ratio [HR] = 1.23; 95% confidence interval [CI], 0.87 to 1.75; P = 0.24).
    - At day 28, 65% (103 out of 158) of patients on remdesivir where deemed clinically improved compared with 58% (46 out of 78) of patients taking placebo (risk difference [RD] = 7.5; 95% CI, −5.7 to 20.7).
- Respiratory support
    - The median duration of invasive mechanical ventilation was 7.0 days (IQR = 4.0 to 16.0) with remdesivir and 15.5 days (IQR = 6.0 to 21.0) with placebo (median difference = −4.0; 95% CI, −14.0 to 2.0).
    - The median duration of oxygen support was 19.0 days (IQR = 11.0 to 30.0 days) with remdesivir and 21.0 days (IQR = 14.0 to 30.5) with placebo (median difference = −2.0; 95% CI, −6.0 to 1.0).
- Mortality
    - At day 28, 14% (22 out of 158) of patients on remdesivir had died compared with 13% (10 out of 78) patients on placebo (RD = 1.1; 95%CI, −8.1 to 10.3).
- Hospitalization
    - The median number of days in hospital for the remdesivir group was 25.0 days (IQR = 16.0 to 38.0) and 24.0 days (IQR = 18.0 to 36.0) with placebo (median difference = 0.0; 95% CI, −4.0 to 4.0).
- Viral load
    - The percent of patients with undetectable viral RNA of nasopharyngeal and oropharyngeal swabs by day 28 was 75.6% (99 out of 131) of patients receiving remdesivir and 83.1% (54 out of 65) of those receiving placebo (RD = −7.5; 95% CI, −19.2 to 4.2).

Table 4: Clinical Outcomes for Wang et al.

Wang et al.[7]	RDV N = 158	PBO N = 78
Time to clinical improvement (days) – ITT		
Number of days, median (IQR)	21.0 (13.0 to 28.0)	23.0 (15.0 to 28.0)
RDV versus PL, HR (95% CI)	1.23 (0.87 to 1.75)	
P value (log-rank)	0.24	
Time to clinical improvement in patients receiving treatment within 10 days of symptom onset (days) – ITT		
Number of patients contributing to the analysis	71	47
Number of days, median (IQR)	18.0 (12.0 to 28.0)	23.0 (15.0 to 28.0)
RDV versus PL, HR (95% CI)	1.52 (0.95 to 2.43)	
Time to clinical improvement in patients receiving treatment > 10 days after symptom onset (days) – ITT		
Number of patients contributing to the analysis	84	31
Number of days, median (IQR)	23.0 (NR)	24.0 (NR)
RDV versus PL, HR (95% CI)	1.07 (0.63 to 1.83)	
Time to clinical deterioration (days)		
RDV versus PL, HR (95% CI)	0.95 (0.55 to 1.64)	
Clinical improvement at day 28 – ITT		
n (%)	103 (65)	45 (58)

Wang et al.[7]	RDV N = 158	PBO N = 78
Risk difference, % (95% CI)	7.5 (–5.7 to 20.7)	
Day 28 mortality – ITT		
n (%)	22 (14)	10 (13)
Risk difference, % (95% CI)	1.1 (–8.1 to 10.3)	
Day 28 mortality in patients receiving treatment within 10 days of symptom onset		
n/N (%)	8/71 (11)	7/47 (15)
Risk difference, % (95% CI)	–3.6 (–16.2 to 8.9)	
Day 28 mortality in patients receiving treatment after 10 days of symptom onset		
n/N (%)	12/84 (14)	3/31 (10)
Risk difference, % (95% CI)	4.6 (–8.2 to 17.4)	
Duration of invasive mechanical ventilation, days		
Number of patients contributing to the analysis	NR	NR
Number of days, median (IQR)	7.0 (4.0 to 16.0)	15.5 (6.0 to 21.0)
RDV versus PL, median difference (95% CI)	–4.0 (–14.0 to 2.0)	
Duration of oxygen support, days		
Number of patients contributing to the analysis	NR	NR
Number of days, median (IQR)	19.0 (11.0 to 30.0)	21.0 (14.0 to 30.5)
RDV versus PL, median difference (95% CI)	–2.0 (–6.0 to 1.0)	
Duration of hospital stay, days		
End of treatment time point (specify), median (IQR)	25.0 (16.0 to 38)	24.0 (18.0 to 36.0)
RDV versus PL, median difference (95% CI)	0.0 (–4.0 to 4.0)	
Distribution of six-category scale at day 28		
RDV versus PL, OR (95% CI)	1.15 (0.67 to 1.96)	
Category 1: Discharge (alive), n/N (%)	92/150 (61)	45/77 (58)
Category 2: Hospital admission, not requiring supplemental oxygen, n/N (%)	14/150 (9)	4/77 (5)
Category 3: Hospital admission, requiring supplemental oxygen, n/N (%)	18/150 (12)	13/77 (17)
Category 4: Hospital admission, requiring HFNC or NIV mechanical ventilation, n/N (%)	2/150 (1)	2/77 (3)
Category 5: Hospital admission, requiring ECMO or invasive mechanical Ventilation, n/N (%)	2/150 (1)	3/77 (4)
Category 6: Death, n/N (%)	22/150 (15)	10/77 (13)
Undetectable viral RNA in upper respiratory tract specimens in viral positive population at day 28		
n/N (%)	99/131 (75.6)	54/65 (83.1)
Risk difference, % (95% CI)	–7.5 (–19.2 to 4.2)	

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; HR = hazard ratio; IQR = interquartile range; ITT = intention to treat; NIV = non-invasive; NR = not reported; OR = odds ratio; PBO = placebo; RDV = remdesivir; RNA = ribonucleic acid.

Adaptive COVID-19 Treatment Trial (ACTT-1)

The clinical efficacy results for the key primary and secondary outcomes of ACTT-1[5] are reported in Table 5.

- Time to recovery
  - The median time to recovery was 10 days (95% CI, 9 to 11) in the remdesivir group versus 15 days (95% CI, 13 to 18) in the placebo group (rate ratio = 1.29; 95% CI, 1.12 to 1.49; P < 0.001) (Table 5). Analyses of the primary outcome were stratified based on the baseline score on the ordinal scale (as a measure of baseline severity); for patients with a baseline score of 5, those who were randomized to the remdesivir group had a statistically significantly shorter recovery compared with patients randomized to the placebo group (rate ratio = 1.45; 95% CI, 1.18 to 1.79). There was no statistically significant difference found between remdesivir and placebo for time to recovery in patients with a baseline clinical status score of 4, 6, or 7.
  - For patients who had severe disease, the rate ratio for recovery was 1.31 (95% CI, 1.12 to 1.52); in the mild-to-moderate disease group it was 1.22 (95% CI, 0.82 to 1.81).
- Clinical status
  - The odds of improvement in clinical status on the eight-point ordinal scale were higher with remdesivir than placebo at day 15 (odds ratio [OR] for improvement = 1.5; 95% CI, 1.2 to 1.9; adjusted for disease severity) (Table 5).
- Mortality
  - By day 15, the Kaplan-Meier estimate of mortality was 6.7% (95% CI, 4.8% to 9.2%) in patients who received remdesivir versus 11.9% (95% CI, 9.4% to 15.0%) in those who received placebo (HR = 0.55; 95% CI, 0.36 to 0.83) (Table 5).
  - Over the 29-day study period, the Kaplan-Meier estimate of all-cause mortality was 11.4% (95% CI, 9.0% to 14.5%) in patients who received remdesivir versus 15.2% (95% CI, 12.3% to 18.6%) in those who received placebo (HR = 0.73; 95% CI, 0.52 to 1.03) (Table 5).

Table 5: Clinical Outcomes for ACTT-1

ACTT-1 (ITT Population)[5]	RDV n = 541	PBO n = 521
Recovery[a]		
Number of recoveries	399	352
Median time to recovery, days (95% CI)	10 (9 to 11)	15 (13 to 18)
Rate ratio (95% CI)[b]	1.29 (1.12 to 1.49)	
P value (stratified log-rank)	< 0.001	
Recovery – severe disease stratum		
Number of recoveries	345/486	306/471
Median time to recovery, days (95% CI)	11 (10 to14)	18 (15 to 20)
Rate ratio (95% CI)	1.31 (1.12 to 1.52)	
Recovery – mild-to-moderate disease stratum		
Number of recoveries	54/55	46/50
Median time to recovery, days (95% CI)	5 (4 to 6)	5 (4 to 7)

ACTT-1 (ITT Population)[5]	RDV n = 541	PBO n = 521
Rate ratio (95% CI)[b]	1.22 (0.82 to 1.81)	
Mortality through day 14[a,c]		
Number of deaths by day 15	35	61
Kaplan-Meier estimate by day 15, % patients (95% CI)	6.7 (4.8 to 9.2)	11.9 (9.4 to 15.0)
Hazard ratio through day 15 (95% CI)	0.55 (0.36 to 0.83)	
Mortality over entire study period[a,c]		
Number of deaths by day 29	59	77
Kaplan-Meier estimate by day 29, % patients (95% CI)	11.4 (9.0 to 14.5)	15.2 (12.3 to 18.6)
Hazard ratio through day 29 (95% CI)	0.73 (0.52 to 1.03)	
Ordinal score at day 15 (± 2 days) – patients with baseline and day 15 score[a,d]		
RDV versus PBO, OR (95% CI) – adjusted for disease severity	1.5 (1.2 to 1.9)	
Category 1: Not hospitalized, no limitations of activities, n (%)	157 (29.0)	115 (22.1)
Category 2: Not hospitalized, limitation of activities, home oxygen requirement, n (%)	117 (21.6)	102 (19.6)
Category 3: Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care, n (%)	14 (2.6)	8 (1.5)
Category 4: Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care, n (%)	38 (7.0)	33 (6.3)
Category 5: Hospitalized, requiring any supplemental oxygen, n (%)	58 (10.7)	60 (11.5)
Category 6: Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices, n (%)	28 (5.2)	24 (4.6)
Category 7: Hospitalized, receiving invasive mechanical ventilation or ECMO, n (%)	95 (17.6)	121 (23.2)
Category 8: Death, n (%)	34 (6.3)	58 (11.1)

ACTT = Adaptive COVID-19 Treatment Trial; CI = confidence interval; ECMO = extracorporeal membrane oxygenation; ITT = intention to treat; OR = odds ratio; PBO = placebo; RDV = remdesivir.

[a] P values and confidence intervals have not been adjusted for multiple comparisons.

[b] Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; the P value for this ratio was calculated with the stratified log-rank test (overall model stratified by actual disease severity).

[c] Mortality over the first 14 days includes data from all patients who were still alive through 14 days post-enrollment, with data censored on day 15, as if 14 days was the maximum follow-up time. Mortality over the entire study period uses the totality of the study data and censors data from patients who completed follow-up alive at 28 days post-enrollment.

[d] The ordinal score at day 15 was the patient's worst score on the ordinal scale during the previous day. Four patients died 15 days after randomization and were recorded as having died for the ordinal score at the day 15 outcome but not for the mortality day 15 outcome.

GS-US-540-5773 — Part A

- Clinical status
  - No statistical difference was found between the remdesivir five-day and 10-day treatment regimens in clinical status at day 14 after adjusting for clinical status at baseline (OR = 0.75; 95% CI, 0.51 to 1.12; P = 0.14) (Table 6).[2]
- Other exploratory efficacy end points
  - The median time to clinical improvement was 10 days in the five-day remdesivir group and 11 days in the 10-day remdesivir group (HR = 0.79; 95% CI, 0.61 to 1.01).
  - Clinical improvement at day 14 was observed in 64% of patients in the five-day treatment group compared with 54% of patients in the 10-day treatment group (adjusted rate difference = –6.5%; 95% CI, –15.7% to 2.8%).

- The median time to recovery was 10 days in the five-day remdesivir group and 11 days in the 10-day remdesivir group (HR = 0.81; 95% CI, 0.64 to 1.04).
- Clinical recovery was achieved at day 14 in 64% of patients treated with remdesivir for five days and 54% of patients treated with remdesivir for 10 days (adjusted rate difference = –6.3%; 95% CI, –15.4% to 2.8%).
- Mortality at day 14 was 8% in the five-day treatment group and 11% in the 10-day treatment group.

Table 6: Clinical Outcomes for GS-US-540-5773 — Part A

GS-US-540-5773[2]	RDV 5 days (n = 200)	RDV 10 days (n = 197)
Clinical status at day 14 on the 7-point ordinal scale		
Baseline-adjusted difference, OR (95% CI)[a]	0.75 (0.51 to 1.12); P = 0.14	
Category 1: Death, n (%)	16 (8)	21 (11)
Category 2: Hospitalized, receiving invasive mechanical ventilation or ECMO, n (%)	16 (8)	33 (17)
Category 3: Hospitalized, receiving non-invasive ventilation or high-flow oxygen, n (%)	9 (4)	10 (5)
Category 4: Hospitalized, requiring low-flow supplemental oxygen, n (%)	19 (10)	14 (7)
Category 5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care, n (%)	11 (6)	13 (7)
Category 6: Hospitalized, not requiring supplemental oxygen or ongoing medical care, n (%)	9 (4)	3 (2)
Category 7: Not hospitalized, n (%)	120 (60)	103 (52)
Clinical improvement[b]		
Time to clinical improvement, median day of 50% cumulative incidence	10	11
5-day versus 10-day, HR (95% CI)[c]	0.79 (0.61 to 1.01)	
Clinical improvement at day 14, n (%)	129 (64)	107 (54)
Baseline-adjusted difference, % (95% CI)[d]	−6.5 (−15.7 to 2.8)	
Clinical recovery[e]		
Time to recovery, median day of 50% cumulative incidence	10	11
5-day versus 10-day, HR (95% CI)[c]	0.81 (0.64 to 1.04)	
Recovery at day 14, n (%)	129 (64)	106 (54)
Baseline-adjusted difference, % (95% CI)[d]	−6.3 (−15.4 to 2.8)	
Modified clinical recovery[f]		
Time to modified recovery for 50% of patients, median days	9	10
5-day versus 10-day, HR (95% CI)[c]	0.82 (0.64 to 1.04)	
Modified recovery at day 14, n (%)	140 (70)	116 (59)
Baseline-adjusted difference, % (95% CI)[d]	−6.7 (−15.3 to 1.9)	

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; OR = odds ratio; RDV = remdesivir.

[a] Odds ratios of less than one indicate lower odds of being in a better category for the 10-day group compared to the five-day group; i.e., the point estimate would favour the five-day group. The P value was calculated from a Wilcoxon rank-sum test (stratified by baseline clinical status).

[b] Clinical improvement was defined as an improvement of at least two points from baseline on the seven-point ordinal scale.

[c] HR and 95% CI estimated from a cause-specific proportional-hazards model that includes treatment and baseline clinical status as covariates.

[d] Rate difference estimated from the Mantel–Haenszel proportions adjusted according to baseline clinical status.

[e] Recovery was defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7.

[f] Modified recovery was defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7.

GS-US-540-5774 — Part A

The clinical efficacy results for GS-US-540-5774 Part A are reported in Table 4.[4]

- Clinical status
  - The odds of improvement in clinical status on the 7-point ordinal scale was statistically significantly higher in the five-day remdesivir group compared with the standard of care group at day 11 (OR = 1.65; 95% CI, 1.09 to 2.48, P = 0.02).
  - The odds of improvement in clinical status on the 7-point ordinal scale was not statistically significantly different in the 10-day remdesivir group compared with the standard of care group at day 11 (P = 0.18).
- Exploratory efficacy end points
  - The median time to clinical improvement (2-point or greater improvement from baseline on the 7-point ordinal scale) was six days in the five-day remdesivir group and eight days in the 10-day remdesivir group, compared with eight days in the standard of care group (HR = 1.15; 95% CI, 0.93 to 1.42 and HR = 1.16; 95% CI, 0.93 to 1.43, for the five-day and 10-day groups versus standard of care, respectively).
    - Clinical improvement at day 11 was observed in 70% of patients in the five-day treatment group and in 65% of patients in the 10-day treatment group, compared with 61% of patients in the standard of care group (difference of 9.7%; 95% CI, 0.1 to 19.1 and difference of 4.8%; 95% CI, –5.0 to 14.4, for the five-day and 10-day groups versus standard of care, respectively).
    - At day 28, 90% of patients in either remdesivir groups and 83% of patients in the standard of care group were clinically improved and 89%, 90%, and 83% of the patients in remdesivir five-day, 10-day, and standard of care groups were no longer hospitalized.
  - The median time to recovery was six days in the five-day remdesivir group and eight days in the 10-day remdesivir group, compared with seven days with the standard of care group (HR = 1.18; 95% CI, 0.96 to 1.45 and HR = 1.11; 95% CI, 0.90 to 1.37 for the five-day and 10-day groups versus standard of care, respectively).
    - By day 11, 74 %, 68%, and 64% of patients had recovered in the remdesivir 5-day, remdesivir 10-day and standard of care groups, respectively.
  - The median time to room air was five days in the 5-day remdesivir group and four days in the 10-day remdesivir group, compared with six days with the standard of care group (HR = 1.31; 95% CI, 0.79 to 2.18 and HR = 1.93; 95% CI, 1.11 to 3.36 for the 5-day and 10-day groups versus standard of care, respectively).
  - There were no differences in the duration of oxygen therapy or hospitalization between groups (data not shown). The proportion of patients with negative PCR was not reported in the publication.
  - All-cause mortality at day 28 was 1% in the 5-day treatment group and 2% in the 10-day treatment group, compared with 2% in the standard of care group. The hazard ratio for death was 0.51 (95% CI, 0.09 to 2.80) and 0.76 (95% CI, 0.17 to 3.4) in the remdesivir five-day and 10-day groups, respectively, compared with standard of care.

Table 7: Clinical Outcomes for GS-US-540-5774 — Part A

GS-US-540-5774[4]	RDV 5 days (n = 191)	RDV 10 days (n = 193)	SOC (n = 200)
Day 11 clinical status on a 7-point ordinal scale			
Category 1: Death, n (%)	0	2 (1)	4 (2)
Category 2: Hospitalized, receiving invasive mechanical ventilation or ECMO, n (%)	0	1 (1)	4 (2)
Category 3: Hospitalized, receiving non-invasive ventilation or high-flow oxygen, n (%)	5 (3)	0	7 (4)
Category 4: Hospitalized, requiring low-flow supplemental oxygen, n (%)	7 (4)	12 (6)	11 (6)
Category 5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care, n (%)	38 (20)	44 (23)	46 (23)
Category 6: Hospitalized, not requiring supplemental oxygen or ongoing medical care, n (%)	7 (4)	9 (5)	8 (4)
Category 7: Not hospitalized, n (%)	134 (70)	125 (65)	120 (6)
Difference in clinical status distribution vs SOC, OR (95% CI)	1.65 (1.1 to 2.5)[a], P = 0.02	P = 0.18[b]	1 (reference)
Day 28 clinical status on a 7-point ordinal scale			
Category 1: Death, n (%)	2 (1)	3 (2)	4 (2)
Category 2: Hospitalized, receiving invasive mechanical ventilation or ECMO, n (%)	0	1 (1)	4 (2)
Category 3: Hospitalized, receiving non-invasive ventilation or high-flow oxygen, n (%)	1 (1)	1 (1)	0
Category 4: Hospitalized, requiring low-flow supplemental oxygen, n (%)	4 (2)	0	5 (3)
Category 5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care, n (%)	9 (5)	10 (5)	17 (9)
Category 6: Hospitalized, not requiring supplemental oxygen or ongoing medical care, n (%)	5 (3)	4 (2)	4 (2)
Category 7: Not hospitalized, n (%)	170 (89)	174 (90)	166 (83)
Difference in clinical status distribution versus SOC, P value[b]	0.08	0.03	reference
Clinical improvement			
Time to ≥ 2-point improvement, median days (25% to 75%)	6 (5 to 14)	8 (4 to 14)	8 (5 to 22)
HR versus SOC (95% CI)[c]	1.2 (0.9 to 1.4)	1.16 (0.9 to 1.4)	
Clinical improvement[d] at day 11, n (%)	134 (70)	126 (65)	121 (61)
% difference vs SOC (95% CI)	9.7 (0.1 to 19.1)	4.8 (–5.0 to 14.4)	
Clinical improvement[d] at day 28, n (%)	171 (90)	174 (90)	166 (83)
Time to ≥ 1-point improvement, median days (25% to 75%)	6 (4 to 9)	7 (4 to 12)	7 (4 to 14)
HR versus SOC (95% CI)[c]	1.18 (0.96 to 1.46)	1.10 (0.9 to 1.37)	
Recovery			
Time to recovery, median days (25% to 75%)	6 (5 to 10)	8 (4 to 13)	7 (4 to 15)
HR versus SOC (95% CI)[c]	1.2 (1.0 to 1.5)	1.1 (0.9 to 1.4)	
Recovery at day 11, n (%)	141 (74)	132 (68)	128 (64)

GS-US-540-5774[4]	RDV 5 days (n = 191)	RDV 10 days (n = 193)	SOC (n = 200)
Difference vs SOC at day 11, % (95% CI)[e]	9.8 (0.3 to 19.0)	4.4 (–5.0 to 13.8)	
Recovery at day 28, n (%)	175 (92)	178 (92)	170 (85)
Time to modified recovery, median days (25% to 75%)	6 (4 to 9)	7 (4 to 12)	7 (4 to 14)
HR versus SOC (95% CI)	1.19 (0.96 to 1.46)	1.10 (0.90 to 1.36)	
Time to room air			
Time to room air, median days (25% to 75%)	5 (3 to7)	4 (2 to 6)	6 (4 to14)
HR versus SOC (95% CI)[c]	1.3 (0.8 to 2.2)	1.9 (1.1 to 3.4)	
Death			
HR versus SOC (95% CI)[f]	0.5 (0.1 to 2.8)	0.8 (0.2 to 3.4)	
All-cause mortality at day 28, % (95% CI)[g]	1 (0.0 to 2.6), P = 0.43[h]	2 (0.0 to 3.6), P = 0.72[h]	2 (0.1 to 4.1)

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; OR = odds ratio; RDV = remdesivir; SOC = standard of care.

[a] The odds ratio and P value estimated using the proportional odds model.

[b] P value calculated using the Wilcoxon rank sum test.

[c] Estimates are from competing risk models and cause-specific proportional hazard models (with death as the competing risk).

[d] An improvement of at least 2 points from baseline on the 7-point ordinal scale.

[e] An improvement from a baseline score of 2 to 5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7.

[f] Estimates from Kaplan-Meier Product Limit Method and cause-specific proportional hazard models.

[g] Kaplan-Meier estimates.

[h] Log-rank test (versus standard of care).

WHO Solidarity

The clinical efficacy results for WHO Solidarity are reported in Table 4.[6]

- In hospital deaths
  - No statistical difference was found between remdesivir and standard of care for in-hospital deaths at 28 days (12.5% versus 12.7%, respectively).
  - There was also no difference between remdesivir and standard of care for any of the disease severity subgroups.
- Pre-specified efficacy end points
  - There was no difference in the number of patients who required ventilation (remdesivir [11.9%] and standard of care [11.5%]).
  - While time to discharge was a pre-specified efficacy end point, the result for this outcome was not reported. However, it is stated in the publication that “each drug delayed discharge by approximately 1 to 3 days while it was being given.”

Table 8: Clinical Outcomes for WHO Solidarity

WHO Solidarity[6]	RDV (n = 2,743)	SOC (n = 2,708)
In-hospital deaths[a]		
Total, n/N (%)	301/2,743 (12.5)	303/2,708 (12.7)
RR, (95% CI)	0.95 (0.81 to 1.11)	
P value	0.50	
In-hospital deaths according to subgroups		
Age at entry		
< 50 years, n/N (%)	61/961 (6.9)	59/952 (6.8)
RR, (99% CI)	1.08 (0.67 to 1.73)	
50 to 69 years, n/N (%)	154/1,282 (13.8)	161/1,287 (14.2)
RR, (99% CI)	0.91 (0.68 to 1.21)	
≥ 70 years, n/N (%)	86/500 (20.5)	83/469 (21.6)
RR, (99% CI)	0.93 (0.63 to 1.39)	
Respiratory support at entry		
No mechanical ventilation, n/N (%)	203/2,489 (9.4)	232/2,475 (10.6)
RR, (99% CI)	0.86 (0.67 to 1.11)	
Mechanical ventilation, n/N (%)	98/254 (43.0)	71/233 (37.8)
RR, (99% CI)	1.20 (0.80 to 1.80)	
Initiation of ventilation		
Not ventilated at entry, n	2,489	2,475
Ventilated later, died	117	108
Ventilated later, discharged	139	146
Ventilated later, pending (not dead or not discharged)	39	30
Total ventilated later, n/N (%)	295/2489 (11.9)	284/2,475 (11.5)

CI = confidence interval; RDV = remdesivir; RR = rate ratio; SOC = standard of care.

[a] The percentage show Kaplan-Meier 28-day mortality

Harms

Wang et al.

The percentage of patients who experienced adverse events, serious adverse events, and adverse events leading to drug discontinuation are detailed in Table 9.[7]

The percentage of patients who experienced any adverse event was similar in the remdesivir and placebo groups, but the percentage of patients who experienced a serious adverse event was higher in the placebo group than the remdesivir group (26% versus 18%, respectively). The percentage of patients who experienced an adverse event that led to treatment discontinuation was higher with remdesivir than with placebo (12% versus 5%, respectively).[7]

Detailed harms are reported in Appendix 6. The most common adverse events reported with remdesivir were constipation (14%), hypoalbuminemia (13%), anemia (13%), hypokalemia (12%), anemia (12%), thrombocytopenia (10%), and increased bilirubin (10%). With placebo, the most common adverse events included constipation (15%), anemia

(15%), hypoalbuminemia (15%), hypokalemia (14%), increased aspartate aminotransferase (AST) (12%), increased blood lipids (10%), and hyperlipidemia (10%). Respiratory failure or acute respiratory distress syndrome (10% with remdesivir and 8% with placebo) and cardiopulmonary failure (5% with remdesivir and 9% with placebo) were the most frequently reported serious adverse events. Respiratory failure or acute respiratory distress syndrome was also the most frequently reported event leading to discontinuation with remdesivir (5%) whereas with placebo, a secondary infection (9%), was the most frequently reported event leading to discontinuation.[7]

Adaptive COVID-19 Treatment Trial (ACTT-1)

The percentage of patients who experienced adverse events, serious adverse events, and adverse events leading to drug discontinuation for ACTT-1 are detailed in Table 9. Serious adverse events occurred in 24.6% of patients in the remdesivir group and 31.6% of patients in the placebo group.[5] The most common serious adverse event was respiratory failure (7.3% of patients in the remdesivir group and 12.8% of patients in the placebo group). Grade 3 or 4 adverse events occurred in 51.3% of patients in the remdesivir group and in 57.2% of patient in the placebo group. Discontinuations due to adverse events or severe adverse events occurred in 11% and 15% in the remdesivir and placebo groups, respectively.[5]

Detailed harms data are presented in Appendix 6. The most common non-serious adverse events in the remdesivir group were decreased glomerular filtration rate (10.3%), decreased hemoglobin level (9.0%), decreased lymphocyte count (8.3%), and anemia (7.9%). The adverse events most prevalent in the placebo group were decreased glomerular filtration rate (14.3%), decreased hemoglobin level (12.0%), decreased lymphocyte count (10.5%), and anemia (10.1%). The combined percentage of patients with increased aminotransaminases (ALT, AST, or both) was 5.6% with remdesivir and 11.0% with placebo.[5]

GS-US-540-5773 — Part A

The percentage of patients who experienced adverse events, serious adverse events, and adverse events leading to drug discontinuation for Part A of GS-US-540-5773 are detailed in Table 9. Detailed harms data are presented in Appendix 6.

Across treatment groups, more than 70% of patients experienced an adverse event.[2] The most common adverse events in the five-day treatment group included nausea (10%), acute respiratory failure (6%), ALT increases (6%), and constipation (6%). In the 10-day treatment group, the most common adverse events were acute respiratory failure (11%), nausea (9%), ALT increases (8%), and acute kidney injury (8%).[2]

Serious adverse events were reported in 21% of patients in the five-day treatment group and in 35% of patients in the 10-day treatment group. The most common serious adverse event was acute respiratory failure for both groups, occurring in 5% of patients in the five-day group and in 9% of patients in the 10-day group. Discontinuation of treatment due to adverse events occurred in 4% of patients in the five-day group and 10% of patients in the 10-day group.[2]

GS-US-540-5774 — Part A

The percentage of patients who experienced adverse events, serious adverse events, and adverse events leading to drug discontinuation for Part A of GS-US-540-5774 are detailed in Table 9. Detailed harms data are presented in Appendix 6.[4]

The proportion of patients experiencing a treatment-emergent adverse event was a planned secondary outcome. Across treatment groups, more than 50% experienced an adverse event. The proportion of patients with an adverse event was higher in the five-day remdesivir group and 10-day remdesivir group compared to the standard of care group (difference 4.8%; 95% CI, –5.2 to 14.7, P = 0.36 and difference 12.0%; 95% CI, 1.6 to 21.8, P = 0.02 for the five-day and 10-day remdesivir groups versus standard of care, respectively). The percentage of adverse events of grade 3 or higher severity in the five-day remdesivir group was 10%, and 12% each in the 10-day remdesivir and standard of care groups, respectively. The adverse events that occurred in greater than 5% of patients in the five-day remdesivir group included nausea (10%), diarrhea (6%), and 5% of patients each for hypokalemia and headache, respectively. The adverse events that occurred in greater than 5% of patients in the 10-day remdesivir group included nausea (9%), hypokalemia (7%), and 5% of patients each for diarrhea and headache, respectively. The most common adverse event that occurred in greater than 5% of patients in the standard of care group was diarrhea (7%).[4]

A serious adverse event was reported in 5% of patients each in the five-day and 10-day remdesivir group and 9% of patients in the standard of care group. The proportion of patients with a serious adverse event was not statistically different in the five-day remdesivir group and 10-day remdesivir group compared with standard of care (–4.3%, 95% CI –9.7 to 0.9, P = 0.11 and –3.8%, 95% CI –9.3 to 1.4, P = 0.17 for the five-day and 10-day remdesivir groups versus standard of care, respectively). There were four patients (2%) in the five-day remdesivir group that experienced an adverse event leading to drug discontinuation compared to eight patients (4%) in the 10-day remdesivir group.[4]

By day 28 after treatment initiation, two patients (1%) died in the five-day remdesivir group, three patients (2%) in the 10-day remdesivir group and four patients (2%) in the standard of care group.[4]

WHO Solidarity

Adverse events were not measured in the WHO Solidarity trial.

Table 9: Summary of Harms (Safety Population)

	Wang et al.[7]		ACTT-1[5]		GS-US-540-5773[2]		GS-US-540-5774[4]		
	RDV N = 155	PBO N = 78	RDV N = 532	PBO N = 516	RDV 5 days N = 200	RDV 10 days N = 197	RDV 5 days N = 191	RDV 10 days N = 193	SOC N = 200
All adverse events, n (%)									
Any grade adverse event	102 (66)	50 (64)	305 (57)	323 (63)	141 (70)	145 (74)	98 (51)	113 (59)	93 (47)
Any grade 3 or grade 4 adverse event	13 (8)	11 (14)	273 (51)	295 (57)	60 (30)	85 (43)	20 (10)	24 (12)	24 (12)
Serious adverse events, n (%)									
Any serious adverse event	28 (18)	20 (26)	131 (25)	163 (32)	42 (21)	68 (35)	9 (5)	10 (5)	18 (9)
Grade 3 or grade 4 serious adverse event	9 (6)	10 (13)	NR	NR	NR	NR	NR	NR	NR
Events leading to drug discontinuation, n (%)									
Any events leading to drug discontinuation	18 (12)	4 (5)	57 (11)	77 (15)	9 (4)	20 (10)	4 (2)	8 (4)	NA
Grade 3 or grade 4 events leading to drug discontinuation	3 (2)	1 (1)	NR	NR	NR	NR	NR	NR	NR

ACTT = Adaptive COVID-19 Treatment Trial; NA = not applicable; NR = not reported; PBO = placebo; RDV = remdesivir SOC = standard of care.

Critical Appraisal

Wang et al.

Internal Validity

In Wang et al., allocation was concealed by providing the treatments in sealed packages distributed through a central pharmacy.[7] Blinding was maintained by using an identical volume of infusion solution for the placebo. Patients were monitored daily by trained nurses using standard forms. Clinical data were recorded on paper case report forms, but then double entered in a database and validated by trial staff.

While randomization was stratified on several factors, there were some imbalances between the remdesivir and placebo groups at baseline. Specifically, the remdesivir group had a higher percentage of patients at baseline with hypertension, diabetes, and coronary heart disease than the placebo group; a higher percentage of patients with a respiratory rate of greater than 24 breaths per minute; and a higher percentage of patients who started treatment more than 10 days after symptom onset. It is possible that these imbalances could bias against remdesivir, and in favour of placebo.

The study was terminated before completion when the COVID-19 epidemic was brought under control in China. As such, the sample size enrolled was smaller than initially planned. The smaller sample size reduced the power to detect a difference between groups in the primary outcome based on the original assumptions of the power calculation. However, it should be noted that the original sample size calculation was based on a larger anticipated treatment effect (HR of 1.4, corresponding to a six-day difference between groups in time to

recovery), in addition to an enrolment of 453 patients (which also allowed for a 10% dropout rate).

The primary analysis was the intention-to-treat population and included all but one randomized patient in the placebo group who withdrew consent. However, three patients in the remdesivir group were randomized, but did not start treatment. Given the lack of description of data imputation or how missing data were handled for the study outcomes, it is unclear how these patients were included in the intention-to-treat analyses. Furthermore, five patients in the remdesivir group and two patients in the placebo group received treatment for fewer than five days. No information was provided to explain the reason for the shorten treatment regimen.

The secondary outcomes and subgroups were analyzed without control of the type I error rate; however, no statistical differences were observed. Further, duration of symptoms at time of randomization and other variables that formed the subgroup analyses were not stratification variables. As such, the subgroup analysis according to symptom duration does not reflect a randomized comparison.

Other treatments were permitted during the trial. The use of a limited number of concomitant medications was reported and appeared to be balanced between treatment groups, except for interferon alfa-2b, which was used by a larger percentage of patients in the placebo group.

Patients were followed for 28 days. For those patients who had not recovered after 28 days, mortality, clinical improvement, or clinical deterioration remains unknown after that point.

External Validity

All patients were considered to have severe COVID-19. Guidelines by the National Institute of Health define moderate and severe disease as follows:

- "Moderate Illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) ≥ 94% on room air at sea level.
- Severe Illness: Individuals who have SpO_2 < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg, respiratory frequency > 30 breaths per minute, or lung infiltrates > 50%."[29]

While the oxygen saturation at room air and the arterial blood gas at room air were not reported at baseline, the inclusion criteria used to select patients into the trial are reflective of the National Institute of Health definition of severe illness. The generalizability of the findings to patients with moderate disease is unknown.

Approximately 71% of patients in each group had comorbidities including hypertension, diabetes, and coronary heart disease, which are known risk factors for more severe COVID-19.

The trial was conducted in a single country. It is unclear if the results would be generalizable to a more diverse demographic population.

The median time to starting treatment was 10 days. More than half of the patients in the remdesivir group and 40% of patients in the placebo group started treatment later (11 to 12 days after symptom onset). It is not clear if the duration of time between symptom onset and initiation of treatment with remdesivir would be reflective of use in clinical practice.

Adaptive COVID-19 Treatment Trial (ACTT-1)

Internal Validity

ACTT was an adaptive, randomized, double-blind, placebo-controlled trial that used a group sequential design, which included interim monitoring to allow for the introduction of new treatment arms and early stopping for safety, efficacy, or futility.[1] ACTT was re-titled ACTT-1 to describe the first stage of ACTT to account for the introduction of new treatment arms. In ACTT-2, remdesivir was compared to baricitinib combined with remdesivir (ClinicalTrials.gov Identifier: NCT0440157941).[30] Results of ACTT-2 were published on December 11, 2020.[31] In the on-going ACTT-3 study, remdesivir is compared to interferon beta-1a combined with remdesivir (ClinicalTrials.gov Identifier: NCT0449247542).[32]

In ACTT-1, although randomization was centralized through an online system, some study personnel where unblinded to treatment allocation (i.e., the pharmacist who prepared the study drug and the nurse who administered the treatment). However, outcomes were assessed by blinded study personnel. The trial used a matched placebo to maintain the double-blind; however, there was a shortage of placebo at some sites, which necessitated the use of normal saline as a replacement. Efforts were made to maintain the blinding by administering the study drugs in opaque bags and tubing.

Baseline characteristics generally appeared to be balanced between treatment arms, with randomization stratified according to treatment site and disease severity. Baseline information on comorbidities was missing or incomplete for 14 (1.3%) patients. The use of co-interventions was permitted according to local protocol during the study. More patients in the placebo group were administered antibiotics (85.9% versus 78.9%), vasopressors (37.8% versus 27.6%), and corticosteroids (24.4% versus 21.6%) compared with the remdesivir group. The use of other concomitant medications appeared balanced between the groups, including the use of hydroxychloroquine and antiviral medications.

The analyses of the secondary outcomes did not control the type I error rate. As such, all other analyses were reported as point estimates and 95% CIs and are not intended for inferences to be drawn from them.

The initially proposed primary outcome of ACTT-1 was a seven-point ordinal clinical status scale assessed on day 15. The protocol allowed for this scale to be evaluated after 100 patients were enrolled to determine if the timing was appropriate or if categories should be collapsed. The scale was revised to an eight-point ordinal clinical status scale during the trial, but it remained the primary end point. A protocol amendment on April 2, 2020, after 72 patients had been enrolled and before any interim data analysis, designated the eight-point ordinal clinical status scale on day 15 as the key secondary outcome. With this amendment, time to recovery over the 29-day study time frame was designated the primary end point of ACTT-1. The rationale for the amendment was that COVID-19 was a more protracted disease than originally anticipated, which necessitated a different primary outcome. Based on the preliminary analyses, both the eight-point ordinal scale on day 15 and the time to recovery over the 29-day study period were statistically significant. Further, the primary end point was changed before data analysis and without knowledge of trial outcome data. As such, the change in primary outcome appears to be less of a threat to the internal validity of ACTT-1 than if the initial primary outcome had not been statistically significant or changed following interim analysis.

Applying standard survival analysis methods such as the Kaplan-Meier method to estimate time to recovery with censoring for people who died has been criticized because recovery time cannot be estimated in these patients. As a result, estimates may be biased, particularly in situations where there is high rate of mortality or censoring. A better approach would be to use a cumulative incidence curve which would provide a summary measure that is more robust than the hazard ratio. However, given the low rates of mortality and censoring in the ACTT-1 study, it is unlikely that the comparison of time to recovery between patients who received remdesivir and patients who received placebo is biased due to the lack of accounting for the competing risk of mortality.[33]

Based on interim monitoring, a decision was made to make the study results public. Treating physicians could request to know a patient's treatment assignment if the patient had not completed the 29-day study period and had worsening clinical status. Thus, patients originally assigned to placebo could be treated with remdesivir. A total of 16 (3.0%) patients in the remdesivir group and 35 (6.7%) patients in the placebo group were unblinded. A total of 26 patients originally in the placebo group who were unblinded were given remdesivir. Sensitivity analyses evaluating the unblinding (patients whose treatment assignments were unblinded had their data censored at the time of unblinding) and crossover (patients in the placebo group treated with remdesivir had their data censored at the initiation of remdesivir treatment) produced results similar to those of the primary analysis.

Several subgroup analyses were performed, although only one was based upon a stratification variable and maintained randomization. There was no control of the type I error rate for the subgroup analyses. However, a number of the subgroup analyses had small sample sizes and were potentially underpowered, such as the subgroup of patients with mild-to-moderate disease severity at baseline (n = 105). Further, according to the information provided in the publication supplemental appendix, the width of the 95% CIs was not adjusted for multiple testing, so the CIs should not be used to make definitive inferences about treatment effects.

External Validity

Approximately 90% of patients were considered to have severe COVID-19 at baseline according to the study criteria, which would align with the previously noted National Institutes of Health definitions based on oxygen saturation. It is unclear if the results of the study would be generalizable to a less severe population given the limited representation of patients with mild-to-moderate disease. Although subgroup analyses were performed according to disease severity, this subgroup analysis had several limitations as previously noted.

Similar to Wang et al., most patients had comorbid medical conditions, with more than one-half of patients having two or more comorbidities. Hypertension, diabetes, and obesity were the most common comorbidities, which are known risk factors for more severe COVID-19.

The trial was conducted in 10 different countries and across 73 different sites, with the intent of generating results that could be generalized across geographic regions. Approximately 80% of patients were recruited from North America; however, there were no Canadian sites included in the study.

The median time from symptom onset to starting treatment was nine days. Although it is unclear if the duration of time between symptom onset and initiation of treatment with

remdesivir would be reflective of use in clinical practice, this is similar to what was observed in Wang et al.

A 10-day dosing duration of remdesivir was evaluated in ACTT-1. Based on the current evidence, Health Canada recommends a total duration of treatment of at least five days and no more than 10 days.[34] In addition, the CADTH Remdesivir Implementation Panel recommends that treatment be assessed at day 5 and that remdesivir be discontinued if treatment goals (as established by a multi-disciplinary care team and a patient or patient representative) are not met.[35]

GS-US-540-5773 — Part A

Internal Validity

Part A of GS-US-540-5773 was a multi-centre, open-label RCT that compared two dosing regimens of remdesivir.[2] The categories of the clinical status ordinal scale were objective in nature, as were other outcomes, such as mortality. As such, the risk of bias related to the open-label design in assessing of these outcomes is anticipated to be lower than for more subjective outcomes such as adverse events.

The trial was designed to compare two dosing regimens of remdesivir, but did not include a control group (i.e., a comparison to standard care), which makes it difficult to interpret the clinical efficacy outcomes of the trial. While both treatment durations appeared to have similar clinical efficacy, it remains unclear in this trial whether either the five-day or 10-day treatment regimen improved clinical status, reduced the time to recovery or to clinical improvement, or improved mortality beyond standard of care in patients with severe COVID-19.

The original protocol of February 24, 2020 underwent three amendments on March 15, 2020, March 20, 2020, and April 12, 2020. The changes with each protocol amendment occurred after enrolment of patients into the trial began, but before data analysis. The protocol amendments included changes to the inclusion and exclusion criteria, study outcomes, and planned statistical analysis. Initially, the primary outcome was specified as the proportion of patients with normalization of fever and oxygen saturation at day 14, which was subsequently modified to the seven-point ordinal clinical status scale. The rationale stated for this amendment was “an evolving understanding of the signs and symptoms of COVID-19 during hospitalization and in recognition of emerging standards for assessment of COVID-19.”[2] The change to the primary outcome occurred before data analysis; however, the original primary outcome was removed as a study outcome completely. Thus, while a clear rationale for changing the primary outcome was provided, from a transparency perspective, it would have been clearer if the initial primary end point could have been analyzed as well (i.e., as a secondary outcome). However, with one of the protocol amendments, patients were no longer required to have a fever as an inclusion criterion, which would make such an analysis infeasible. The inclusion of children 12 years or older was another protocol change. Limited baseline characteristics were presented in the publication. Without knowing the temperature and the distribution of age categories at baseline, it is unclear if these protocol changes affected balance in the baseline characteristics of the two groups.

Patients in the 10-day treatment group had more severe disease at baseline, with 35% of patients receiving invasive mechanical ventilation, ECMO, non-invasive ventilation, or high-flow oxygen, compared with 28% of patients in the five-day treatment group. Further, four

(2%) patients and nine (5%) patients in the five-day and 10-day treatment groups, respectively, were receiving mechanical ventilation or ECMO at baseline, which is a protocol violation. The percentage was higher in the 10-day treatment group and contributed to the baseline imbalance in disease severity between groups.

The statistical analyses were adjusted for baseline clinical status, although this adjustment was not specified until a later protocol revision to the statistical analysis plan (but before data analysis). Given the limited reporting of baseline characteristics, it is unclear if other imbalances between treatment groups existed at baseline that were not adjusted for in the analysis.

The analyses of the secondary outcomes did not control the type I error rate for multiple statistical testing. As such, a P value was only reported for the key secondary outcome and all other analyses were reported as point estimates and 95% CIs (without adjustment of the width of the CIs), and were not intended for inferences to be drawn from. However, given that all CIs for the secondary outcomes include the null value of 1.0, there is no risk of a type I error, but the uncertainty reflected in the interval remains underestimated.

Post-hoc subgroup and exploratory analyses were conducted, the results for which are not reported in this review as they were not pre-specified and have several other limitations.

The full analysis set was defined as all patients who were randomized and received at least one dose of remdesivir, which is not a true intention-to-treat approach. However, the full analysis set excluded five patients in total (two from the five-day treatment group and three from the 10-day treatment group). Furthermore, there was additional missing data for some adverse events (such as measures of hepatic function). Patients who recovered before the end of the trial could be discharged from hospital and stop remdesivir treatment. As such, only 43% of patients in the 10-day group received a full course of treatment, whereas 85% of patients completed a full course of treatment in the 5-day group. While the median treatment course in the 10-day group was nine days, it is unclear whether similar findings for the comparative efficacy of the five-day and 10-day regimens would be observed if all patients received full treatment courses. Further, it is unclear what proportion of data for the primary outcome was imputed in each group, the reason for imputation, and if there was an imbalance between groups.

No information was provided for Part A of GS-US-540-5773 on the use of cointerventions before enrolment or throughout the trial (supportive pharmacotherapies and treatments directed at COVID-19). Thus, it is unclear what background care was received in addition to remdesivir (if any) and if that was balanced between treatment groups.

External Validity

Limited information on baseline demographic and clinical characteristics were provided in the publication for Part A of GS-US-540-5773. Hypertension, diabetes, and asthma were the most common comorbidities, which are all known risk factors for more severe COVID-19. The median body mass index was 29 for both group, which is considered overweight. However, the percentage of patients who were obese was not reported. Furthermore, it is unknown if the patients had more than one comorbidity; as such, the degree of risk for poor outcome in the study population in general was unclear.

The inclusion criteria used to select patients into the trial are reflective of the National Institute of Health definition of severe COVID-19. Furthermore, as per the inclusion criteria,

few included patients were mechanically ventilated at baseline which makes the results generalizable to non-mechanically ventilated patients.

The inclusion criteria were amended to include children 12 years and older, but it is unclear if Part A of the trial had enrolled children. The 25th percentile of age in each group was 50 years. Thus, 75% of trial participants were over the age of 50, making the results generalizable to an adult population.

Similar to ACTT-1, Part A of GS-US-540-5773 was conducted in multiple countries and across 55 different sites, which improves the generalizability across geographic regions. It is unclear what percentage of study participants were recruited from North America, but there were no Canadian sites.

Part A of GS-US-540-5773 evaluated two different treatment durations of remdesivir and provides initial evidence of efficacy for a shortened duration in severe COVID-19.

GS-US-540-5774 — Part A

Internal Validity

Part A of GS-US-540-5774 was a multi-centre, open-label RCT that compared two regimens of remdesivir (five-day or 10-day) with standard of care.[4] Since there was no treatment blinding and no placebo arm, the results reported for end points may be biased in favour of treatment with five-day or 10-day remdesivir.

The original protocol of February 24, 2020 underwent two amendments on March 15, 2020, and April 29, 2020. The changes with each protocol amendment occurred after the enrollment of patients into the trial began, but before data analysis. The protocol amendments included changes to the study objective, the inclusion and exclusion criteria, and the statistical methodology and analysis (due to change in the primary end point). Initially, the definition of the primary objective was: “to evaluate the efficacy of a five-day course of remdesivir, 10-day course of remdesivir against standard of care, with respect to the proportion of participants discharged on or before day 14.”(Supplement 3, p2)[4] This primary objective was subsequently modified to the 7-point ordinal clinical status scale on day 11 instead. The rationale stated for this amendment was: “to allow for more robust analysis.”(Supplement 3, p2)[4] While the 7-point ordinal scale was used in GS-US-540-5774,[4] the WHO Target Product Profiles for COVID-19 Therapeutics guide developed by experts does not specify clinical scales in the research of patients with moderate COVID-19.[36] In addition, each category of the 7-point ordinal scale is not necessarily of equal clinical significance and it is not possible to translate a summary OR into a clinically meaningful improvement. Furthermore, it is unclear why the primary end point of clinical status was assessed at day 11 instead of day 14. Finally, an amendment was made that lowered patient’s age of entry from 18 years to 12 years and the minimum temperature was no longer an inclusion criterion.

One of the study design criteria excluded patients receiving “concurrent treatment with drugs with actual or possible antiviral activity against SARS-CoV-2 less than 24 hours before study drug dosing of remdesivir.” (Supplement 3, p2)[4] However, patients received other medications during the study including corticosteroids, hydroxychloroquine or chloroquine and lopinavir-ritonavir. The use of these drugs was more frequent in the standard of care patient group compared to the remdesivir patient groups. While studies in patients with moderate COVID-19 suggest that hydroxychloroquine or chloroquine[37] and lopinavir-ritonavir[38] are not effective for the treatment of COVID-19, systemic corticosteroids

are recommended for patients with severe COVID-19 by the WHO and Health Canada,[39,40] based on a number of published studies. It is unclear what impact, if any, corticosteroids have on patients with moderate COVID-19, but given the difference in use between the standard of care group (19%) and the remdesivir groups (17% in the five-day group and 15% in the 10-day group), it is unclear whether the use of corticosteroids impacted the comparison of clinical efficacy of remdesivir relative to standard of care.

An amendment was made to the statistical analysis plan on June 26, 2020 to conduct analysis through day 28. However, a clear rationale was not provided for this amendment and the protocol was not updated to reflect which end points would have data collected through day 28.

It is unclear how standard of care was defined in the protocol and whether there was variation across hospitals in the standard of care patients received.

The study was powered to detect an OR of 1.8 using a two-sided significance level of 0.05 for comparing the five-day and 10-day remdesivir group against standard of care for the primary end point of clinical status. Although there was testing of multiple comparisons, the Bonferroni method was applied to control for type I error for the primary outcome only (that is, a P value of < 0.025 was considered statistically significant for each comparison between the remdesivir treatment groups and the standard of care group). Therefore, results reported for the secondary and exploratory end points should be interpreted with caution.

Based on the median duration of treatment in the 10-day remdesivir group of 6 days (IQR 3 to 10), this suggests that the 10-day remdesivir group had a similar duration of therapy to the five-day remdesivir group. Furthermore, only 38% of patients in the 10-day remdesivir group completed treatment. While the odds of improvement in clinical status were higher between the five-day remdesivir group compared to standard of care, no difference was found between the 10-day remdesivir group and standard of care. Based on this result, it is difficult to draw conclusions regarding the comparison between 10-day remdesivir treatment and standard of care.

While subgroup analyses for the primary outcome were pre-specified in the statistical analysis plan, no results were reported in the publication. In addition, post hoc (e.g., sensitivity) analyses were not pre-specified in the statistical analysis plan. Therefore, results for subgroup and post-hoc analyses were not reported in this report.

The full analysis set was defined as all patients who were randomized and received at least one dose of remdesivir, which is not a true intention-to-treat approach. Thus, the full analysis set excluded 12 patients in total (eight from the five-day treatment group and four from the 10-day treatment group).

External Validity

Similar to ACTT and Part A of GS-US-540-5773, Part A of GS-US-540-5774 was conducted in multiple countries and across 105 hospitals, which improves the generalizability across geographic regions. However, there were no Canadian locations.

Although coexisting conditions at baseline were reported for each treatment group, it is unknown if the patients had more than one comorbidity. Thus, the degree of risk for poor outcome in the study population in general was unclear.

While the study inclusion criteria were amended to include patients aged 12 years and older, it is unclear if Part A of the trial had enrolled children. The 25th percentile of age in each group was at least 45 years. Thus, 75% of trial participants were over the age of 45, making the results generalizable to an adult population.

WHO Solidarity

Internal Validity

WHO Solidarity was a multi-centre, open-label, adaptive, randomized trial that examined the use of remdesivir as one of multiple treatment arms, (hydroxychloroquine, lopinavir-ritonavir, and interferon beta-1a) in patients diagnosed with COVID-19.[6] It included interim monitoring to allow for the introduction of new treatment arms or early stopping of existing treatment arms for futility. Only the results of the remdesivir and associated control group are pertinent to this report.

Since the study was open-label and included no placebo arm, there is greater potential of bias. However, this risk was of less concern because the outcomes of interest (in-hospital deaths and incidence of mechanical ventilation) could be measured objectively. Another limitation was that local standard of care may have varied across hospitals.

Study randomization was performed twice. The first randomization identified to which of the four treatment groups patients would be assigned to, and the second randomization identified whether patients would be part of the treatment or control group. However, stratified randomization was not performed on the basis of disease severity or patient characteristics.

Since there was no specific sample size specified in the public health emergency core protocol, there may be insufficient power to detect a statistically significant association had one been present for the prespecified primary and secondary outcomes for remdesivir and its control.

There were pre-specified subgroup analyses according to disease severity at baseline (severe or not severe). Severity was not pre-defined, and analyses were performed according to whether patients were receiving supplemental oxygen (or no supplemental oxygen) and receiving mechanical ventilation at entry (or no mechanical ventilation). Results are reported for additional subgroups according to age, geographic region, glucocorticoid use, and other baseline characteristics. There was no control of the type I error rate for the subgroup analyses.

It is unclear whether adjustments were made in the statistical analyses for testing of multiple comparisons. Furthermore, there is no mention as to whether there was control for type I error for the prespecified primary and secondary outcomes.

External Validity

While the inclusion criteria in the trial included patients diagnosed with COVID-19, it is unclear how the diagnosis was confirmed for eligibility.

This trial was conducted across 405 hospitals in 30 countries which improves the generalizability across regions. Although Canada was included as one of the participating countries in the trial, the interim results do not indicate the proportion of the patients that were recruited from Canada. Therefore, caution should be advised when directly inferring results from this study to a Canadian population.

Discussion

Summary of Available Evidence

Five key studies of remdesivir were the focus of this review: two RCTs published in full (Wang et al. and ACTT-1)[5,7] interim results for WHO Solidarity,[6] and Part A of two manufacturer-conducted RCTs (GS-US-540-5773 Part A and GS-US-540-5774 Part A),[2,4] Data for Part B of GS-US-540-5773 and GS-US-540-5774 are not yet published.[8,9] Other ongoing trials of remdesivir are presented in Appendix 2. CATCO, the Canadian arm of the WHO Solidarity trial is still recruiting patients.[28]

Wang et al. was a phase III randomized, double-blind, placebo-controlled trial of patients with severe COVID-19.[7] Originally, the trial had a planned enrolment of 457 patients; however, the trial was terminated early with 237 patients randomized into the study. The primary end point was the time to clinical improvement within 28 days after randomization. The median age of patients was 66 years in the remdesivir group and 64 years in the placebo group. A total of 71% of patients in each group had comorbidities including hypertension, diabetes, and coronary heart disease.[7]

ACTT-1 was a phase III adaptive, double-blind, placebo-controlled trial of remdesivir compared with placebo in adult patients hospitalized with COVID-19.[1,5,27] The study randomized 1,062 patients; 541 were randomized to remdesivir and 521 were randomized to placebo. The primary end point of the trial was time to recovery measured over day 1 to day 29. The mean age was 58.6 years (SD 14.6) in the remdesivir group and 59.2 years (SD 15.4) in the placebo group, and overall, 53.3% of the study population was white. A total of 55% of patients had two or more coexisting conditions, including hypertension (50.7%), obesity (45.4%) and type 2 diabetes (30.6%). Approximately 90% of the study population had severe COVID-19 at baseline.[5]

Part A of GS-US-540-5773 was a manufacturer-conducted, open-label, RCT that compared two remdesivir treatment regimens in patients aged 12 years and older with severe COVID-19.[2] The original study protocol targeted a sample size of 400 patients (Part A: 397 patients not mechanically ventilated). The primary end point of Part A of the trial was clinical status measured on day 14. The mean age of patients were 61 years (IQR = 50 to 69) and 62 years (IQR = 50 to 71) in the five-day and 10-day treatment groups, respectively. Approximately 70% of the population was white, the majority were male, and 50% had hypertension.

Part A of GS-US-540-5774 was a manufacturer-conducted, open-label, RCT that compared five-day or 10-day remdesivir regimens with standard of care in patients aged 12 years and older with moderate COVID-19.[4] The original study protocol targeted a sample size of 600 patients (Part A: 584 patients). The primary end point of Part A of the trial was clinical status measured on day 11 compared to standard of care. The mean age of patients in the five-day remdesivir group was 58 years (IQR = 48 to 66), 56 years (IQR = 45 to 66) in the 10-day remdesivir group and 57 years (IQR = 45 to 66) in the standard of care group. The majority of patients were males and cardiovascular disease was the most prevalent coexisting condition in each treatment group. Azithromycin was the most common concomitant medication used by patients in the five-day and 10-day remdesivir group compared to hydroxychloroquine or chloroquine in the standard of care group. A larger proportion of patients in the standard of care group received concomitant medications compared to the remdesivir groups.

WHO Solidarity was a multi-centre, open-label, adaptive, randomized trial that compared remdesivir, hydroxychloroquine, lopinavir-ritonavir, and interferon beta-1a in patients diagnosed with COVID-19.[6] While there were four treatment groups, only the results of the remdesivir group and associated control are pertinent to this report.[6] A total of 2,743 patients were randomized to the remdesivir treatment group and 2,708 patients randomized to receive standard of care according to local practices. The primary end point was in-hospital mortality. Most patients were male, 50 years or older, and required supplemental oxygen at baseline.

Interpretation of Results

Efficacy

In the study by Wang et al., no statistically significant differences were observed between remdesivir and placebo. This can be attributed, in part, to early termination of the study and a smaller sample size than anticipated. However, the observed treatment effect for the primary outcome was also smaller than anticipated, based on parameters used in an a priori power calculation. The time to clinical improvement was 21 days for remdesivir compared with 23 days for placebo. The HR was not statistically significant. Mortality (14% with remdesivir and 13% with placebo) and the number of days in hospital (25 days with remdesivir and 24 days with placebo) were similar between groups. While Wang et al. performed stratified analyses based on symptom duration before treatment with remdesivir (i.e., in those who received treatment within 10 days of symptom onset and in those who received treated treatment within 11 or 12 days of symptom onset), these subgroup analyses were both statistically nonsignificant versus placebo and had a number of limitations (as noted in the critical appraisal). Thus, it remains unknown if a larger treatment effect could be expected with earlier administration of remdesivir.

In ACTT-1, the median time to recovery was shorter with remdesivir than placebo (10 days versus 15 days), with a statistically significant rate ratio of 1.29 (95% CI, 1.12 to 1.49). The odds of improvement in clinical status was statistically higher with remdesivir than placebo at day 15 (OR = 1.5; 95% CI, 1.2 to 1.9). Mortality over the entire study period was not different between remdesivir and placebo based on Kaplan-Meier estimates (11.4% versus 15.2%; HR = 0.73; 95% CI, 0.52 to 1.03).

In Part A of GS-US-540-5773, there was no difference in clinical status between remdesivir administered for five days and remdesivir administered for 10 days, assessed on day 14. However, only 43% of the patients in the 10-day cohort received the full treatment course. Time to recovery and time to clinical improvement were similar between the two treatment groups. Mortality at day 14 with the five-day regimen was 8% and was 11% with the 10-day regimen. However, given the lack of a standard of care comparator group to understand expected outcomes in the study population in the absence of treatment with remdesivir, the trial outcomes are difficult to interpret.

In Part A of GS-US-540-5774, the odds of improvement in clinical status on the 7-point ordinal scale was statistically significantly higher in the five-day remdesivir group compared with the standard of care group at day 11, however, it is unclear if this improvement is clinically meaningful. There was no difference in the odds of improvement in clinical status on the 7-point ordinal between the 10-day remdesivir group compared with the standard of care group at day 11. There were no differences between the five-day and 10-day remdesivir group versus standard of care for the following pre-specified exploratory end points: number of patients improved or recovered, time to clinical improvement, time to

recovery, or time to room air. Mortality at day 28 was 1% in the five-day remdesivir group and 2% each in the 10-day remdesivir and standard of care group.

In WHO Solidarity, interim results for remdesivir compared with standard of care were pertinent to this report. While the other treatment groups were terminated due to futility, the trial is ongoing for remdesivir compared to standard of care. The current evidence showed no difference between remdesivir and standard of care for in-hospital deaths and incidence of mechanical ventilation, and no difference for any of the subgroups. Adverse events were note measured in this trial.

Two of the RCTs were conducted in patients with severe COVID-19, and in ACTT-1, 90% of patients had severe COVID-19. Further, the Wang et al. study was conducted in a single country and in patients with comorbid conditions, so generalizability to other populations remains unknown.

It is challenging to interpret the body of evidence generated from the RCTs that assessed the efficacy of remdesivir to date. The trial by Wang et al. was terminated early. Part A of GS-US-540-5773 had no standard of care comparator and, as such, limited conclusions can be made regarding the efficacy of remdesivir from this trial. While Part A of GS-US-540-5774 included a standard of care comparison group, the study was open-labelled which may have biased the results in favour of remdesivir, although the outcomes were objective in nature. Furthermore, there are no details to define standard of care and if the study sites used the same standard of care guidelines. A larger proportion of patients in the standard of care group received concomitant medications including steroids, lopinavir-ritonavir, and hydroxychloroquine or chloroquine. While lopinavir-ritonavir and hydroxychloroquine or chloroquine do not appear to be effective in patients with moderate COVID-19, it is unclear what impact, if any, the use of steroids had on the comparison between the remdesivir treatment groups and standard of care.

The RCTs differed in important aspects of their design, including trial location (single centre versus multi-centre and multi-country), inclusion criteria, comparators (e.g., placebo versus different treatment regimens), primary outcomes, and outcome definitions, which precludes the direct comparison of results across studies.

Harms

Harms data were reported for Wang et al., ACTT-1, Part A of GS-US-540-5773 and Part A of GS-US-540-5774. In Wang et al., the percentage of patients with any adverse events was similar between remdesivir and placebo. While more patients in the placebo group reported serious adverse events (26% versus 18% with remdesivir), more patients in the remdesivir group discontinued treatment due to an adverse event (12% versus 5% with placebo). In ACTT-1, the percentage of patients with serious adverse events was higher in the placebo group than in the remdesivir group (31.6% versus 24.6%, respectively). In ACTT-1, grade 3 and grade 4 adverse events were reported in 51.3% and 57.2% of the remdesivir and placebo groups, respectively. Discontinuations due to adverse events were higher with placebo (15%) compared with remdesivir (11%). In GS-US-540-5773, there were more serious adverse events and discontinuations due to adverse events when remdesivir was administered for 10 days than for five days. In GS-US-540-5774, there was no difference in the percentage of patients experiencing an adverse event that occurred in the five-day remdesivir group compared to the standard of care group (4.8%, 95% CI –5.2 to 14.7, P =0.36). There was a difference between the 10-day remdesivir group compared

to standard of care group (12.0%, 95% CI 1.6 to 21.8, P =0.02), with more patients experiencing an adverse event in the 10-day remdesivir group.

Because of concerns with hepatic adverse events, the percentage of patients with elevated hepatic enzymes (AST and ALT) and total bilirubin were reported in Part A of GS-US-540-5773. These appeared to be similar between the five-day and the 10-day regimen groups. The percentage of patients with elevated hepatic enzymes (AST and ALT) reported in Part A of GS-US-540-5774 were balanced in the five-day remdesivir group, 10-day remdesivir group and standard of care group. Wang et al. reported that 5% of patients had an increased in AST whereas Part A of GS-US-540-5773 had 2% to 6% of patients with increased ALT and increased AST with remdesivir, respectively. In ACTT-1, the combined percentage of patients with increases in aminotransaminases, ALT, or AST was 5.6% with remdesivir and 11.0% with placebo.

Conclusions

Five RCTs, Wang et al. (which was stopped early), ACTT-1, WHO Solidarity, Part A of GS-US-540-5773, and Part A of GS-US-540-5774 provide the information to date regarding the efficacy and safety of remdesivir. Two of the RCTs were conducted in patients with severe COVID-19, and in ACTT-1, 90% of patients had severe COVID-19. GS-US-540-5774 provided data on patients with moderate COVID-19 disease. Wang et al. did not find remdesivir to be more effective than placebo for any outcome, but the study was potentially underpowered to detect a difference between groups due to a smaller sample size than planned and a smaller than anticipated treatment effect with remdesivir. ACTT-1 showed a statistically significantly reduced time to recovery with remdesivir compared with placebo, however, mortality over the entire study period was not statistically different than for those treated with placebo. Clinical efficacy appears to be similar for the five-day and 10-day treatment regimens based on Part A of GS-US-540-5773; however, as previously noted, there are limitations to this trial. In GS-US-540-5774, patients receiving the 5-day treatment regimen had improved clinical status at day 11 compared with standard of care, but not those receiving the 10-day treatment regimen. There were no differences between remdesivir and standard of care for any of the outcomes or subgroups in the interim results of WHO Solidarity.

The trial results available are conflicting and methodological issues make the results of Wang et al. difficult to interpret. GS-US-540-5773 showed that a shorter course (five days) of remdesivir may offer the same benefits as a longer course of treatment in patients who do not require mechanical ventilation, but most patients did not complete the 10-day treatment regimen. In GS-US-540-5774, the 10-day treatment group only received a median of 6 days of treatment. Hence, the results for this trial are difficult to interpret and not comparable across trials.

Appendix 1: Excluded Studies

Table 10: Excluded Studies

Reference	Reason for exclusion
Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med. 2020.	Study design (case series)
Antinori S, Cossu MV, Ridolfo AL, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: clinical outcome and differences in post-treatment hospitalisation status. Pharmacol Res. 2020 May 11:104899.	Study design (case series)
ACTT-2: Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. NEJM 2020 December 11.	The drug of interest is baricitinib; and remdesivir is used as standard of care.

Appendix 2: Ongoing RCTs

The information provided in this table relies on the information posted on the ClinicalTrials.gov registry. Not all ongoing trials of remdesivir are posted to the website and, as such, ClinicalTrials.gov may provide an incomplete picture of the ongoing clinical trials related to remdesivir. Furthermore, there may be reporting errors in the study records posted on ClinicalTrials.gov. Finally, given the rapid changes occurring with the scientific evidence related to COVID-19, the reporting of amendments to the included trial protocols may be delayed.

Table 11: Ongoing Randomized Controlled Trials

Study information	Study design	Population	Interventions	Key clinical outcomes
Sponsor: ViralClear Pharmaceuticals, Inc. ClinicalTrials.gov Identifier: NCT04410354[41] Estimated primary completion date: November 2020 Estimated study completion date: December 2020 **STATUS:** Terminated (failure to meet primary endpoint)	Phase II, double-blind, placebo-controlled, multi-centre N = 80 patients	Adult patients with confirmed SARS-CoV-2 infection, with a score of 3 or 4 on NIAID 8-point ordinal scale	**Merimepodib and remdesivir** Merimepodib 400 mg orally three time daily for 10 days Remdesivir 200 mg IV loading dose on day 0 followed by 100 mg daily IV for 4 days. If patient does not demonstrate clinical improvement, 100 mg daily IV may be extended for up to 5 additional days (for a total of up to 10 days) **Remdesivir and placebo** Remdesivir 200 mg IV loading dose on day 0 followed by 100 mg daily IV for 4 days. If patient does not demonstrate clinical improvement, 100 mg daily IV may be extended for up to 5 additional days (for a total of up to 10 days) Matching placebo to merimepodib	• Proportion of patients alive at day 28 who are not hospitalized or if hospitalized are free of respiratory failure • Adverse events • Change in NIAID 8-point ordinal scale • Number of deaths • Need and duration of mechanical ventilation
Sponsor: Dr. Md. Alimur Reza, Beximco Pharmaceuticals Ltd. ClinicalTrials.gov Identifier: NCT04596839[42] Estimated primary completion date: February 28, 2021	Open-label, multi-centre N = 60	Hospitalized adult patients with a diagnosis of COVID-19 laboratory-confirmed with RT-PCR test ≤ 7 days before randomization	Remdesivir 200 mg IV on day 1 and 100 mg IV on days 2 to 5 Standard of care	• Duration of hospital stay • Time to clinical improvement • All-cause mortality • Duration of mechanical ventilation • Duration of supplemental oxygenation

Study information	Study design	Population	Interventions	Key clinical outcomes
Estimated study completion date: April 30, 2021 **Status**: recruiting				• Time to negative RT-PCR • Safety
REMDACTA Sponsor: Hoffman-La Roche ClinicalTrials.gov Identifier: NCT04409262[43] Estimated primary completion date: February 12, 2021 Estimated study completion date: March 16, 2021 **Status:** Active, not recruiting	Phase III, double-blind, multi-centre N = 650	Hospitalized patients ≥ 12 years and older, with confirmed COVID-19 pneumonia	**Tocilizumab and remdesivir** Remdesivir loading dose with one infusion of tocilizumab on day 1 then remdesivir once-daily maintenance dose on days 2 to 10[b] **Remdesivir and placebo** Remdesivir loading dose with one infusion of placebo on day 1 then remdesivir once-daily maintenance dose on days 2 to 10 [b]	• Time to discharge • Time to mechanical ventilation or death • Time to clinical improvement • Clinical status using a 7-category ordinal scale • Proportion of patients requiring initiation of mechanical ventilation • Ventilator-free days • Proportion of patients requiring initiation of ICU care • Duration of ICU stay • Time to clinical failure • Mortality • Safety
Sponsor: Gilead Sciences ClinicalTrials.gov Identifier: NCT04501952[44] Estimated primary completion date: April 2021 Estimated study completion date: April 2021 **Status:** recruiting	Phase III, double-blind, placebo-controlled N = 1,264	Out-patients 12 years and older with confirmed SARS-CoV-2 infection SARS-CoV-2 infection confirmed by molecular diagnosis ≤ 4 days prior to screening Presence of ≥ 1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomization Not currently requiring hospitalization (hospitalization defined as ≥ 24 hours of acute care)	Remdesivir 200 mg on IV day 1 followed by remdesivir IV 100 mg on days 2 and 3. Matching placebo to remdesivir	• Composite endpoint of all cause medically attended visits or death by day 28 • Proportion of patients experiencing TEAEs • All-cause mortality at day 28 • Rate of hospitalization by day 28 • Composite endpoint of all cause medically attended visits or death by day 14 • Change in SARS-CoV-2 viral load • Time to resolution of COVID-19-related symptoms • Proportion of patients progressing to oxygen supplementation by day 28
ACTIV-5/ BET-A	Phase II, double-blind, multi-centre	Hospitalized adult patients with confirmed	**Risankizumab and remdesivir**	• Clinical status on an 8-point ordinal scale

Study information	Study design	Population	Interventions	Key clinical outcomes
Sponsor: National Institute of Allergy and Infectious Diseases ClinicalTrials.gov Identifier: NCT04583956[45] Estimated primary completion date: December 31, 2021 Estimated study completion date: December 31, 2021 **Status:** recruiting	N = 200	SARS-CoV-2 infection and symptoms of COVD-19 and requiring ongoing medical care Illness of any duration and requiring supplemental oxygen, mechanical ventilation, or ECMO	Risankizumab: 1,200 mg IV infusion once on day 1 Remdesivir: 200 mg IV loading dose on day 1 followed by 100 mg IV daily while hospitalized and up to 10 days total course **Remdesivir and placebo** Remdesivir: 200 mg IV loading dose on day 1 followed by 100 mg IV daily while hospitalized and up to 10 days total course Matching placebo of risankizumab	• Change in baseline from various laboratory values • Time to recovery • Duration of hospitalization • Duration of new mechanical ventilation, ECMO, non-invasive ventilation, high-flow oxygen use, or oxygen use • Safety
ACTIV-5/ BET-B Sponsor: National Institute of Allergy and Infectious Diseases ClinicalTrials.gov Identifier: NCT04583969[46] Estimated primary completion date: December 31, 2021 Estimated study completion date: December 31, 2021 **Status:** recruiting	Phase II, double-blind, multi-centre N = 200	Hospitalized adult patients with confirmed SARS-CoV-2 infection and symptoms of COVD-19 and requiring ongoing medical care Illness of any duration and requiring supplemental oxygen, mechanical ventilation, or ECMO	**Lenzilumab and remdesivir** Lenzilumab: 600 mg IV infusion every 8 hours starting on day 1 for a total of 3 doses Remdesivir: 200 mg IV loading dose followed by 100 mg IV daily for the duration of the hospitalization and up to 10 days total course **Remdesivir and placebo** Remdesivir: 200 mg IV loading dose followed by 100 mg IV daily for the duration of the hospitalization and up to 10 days total course Matching placebo of lenzilumab	• Clinical status on an 8-point ordinal scale • Change in baseline from various laboratory values • Time to recovery • Duration of hospitalization • Duration of new mechanical ventilation, ECMO, non-invasive ventilation, high-flow oxygen use, or oxygen use • Safety
ACTIV-1 IM Sponsor: Donald Benjamin, Duke University ClinicalTrials.gov Identifier: NCT04593940[47]	Phase III, double-blind, multi-centre N = 2,160	Hospitalized adult patients with laboratory-confirmed SARS-CoV-2 infection and symptoms of COVID-19	**Infliximab (or placebo) and remdesivir** Infliximab: single dose of 5 mg/kg IV on day 1	• Number of patients recovered • Change in number of patients hospitalized on invasive mechanical ventilation • Number of patients that improved clinically

Study information	Study design	Population	Interventions	Key clinical outcomes
Estimated primary completion date: February 2021 Estimated study completion date: September 2021 **Status:** recruiting			**Abatacept (or placebo) and remdesivir** Abatacept: single dose 10 mg/kg up to 1,000 mg IV on day 1 **Cenicriviroc (or placebo) and remdesivir** Cenicriviroc: 450 mg orally on day 1 and 300 mg on day 2 to day 29 Remdesivir is standard of care	• Number of patient deaths • Number of patients with decreased supplemental oxygen • Change in number of patients needing non-invasive ventilation or high-flow oxygen • Number of days in hospital • Number of patients with NEWS ≤ 2 • Safety
ACTIV-3 (TICO) Sponsor: National Institute of Allergy and Infectious Diseases ClinicalTrials.gov Identifier NCT04501978[48] Estimated primary completion date: July 2022 Estimated study completion date: July 2022 **Status:** recruiting	Phase III, adaptive, double-blind, platform, multi-centre N = 10,000	Adult patients with COVID-19 infection with symptoms for 12 days or less who require hospitalization for acute medical care	VIR-7831[b] IV and remdesivir[b] (standard of care) BRII-196/BRII-198[b] IV and remdesivir[b] (standard of care) Matching placebo and remdesivir[b] Remdesivir is standard of care	• Pulmonary ordinal outcome • Time to recovery All-cause mortality • Composite of time to sustained recovery and mortality • Days alive outside short-term acute care hospital • Change in New Early Warning Score • Incidence of clinical organ failure • Composite of death or serious clinical COVID-19 related events • Composite of cardiovascular events and thromboembolic events • Safety • Antibody levels

Study information	Study design	Population	Interventions	Key clinical outcomes
ITAC Sponsor: University of Minnesota ClinicalTrials.gov Identifier: NCT04546581[49] Estimated primary completion date: July 2021 Estimated study completion date: July 2021 **Status:** recruiting	Phase III, adaptive, double-blind, placebo-controlled, multi-centre N = 500	Adult patients with SARS-CoV-2 infection and COVID-19 symptoms for 12 days or less who require hospitalization for acute medical care	Hyperimmune immunoglobulin to SARS-CoV-2 single infusion and remdesivir[b] (standard of care) Matching placebo and remdesivir[b] Remdesivir is standard of care	• Clinical status of patients on day 7 measured using an ordinal scale • All-cause mortality • Clinical status of patients in each group on day 3, 5, 14, and 28 of follow-up using the primary ordinal outcome • Change in New Early Warning Score • Time to worsening • Discharge status • Days alive outside of hospital • Clinical status of patients in each group on day 3, 5, 7, 14, and 28 post-treatment, limited to using the pulmonary elements or the thrombotic components of the primary ordinal outcome • Time to recovery • Clinical organ dysfunction • Change in neutralizing antibody • Safety
CATCO – Canadian Arm of the Solidarity Trial[a] Sponsor: Sunnybrook Health Sciences Centre ClinicalTrials.gov Identifier: NCT04330690[28] Estimated primary completion date: March 18, 2022 Estimated study completion date: May 18, 2022 **Status:** recruiting	Phase II, adaptive, open label, multi-centre N = 2,900 Conducted in collaboration with countries around the world through the World Health Organization	Hospitalized adult patients with confirmed SARS-CoV-2 infection	Remdesivir 200 mg IV on day 1, followed by 100 mg IV daily for 9 days + supportive care Interferon beta-1a 22 mcg or 44 mcg on days 1, 3, and 6 + supportive care Supportive care	• All-cause mortality • Time to improvement • Change in clinical status • Oxygen free • Incidence of oxygen use • Duration of oxygen use • Incidence of new mechanical ventilation • Duration of mechanical ventilation • Duration of hospitalization • Mortality • Safety

Study information	Study design	Population	Interventions	Key clinical outcomes
I-SPY_COVID Sponsor: QuantumLeap Healthcare Collaborative ClinicalTrials.gov Identifier: NCT04488081[50] Estimated primary completion date: July 24, 2022 Estimated study completion date: November 1, 2022 **Status:** recruiting	Phase II, adaptive, open label platform trial N = 1,500	Hospitalized critically ill adult patients with confirmation of SARS-CoV-2 infection by PCR	**Remdesivir and standard of care** Remdesivir 200 mg loading dose on day 1, followed by 100 mg IV once-daily maintenance doses for 4 or 9 days **Cenicriviroc and remdesivir** Cenicriviroc 150 mg tablets twice daily for 28 days of until discharge (minimum of 14 days) **Icatibant and remdesivir** Icatibant 30 mg subcutaneous injection every 8 hours daily for 3 days **Razuprotafib and remdesivir** Razuprotafib subcutaneous injection 10 mg every 8 hours for 7 days, advancing to 20 mg every 8 hours for 7 days once the safety run-in confirms tolerability. **Apremilast and remdesivir** Apremilast 30 mg twice daily for 14 days	• Time to achieve durable change in COVID-19 to ordinal level 4 or less for at least 48 hours • Disease severity • Health care utilization • Safety • Mortality
DisCoVeRy Sponsor: INSER–Institut national de la santé et de la recherche médicale ClinicalTrials.gov Identifier: NCT04315948[51] Estimated primary completion date: March 2023 Estimated study completion date: March 2023	Phase III, adaptive open label, multi-centre N = 3,100	Hospitalized adult patients with confirmed SARS-CoV-2 infection	Remdesivir 200 mg IV on day 1 followed by a 100 mg dose IV once daily for the duration of the hospitalization, up to 10 days Standard of care	• Percentage of patients reporting each severity rating on a 7-point ordinal scale • Time to discharge • Number of oxygenation-free days in the first 28 days • Incidence and duration of new oxygen use • Incidence of new mechanical ventilation use • Duration of hospitalization • Mortality

Study information	Study design	Population	Interventions	Key clinical outcomes
Status: recruiting				• Safety
ACTT-2[31] Sponsor: National Institute of Allergy and Infectious Diseases ClinicalTrials.gov Identifier: NCT04401579[30] Estimated primary completion date: July 31, 2020 Estimated study completion date: July 31, 2020 **Status:** completed; results published[31]	Phase III, adaptive, double-blind, multi-centre N =1,034	Hospitalized adult patients with symptoms suggestive of COVID-19	**Baricitinib and remdesivir** Baricitinib 4 mg oral dose (or crushed and given through a nasogastric tube, if necessary) for the duration of hospitalization up to a 14-day total course of treatment Remdesivir 200 mg IV followed by a 100 mg once-daily IV dose for the duration of hospitalization up to a 10-day total course of treatment **Remdesivir and placebo** Remdesivir 200 mg IV followed by a 100 mg once-daily IV dose for the duration of hospitalization up to a 10-day total course of treatment Matching placebo to baricitinib	• Time to recovery (up to 29 days of follow-up) • Change in laboratory values • Change in national early warning score • Clinical status at day 15 using an ordinal eight-point scale ranging from fully recovered to death • Duration of hospitalization • Duration of mechanical ventilation • Duration of oxygen use • Mortality • Safety
ACTT-3 Sponsor: National Institute of Allergy and Infectious Diseases ClinicalTrials.gov Identifier: NCT04492475[32] Estimated primary completion date: December 15, 2020 Estimated study completion date: December 30, 2020 **Status:** active, not recruiting	Phase III, adaptive, double-blind, multi-centre N = 969	Hospitalized adult patients with symptoms suggestive of COVID-19	**Interferon beta-1a and remdesivir** Interferon beta-1a 44 mcg subcutaneous injection on days 1, 3, 5 and 7 while hospitalized for a total of 4 doses Remdesivir 200 mg IV on day 1, followed by a 100 mg once-daily maintenance dose while hospitalized for up to a 10-day total course **Remdesivir and placebo** Remdesivir 200 mg IV on day 1, followed by a 100 mg once-daily maintenance dose while	• Time to recovery • Change from baseline of various lab values • Change from baseline in the national early warning score • Safety • Duration of hospitalization • Duration of invasive mechanical ventilation, new non-invasive ventilation or high-flow oxygen use, new oxygen use, new ventilator or extracorporeal membrane oxygenation use, non-invasive ventilation/high-flow

Study information	Study design	Population	Interventions	Key clinical outcomes
			hospitalized for up to a 10-day total course Matching placebo to Interferon beta-1a	oxygen use, oxygen use • Mortality • Change in clinical status on a 7-point ordinal scale
Sponsor: Tanta University ClinicalTrials.gov Identifier: NCT04345419[52] Estimated primary completion date: December 2029 Estimated study completion date: December 2029 **Status:** recruiting	Phase II/III, single-blind N = 120	COVID-19 patients	Remdesivir[b] Chloroquine or hydroxychloroquine[b]	• Number of patients with improvement or mortality

ACTT = Adaptive COVID-19 Treatment Trial; ECMO = extracorporeal membrane; ICU = intensive care unit; IV = intravenous; NEWS = National Early Warning Score; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TEAEs = treatment-emergent adverse events.

[a] The Solidarity study is an international clinical trial launched by WHO. There are many countries partnering with WHO.[53]

[b] Dosages not reported.

Appendix 3: Statistical Analysis

Table 12: Statistical Analysis of Efficacy End Points

	Power calculation assumptions	Outcome, test, and treatment effect estimate	Imputation of missing data	Control of type I error	Subgroup analyses	Analysis sets
Wang et al.[7]	325 events across both groups required to provide 80% power under a one-sided type I error of 2.5% under the following assumptions: • a hazard ratio of 1.4 • a corresponding change in time to clinical improvement of six days • time to clinical improvement is 21 days on placebo. 453 patients (151 on placebo and 302 on remdesivir) required based on the following assumptions: • 80% event rate within 28 days across both groups • 10% dropout rate	Time to clinical improvement: Kaplan–Meier plot compared with a log-rank test. Clinical improvement: Cox proportional-hazards model (HR and 95% CI). Clinical deterioration: Cox proportional-hazards model (HR and 95% CI). Continuous outcomes: Between groups differences compared with Hodges-Lehmann estimation. Clinical status: Proportion of patients in each category of the six-point scale based on ordinal logistic regression model (OR and 95% CI).	Methods for handling of missing outcome data were not reported.	No methods were reported that would control the type I error rate in relation to multiple statistical testing of secondary end points and subgroup analyses.	Subgroup analyses: Treatment within 10 days or less versus more than 10 days after symptom onset. Time to clinical deterioration (defined as one category increase or death). Viral RNA load at entry.	ITT primary efficacy analysis that included all randomly assigned patients. Safety population: Patients who started study treatment

	Power calculation assumptions	Outcome, test, and treatment effect estimate	Imputation of missing data	Control of type I error	Subgroup analyses	Analysis sets
Beigel et al.[5]	Study designed to have 85% power for detecting a recovery ratio of 1.35. At least 400 recoveries were required and for subgroup analysis. Two-sided type I error rate of 5%.	Time to recovery: primary analysis was a log-rank test of time to recovery between remdesivir and placebo, stratified by disease severity at baseline. Treatment effect estimate was reported as a recovery rate ratio. Mortality estimates: Based on Kaplan-Meier estimator. Clinical status: the key secondary analysis was a proportional odds model, stratified by baseline disease severity. Tested difference in ordinal score distribution between remdesivir and placebo at day 15 using common OR.	Patients who did not recover were censored at day 29. Patients who died before experiencing an event were censored at day 29. Imputation rules were developed for secondary outcomes (i.e., those related to ventilation, hospitalization, and oxygen).	To account for the interim analysis, the group sequential design used the Lan-DeMets spending function analogue of the O'Brien-Fleming boundary to maintain the type I error rate at 0.05. No adjustments for multiple comparisons were made for the secondary outcomes, so the results are reported as point estimates and 95% CIs only. The widths of the 95% CIs were not adjusted for multiple comparisons and should not be used inferentially.	Pre-specified subgroup analyses were defined according to: • Site location • Sex • Disease severity (severe versus mild to moderate and based on the ordinal scale) • Age 18 to 39 years, 40 to 64 years, or ≥ 65 years • Race • Ethnic group • Duration of symptoms before randomization (≤ 10 days or > 10 days, in quartiles, and as the median) • Presence of comorbidities	ITT: All patients who were randomized mITT: Patients who received at least one infusion As-treated population: based on mITT population
Goldman et al.[2] Part A	A total sample size of 400 participants (200 in each group) were required to achieve > 85 % power to detect an odds ratio of 1.75	Clinical status at day 14: Proportional odds model that included treatment as the independent variable and baseline clinical status as a continuous	Primary end point: If a patient died before day 14, the day 14 category on the ordinal scale was	No adjustments for multiple comparisons. The widths of the 95% CIs were not adjusted for multiple comparisons and	Randomization not stratified. Subgroups for efficacy analysis specified in the protocol (but not reported in the publication):	Randomized analysis set: All patients randomized into Part A. Full analysis set: All patients randomized into Part A and who received

	Power calculation assumptions	Outcome, test, and treatment effect estimate	Imputation of missing data	Control of type I error	Subgroup analyses	Analysis sets
	using a two-sided significance level of 0.05.	covariate. The treatment groups were compared using a Wilcoxon rank-sum test, which was pre-specified in case the proportional odds assumption was not met. Time to clinical improvement, time to recovery, and time to modified recovery: Estimated from a cause-specific proportional-hazards model that included treatment and baseline clinical status as covariates and treated death as the competing risk. All-cause mortality: Log-rank test (results not reported in publication). Treatment differences in proportion of patients: Mantel-Haenszel, stratified by baseline clinical status.	recorded as died; if a patient was discharged before day 14, the category was recorded as "not hospitalized;" otherwise, the most recent assessment was used for missing day 14 values. Time to event outcomes: Censoring rules were applied to the time to event outcomes.	should not be used inferentially.	• age • sex at birth • oxygen support status • country Subgroups for safety analysis specified in the protocol (but not reported in the publication): • age • sex at birth • country	at least one dose of remdesivir. Safety analysis set: All patients randomized into Part A and who had received at least one dose of remdesivir.

	Power calculation assumptions	Outcome, test, and treatment effect estimate	Imputation of missing data	Control of type I error	Subgroup analyses	Analysis sets
Spinner et al.[4] Part A	A total sample size of 600 patients (200 patients in each group) were required to achieve > 85 % power to detect an odds ratio of 1.8 using a two-sided significance level of 0.05. The sample size computation is based on an assumed distribution of the 7-point ordinal scale on day 11 for the SOC treatment group.	Primary analysis of clinical status at day 11: proportional odds model of patients in each treatment group compared with SOC, and treatment was the independent variable. The proportional odds assumption was assessed using a score test. If the proportional odds assumption was not met, a Wilcoxon rank sum test was performed. Secondary end point of TEAE: A Fisher exact test was used to compare each remdesivir treatment group to the standard of care group. Time to clinical improvement, time to recovery, time to modified recovery and time to room air: Estimated from a cause-specific proportional-hazards model that included treatment and baseline clinical status	Primary end point: If a patient died before day 28, the category on the ordinal scale was recorded as "died" from the date of death and subsequent days; if a patient was discharged before day 28, the category was recorded as "not hospitalized" from the date of discharge and subsequent days. The same category applied to a patient that was discharged alive and died on the same day or a later day. Otherwise, the most recent assessment was used for ordinal scale score values missing from day 2 to day 14 and day 28. Time to event outcomes: Patients who did	The Bonferroni method was applied to control the type I error rate for the statistical significance of the primary end point only. An alpha level of 0.025 was applied to for each comparison of 5-day remdesivir versus standard of care and 10-day remdesivir versus standard of care. There was no adjustment for multiple comparisons for the secondary and exploratory end points.	Randomization not stratified. Subgroups for the primary end point were specified in the statistical analysis plan (but not reported in the publication): • age (<65 and ≥65 years) • sex at birth • oxygen support status • race Subgroups for safety analysis specified in the statistical analysis plan (but not reported in the publication): • age (<65 and ≥65 years) • sex at birth • race Sensitivity analyses for primary end point: • adjusting for day 1 clinical score • adjusting for duration • of symptoms • using day 28 visit data to confirm day 11 clinical status and imputing patients with missing status as dead • using all randomized patients whether they	All randomized analysis set: All patients randomized into Part A. Full analysis set: All patients randomized into Part A and who received at least one dose of treatment if randomized to either remdesivir group (5-day or 10-day) and all patients in the standard of care group who completed a day 1 visit. Safety analysis set: All patients randomized into Part A and who had received at least one dose of treatment if randomized to either remdesivir group (5-day or 10-day) and all patients in the standard of care group who completed a day 1 visit.

	Power calculation assumptions	Outcome, test, and treatment effect estimate	Imputation of missing data	Control of type I error	Subgroup analyses	Analysis sets
		as covariates and treated death as the competing risk. All-cause mortality: Kaplan-Meier product limit method where each remdesivir group (5-day or 10-day) was compared with standard of care using a log-rank test and hazard ratios and 95% CIs were reported. Durations of oxygen therapy and hospitalization were compared between remdesivir treatment groups and the standard of care group using a Wilcoxon rank sum test.	not die were censored at the last study day.		• received treatment or not (intention-to-treat population).	
WHO Solidarity Consortium[6]	No sample size calculations done	Rate ratios for death (and P values are from log-rank analyses stratified according to six strata of age and ventilation status at entry. All rate ratios described proportional risk reductions.	Not reported	Not reported	Death stratified according to age and ventilation status. Other subgroups included age, ventilation status at entry, other entry characteristics, geographic region, or glucocorticoid use.	Not defined

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; mITT = modified intention-to-treat analysis; OR = odds ratio; RNA = ribonucleic acid.

Appendix 4: Patient Disposition of Published Trials

Table 13: Patient Disposition for Wang et al.

	Wang et al.[7]	
	RDV	PBO
Screened, N	255	
Randomized, N (%)	158 (62)	79 (31)
Discontinued from study, N (%)	0	1 (1.3)
Reason for discontinuation, N (%)		
Withdrawal of consent	0	1 (1.3)
ITT, N	158	78
PP, N	150	76
Safety, N	155	78

ACTT = Adaptive COVID-19 Treatment Trial; ITT = intention to treat; PBO = placebo; PP = per protocol; RDV = remdesivir.

[a] In the remdesivir group, three (1.9%) patients did not start the study and five (3.2%) patients received fewer than five days of treatment. In the placebo group, two (2.2%) patients received fewer than five days of treatment.

Table 14: Patient Disposition for ACTT-1

	ACTT-1[5]	
	RDV	PBO
Screened, N	1,114	
Randomized, N	541	521
Completed study through day 29, N (%)	517 (95.6)	508 (97.5)
Did not receive assigned treatment, N (%)	10 (1.8)	4 (0.8)
Discontinued from study before day 29, N (%)	14 (2.6)	9 (1.7)
Reason for discontinuation, N (%)		
Withdrawal of consent	6 (1.1)	5 (0.9)
Withdrawal by investigator	0	1 (0.2)
Withdrawal and transition to comfort care	3 (0.6)	2 (0.4)
Transfer to another hospital	1 (0.2)	1 (0.2)
Adverse event or severe adverse event other than death	4 (0.7)	0
ITT, N	541	521
As-treated, N	532	516

ACTT = Adaptive COVID-19 Treatment Trial; ITT = intention to treat; PBO = placebo; RDV = remdesivir.

Table 15: Patient Disposition for GS-US-540-5773

	GS-US-540-5773[2]	
	RDV 5 days	RDV 10 days
Screened, N	408	
Randomized, N	202	200
Did not receive assigned treatment, N (%)	2 (1.0)	3 (1.5)
Discontinued treatment, N (%)	28 (13.9)	111 (55.5)
Reason for discontinuation, N (%)		
Discharged	16 (7.9)	68 (34.0)
Withdrew	2 (1.0)	3 (1.5)
Withdrawal initiated by investigator	0	5 (2.5)
Protocol violation	1 (0.5)	1 (0.5)
Adverse event	9 (4.5)	22 (11.0)
Death	0	12 (6.0)
Completed treatment, N (%)	172 (85.1)	86 (43.0)
Full analysis set, N	200	197
Safety, N	200	197

RDV = remdesivir.

Table 16: Patient Disposition for GS-US-540-5774

	GS-US-540-5774[4]		
	RDV 5 days	RDV 10 days	SOC
Screened, N	612		
Randomized, N	199	197	200
Started treatment as randomized	191	193	200
Did not receive assigned treatment, N (%)	8 (4.0)	4 (2.0)	NA
Discontinued treatment, N (%)	46 (23.1)	120 (60.9)	NA
Reason for discontinuation, N (%)			
Discharged	35 (17.6)	98 (49.7)	NA
Withdrew consent	5 (2.5)	6 (3.0)	NA
Investigator decision	1 (0.5)	4 (2.0)	NA
Protocol violation	0	2 (1.0)	NA
Adverse event	4 (2.0)	8 (4.1)	NA
Lost to follow-up	1 (0.5)	0	NA
Nonadherence	0	1 (0.5)	NA
Death	0	1 (0.5)	NA
Completed treatment, N (%)	145 (72.9)	73 (37.1)	NA
Full analysis set, N	191	193	200
Safety, N	191	193	200

Table 17: Patient Disposition for WHO Solidarity

	WHO Solidarity[6]	
	RDV	SOC
Screened, N	NR	
Randomized[a], N	11,330	
Randomized to remdesivir and control group, N	5,475	
Assigned to group, N	2,750	2,725
No or unknown consent to follow-up, N (%)	7 (0.3)	17 (0.6)
Included in the ITT analysis, N	2,743	2,708
Died or left the hospital, N (%)	2,260 (82.4)	2,252 (83.2)
Entered trial before September; still an inpatient in late September, N (%)	88 (3.2)	72 (2.7)
Entered trial before September; not yet reported on in late September, N (%)	67 (2.4)	76 (2.8)
Entered trial in or after September; not reported on in late September, N (%)	328 (11.9)	308 (11.4)

NR = not reported; ITT = intention to treat; SOC = local standard of care; RDV = remdesivir

[a] The WHO Solidarity trial included four different treatment groups (remdesivir, hydroxychloroquine, lopinavir-ritonavir, and interferon beta-1a) and control groups. Only the patient disposition for remdesivir and the corresponding controls are reported beyond initial randomization.

Appendix 5: Baseline Characteristics

Table 18: Demographic and Clinical Characteristics at Baseline for Wang et al.

Characteristics	Wang et al. (ITT)[7]	
	RDV (n = 158)	PBO (n = 78)
Age, median years (IQR)	66.0 (57.0 to 73.0)	64.0 (53.0 to 70.0)
Men, n (%)	89 (56)	51 (65)
Any comorbidities, n (%)	112 (71)	55 (71)
Hypertension, n (%)	72 (46)	30 (38)
Diabetes, n (%)	40 (25)	16 (21)
Coronary heart disease, n (%)	15 (9)	2 (3)
Body temperature, Celsius, median (IQR)	36.8 (36.5 to 37.2)	36.8 (36.5 to 37.2)
Fever, n (%)	56 (35)	31 (40)
Respiratory rate > 24 breaths per minute, n (%)	36 (23)	11 (14)
Viral load of nasopharyngeal and oropharyngeal swabs, log_{10} copies per mL, mean (SE)	4.7 (0.3)	4.7 (0.4)
Six-category scale at day 1		
Category 2: Hospital admission, not requiring supplemental oxygen, n (%)	0	3 (4)
Category 3: Hospital admission, requiring supplemental oxygen, n (%)	129 (82)	65 (83)
Category 4: Hospital admission, requiring HFNC or NIV mechanical ventilation	28 (18)	9 (12)
Category 5: Hospital admission, requiring ECMO or invasive mechanical ventilation	0	1 (1)
Category 6: Death	1 (1)	0
Time from symptom onset to starting study treatment, median days (IQR)	11 (9 to 11)	10 (9 to 12)
Early (≤ 10 days from symptom onset), n/N (%)	71/155 (46)	47 (60)
Late (> 10 days from symptom onset), n/N (%)	84/155 (54)	31 (40)
On interferon alfa-2b, n (%)	29 (18)	15 (19)
On lopinavir-ritonavir, n (%)	27 (17)	15 (19)
On antibiotic treatment, n (%)	121 (77)	63 (81)
On corticosteroids, n (%)	60 (38)	31 (40)

ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; IQR = interquartile range; NIV = non-invasive; PBO = placebo; RDV = remdesivir; SE = standard error.

Table 19: Demographic and Clinical Characteristics at Baseline for ACTT-1

Characteristics	ACTT-1[5]	
	RDV (n = 541)	PBO (n = 521)
Age, mean years (SD)	58.6 (14.6)	59.2 (15.4)
Men, n (%)	352 (65.1)	332 (63.7)
Race or ethnic group, n (%)		
American Indian or Alaskan Native	4 (0.7)	3 (0.6)
Asian	79 (14.6)	56 (10.7)
Black or African-American	109 (20.1)	117 (22.5)
White	279 (51.6)	287 (55.1)
Hispanic or Latino	134 (24.8)	116 (22.3)
Time from symptom onset to randomization, median days (IQR)[a]	9 (6 to 12)	9 (7 to 13)
Comorbidities, n/N (%)[a]		
Hypertension	269/532 (50.6)	264/519 (50.9)
Type 2 diabetes	164/532 (30.8)	158/519 (30.4)
Obesity	242/531 (45.6)	234/518 (45.2)
Number of coexisting conditions, n/N (%)[a]		
None	97/531 (18.3)	97/517 (18.8)
One	138/531 (26.0)	137/517 (26.5)
Two or more	296/531 (55.7)	283/517 (54.7)
Disease severity, n (%)		
Mild or moderate disease	105 (9.9)	
Severe disease	957 (90.1)	
Score on ordinal scale, n (%)		
Category 4: Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19-related or otherwise)	75 (13.9)	63 (12.1)
Category 5: Hospitalized, requiring supplemental oxygen	232 (42.9)	203 (39.0)
Category 6: Hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices	95 (17.6)	98 (18.8)
Category 7: Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation	131 (24.2)	154 (29.6)
Baseline score missing	8 (1.5)	3 (0.6)

ACTT = Adaptive COVID-19 Treatment Trial; IQR = interquartile range; PBO = placebo; RDV = remdesivir; SD = standard deviation.

[a] Data on symptom onset were missing for 3 patients; data on coexisting conditions were missing for 11 patients and were incomplete for 3 patients.

Table 20: Demographic and Clinical Characteristics at Baseline for GS-US-540-5773

Characteristics	GS-US-540-5773[2]	
	RDV days (n = 200)	RDV days (n = 197)
Age, median years (IQR)	61 (50 to 69)	62 (50 to 71)
Men, n (%)	120 (60)	133 (68)
Race, n/N (%)		
White	142/200 (71)	134/192 (70)
Black	21 /200 (10)	23/192 (12)
Asian	20/200 (10)	25/192 (13)
Other	17/200 (8)	10/192 (5)
Body mass index, median (IQR)	29 (25 to 34)	29 (25 to 33)
Coexisting conditions, n (%)		
Hypertension	100 (50)	98 (50)
Diabetes	47 (24)	43 (22)
Hyperlipidemia	40 (20)	49 (25)
Asthma	27 (14)	22 (11)
Clinical Status on the 7-point ordinal scale, n (%)[a,b]		
2: receiving invasive mechanical ventilation or ECMO	4 (2)	9 (5)
3: receiving non-invasive ventilation or high-flow oxygen	49 (24)	60 (30)
4: receiving low-flow supplemental oxygen	113 (56)	107 (54)
5: not receiving supplemental oxygen but requiring medical care	34 (17)	21 (11)
Duration of hospitalization before first dose of RDV, median days (IQR)	2 (1 to 3)	2 (1 to 3)
Duration of symptoms before first dose of RDV, median days (IQR)	8 (5 to 11)	9 (6 to 12)
AST level, median U/ litre (IQR)	41 (29 to 58)	46 (34 to 67)
ALT level, median U/litre (IQR)	32 (22 to 50)	36 (23 to 58)
Creatinine clearance by Cockcroft-Gault, median mL/minute (IQR)	106 (80 to 142)	103 (80 to 140)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; RDV = remdesivir.

[a] P = 0.02 for the comparison between the five-day group and the 10-day group by the Wilcoxon rank-sum test.

[b] Clinical status scale is as follows: 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on non-invasive ventilation or high-flow oxygen devices; 4 = Hospitalized, requiring low-flow supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise).

Table 21: Demographic and Clinical Characteristics at Baseline for GS-US-540-5774

Characteristics	GS-US-540-5774[4]		
	RDV 5 days (n = 191)	RDV 10 days (n = 193)	SOC (n = 200)
Age, median years (IQR)	58 (48 to 66)	56 (45 to 66)	57 (45 to 66)
Men, n (%)	114 (60)	118 (61)	125 (63)
Race, n/N (%)			
White	109/186 (59)	107/188 (57)	112/193 (58)
Black	35/186 (19)	37/188 (20)	27/193 (14)
Asian	34/186 (18)	31/188 (16)	37/193 (19)
Other[a]	8/186 (4)	13/188 (7)	17/193 (9)

Characteristics	GS-US-540-5774[4]		
	RDV 5 days (n = 191)	RDV 10 days (n = 193)	SOC (n = 200)
Hispanic or Latino ethnicity[b], n/N (%)	25/187 (13)	42/186 (23)	34/186 (18)
Body mass index[c], median (IQR)	27 (24 to 30)	28 (25 to 32)	27 (24 to 31)
Coexisting conditions, n (%)			
Cardiovascular disease	111 (58)	111 (58)	107 (54)
Hypertension	82 (43)	85 (44)	81 (41)
Diabetes	71 (37)	85 (44)	76 (38)
Asthma	22 (12)	31 (16)	28 (14)
Day 1 clinical status on the 7-point ordinal scale, n (%)			
3: hospitalized, receiving non-invasive ventilation or high-flow oxygen	2 (1)	1 (1)	2 (1)
4: hospitalized, receiving low-flow supplemental oxygen	29 (15)	23 (12)	36 (18)
5: hospitalized, not requiring supplemental oxygen but requiring ongoing medical care	160 (84)	163 (84)	160 (80)
6: hospitalized, not requiring supplemental oxygen or ongoing medical care[d]	0	6 (3)	2 (1)
Duration of hospitalization before first dose of RDV, median days (IQR)	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)
Duration of symptoms before first dose of RDV, median days (IQR)	8 (5 to 11)	8 (5 to 11)	9 (6 to 11)
Concomitant medications[e], n (%)			
Steroids	33 (17)	29 (15)	38 (19)
Hydroxychloroquine or chloroquine	16 (8)	22 (11)	89 (45)
Lopinavir-ritonavir	10 (5)	11 (6)	43 (22)
Tocilizumab	1 (1)	1 (1)	10 (5)
Azithromycin	35 (18)	41 (21)	62 (31)
AST level, median U/litre (IQR)	32 (25 to 48)	34 (23 to 48)	34 (24 to 49)
ALT level, median U/litre (IQR)	30 (19 to 51)	28 (21 to 47)	30 (19 to 49)
Estimated GFR[f], median mL/minute (IQR)	99 (75 to 130)	110 (86 to 143)	103 (78 to 130)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GFR = glomerular filtration rate; IQR = interquartile range; RDV = remdesivir, SOC = standard of care.

[a] Includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Arab, unknown, and not specified.

[b] In patients with available ethnicity data.

[c] Calculated as weight in kilograms divided by height in metres squared.

[d] Some patients remained hospitalized for other reasons even if they did not require medical care.

[e] Includes medications taken between first and last dose of RDV or after day 1 for SOC group.

[f] Glomerular filtration rate estimated by the Cockcroft-Gault formula.

Table 22: Demographic and Clinical Characteristics at Baseline for WHO Solidarity

Characteristics	WHO Solidarity[6]	
	RDV (n = 2,743)	SOC (n = 2,708)
Age, n (%)		
< 50 years	961 (35.0)	952 (35.2)
50 to 69 years	1,282 (46.7)	1,287 (47.5)
≥ 70 years	500 (18.2)	469 (17.3)
Men, n (%)	1,706 62.2)	1,725 (63.7)
Geographic region, n (%)		
Europe and Canada[a]	715 (26.1)	698 (25.8)
Latin America[b]	470 (17.1)	514 (19.0)
Asia and Africa[c]	1,558 (56.8)	1,496 (55.2)
Current smoker, n (%)	178 (6.5)	161 (5.9)
Coexisting conditions, n (%)		
Diabetes	707 (25.8)	666 (24.6)
Heart disease	571 (20.8)	567 (20.9)
Chronic lung disease	151 (5.5)	145 (5.4)
Asthma	139 (5.1)	139 (5.1)
Chronic liver disease	36 (1.3)	41 (1.5)
Respiratory support, n (%)		
No supplemental oxygen at entry	661 (24.1)	664 (24.5)
Supplemental oxygen at entry	1,828 (66.6)	1,811 (66.9)
Already receiving ventilation	254 (9.3)	233 (8.6)
Lesions in both lungs, n (%)		
No	287 (10.5)	259 (9.6)
Yes	2,175 (79.3)	2,153 (79.5)
Not imaged at entry	281 (10.2)	296 (10.9)
Previous days in hospital, n (%)		
0	724 (26.4)	712 (26.3)
1	917 (33.4)	938 (34.6)
≥ 2	1,102 (40.2)	1,058 (39.1)

RDV = remdesivir; SOC= local standard of care

[a] Countries in Europe were Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, and Switzerland.

[b] Countries included Argentina, Brazil, Colombia, Honduras, and Peru.

[c] Countries included Egypt, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Pakistan, the Philippines, Saudi Arabia, and South Africa.

Appendix 6: Harms Data

Table 23: Harms Outcomes for Wang et al.

	Wang et al. (safety population)[7]	
	RDV N = 155	PBO N = 78
All adverse events, n (%)		
Any adverse events	102 (66)	50 (64)
Grade 3 or 4 adverse events	13 (8)	11 (14)
Most common adverse events[a]		
Hypoalbuminemia	20 (13)	12 (15)
Hypokalemia	18 (12)	11 (14)
Increased blood glucose	11 (7)	6 (8)
Anemia	18 (12)	12 (15)
Rash	11 (7)	2 (3)
Thrombocytopenia	16 (10)	5 (6)
Increased total bilirubin	15 (10)	7 (9)
Increased blood lipids	10 (6)	8 (10)
Increased white blood cells count	11 (7)	6 (8)
Hyperlipidemia	10 (6)	8 (10)
Increased blood urea nitrogen	10 (6)	5 (6)
Increased neutrophil	10 (6)	4 (5)
Increased aspartate aminotransferase	7 (5)	9 (12)
Constipation	21 (14)	12 (15)
Nausea	8 (5)	2 (3)
Diarrhea	5 (3)	2 (3)
Vomiting	4 (3)	2 (3)
Reduced serum sodium	4 (3)	2 (3)
Increased serum potassium	4 (3)	1 (1)
Serious adverse events, n (%)		
Any serious adverse event	28 (18)	20 (26)
Grade 3 or 4 serious adverse events	9 (6)	10 (13)
Most common serious adverse events		
Respiratory failure or ARDS	16 (10)	6 (8)
Cardiopulmonary failure	8 (5)	7 (9)
Pulmonary embolism	1 (1)	1 (1)
Recurrence of COVID-19	1 (1)	0
Cardiac arrest	1 (1)	0
Acute coronary syndrome	0	1 (1)
Tachycardia	0	1 (1)
Septic shock	1 (1)	1 (1)
Lung abscess	0	1 (1)
Sepsis	0	1 (1)

	Wang et al. (safety population)[7]	
	RDV N = 155	PBO N = 78
Bronchitis	0	1 (1)
Thrombocytopenia	1 (1)	0
Increased D dimer	0	1 (1)
Lower GI hemorrhage	1 (1)	0
Ileus	0	1 (1)
Deep vein thrombosis	1 (1)	1 (1)
Acute kidney injury	1 (1)	0
Diabetic ketoacidosis	0	1 (1)
Multiple organ dysfunction syndrome	1 (1)	2 (3)
Events leading to drug discontinuation, n (%)		
Any event leading to drug discontinuation	18 (12)	4 (5)
Grade 3 or 4 events leading to drug discontinuation	3 (2)	1 (1)
Most common events leading to drug discontinuation		
Respiratory failure or ARDS	7 (5)	1 (1)
Secondary infection	4 (3)	7 (9)
Cardiopulmonary failure	3 (2)	1 (1)
Nausea	1 (1)	0
Vomiting	1 (1)	0
Ileus	0	1 (1)
Increased alanine aminotransferase	2 (1)	0
Rash	2 (1)	0
Poor appetite	1 (1)	0
Increased total bilirubin	1 (1)	0
Acute kidney injury	1 (1)	0
Seizure	0	1 (1)
Aggravated schizophrenia	0	1 (1)
Aggravated depression	0	1 (1)

ARDS = acute respiratory distress syndrome; GI = gastrointestinal; PBO = placebo; RDV = remdesivir.

[a] Frequency of any grade of adverse event greater than 2% of patients in any treatment group; some patients may have had more than one event.

Table 24: Harms Outcomes for ACTT-1

MedDRA organ system class		ACTT-1 (as-treated population)[5]	
		RDV n = 532	PBO n = 516
Adverse events, n[a] (%)			
Any system organ class	Any preferred term	276 (51.9)	295 (57.2)
Non-serious adverse events occurring in ≥ 5 patients			
Blood and lymphatic system disorders	Anemia	42 (7.9)	52 (10.1)
	Lymphopenia	13 (2.4)	30 (5.8)
Cardiac disorders	Atrial fibrillation	5 (0.9)	10 (1.9)
	Arrythmia	4 (0.8)	1 (0.2)
	Supraventricular tachycardia	3 (0.6)	2 (0.4)
General disorders and administration site conditions	Pyrexia	38 (7.1)	32 (6.2)
Hepatobiliary disorders	Hyperbilirubinemia	2 (0.4)	3 (0.6)
Infections and infestations	Pneumonia	12 (2.3)	6 (1.2)
	Bacteremia	0	10 (1.9)
	Sepsis	4 (0.8)	4 (0.8)
	Pneumonia, bacterial	4 (0.8)	3 (0.6)
	Pneumonia, staphylococcal	3 (0.6)	4 (0.8)
	Septic shock	3 (0.6)	3 (0.6)
Investigations	Hemoglobin decreased	48 (9.0)	62 (12.0)
	Glomerular filtration rate decreased	55 (10.3)	74 (14.3)
	Aspartate aminotransferase increased	18 (3.4)	33 (6.4)
	Lymphocyte count decreased	44 (8.3)	54 (10.5)
	Blood glucose increased	39 (7.3)	27 (5.2)
	Alanine aminotransferase increased	12 (2.3)	24 (4.7)
	Blood bilirubin increased	9 (1.7)	16 (3.1)
	Blood creatinine increased	31 (5.8))	36 (7.0)
	Prothrombin time prolonged	26 (4.9))	8 (1.6)
	Blood albumin decreased	7 (1.3)	4 (0.8)
	Transaminases increased	7 (1.3)	11 (2.1)
	Creatinine renal clearance decreased	4 (0.8)	6 (1.2)
	Platelet count decreased	6 (1.1)	2 (0.4)
	Electrocardiogram QT prolonged	2 (0.4)	5 (1.0)
	Liver function test increased	3 (0.6)	3 (0.6)
	Troponin increased	1 (0.2)	5 (1.0)
	Blood creatine phosphokinase increased	2 (0.4)	3 (0.6)
Metabolism and nutrition disorders	Hyperglycemia	34 (6.4)	34 (6.6)
	Acidosis	8 (1.5)	5 (1.0)
	Hypoalbuminemia	6 (1.1)	7 (1.4)
	Hypernatremia	4 (0.8)	4 (0.8)
	Alkalosis	3 (0.6)	3 (0.6)

MedDRA organ system class		ACTT-1 (as-treated population)[5]	
		RDV n = 532	PBO n = 516
	Hypocalcemia	3 (0.6)	2 (0.4)
Musculoskeletal and connective tissue disorders	Muscular weakness	3 (0.6)	2 (0.4)
Psychiatric disorders	Delirium	10 (1.9)	8 (1.6)
	Mental status change	2 (0.4)	4 (0.8)
Renal and urinary disorders	Acute kidney injury	21 (3.9)	21 (4.1)
Respiratory, thoracic, and mediastinal disorders	Respiratory distress	12 (2.3)	16 (3.1)
	Hypoxia	10 (1.9)	13 (2.5)
	Dyspnea	9 (1.7)	6 (1.2)
Vascular disorders	Hypertension	23 (4.3)	20 (3.9)
	Hypotension	14 (2.6)	11 (2.1)
	Deep vein thrombosis	8 (1.5)	14 (2.7)
	Thrombosis	3 (0.6)	4 (0.8)
Serious adverse events, n (%)			
Any system organ class	Any preferred term	131 (24.6)	163 (31.6)
Serious adverse events occurring in ≥ 5 patients			
Cardiac disorders	Cardiac arrest	10 (1.9)	7 (1.4)
	Atrial fibrillation	5 (0.9)	1 (0.2)
General disorders and administration site conditions	Multiple organ dysfunction syndrome	5 (0.9)	3 (0.6)
Infections and infestations	Septic shock	8 (1.5)	15 (2.9)
	COVID-19	2 (0.4)	5 (1.0)
Investigations	Glomerular filtration rate decreased	5 (0.9)	2 (0.4)
Renal and urinary disorders	Acute kidney injury	7 (1.3)	12 (2.3)
	Renal failure	2 (0.4)	5 (1.0)
Respiratory, thoracic, and mediastinal disorders	Respiratory failure	39 (7.3)	66 (12.8)
	Acute respiratory failure	8 (1.5)	14 (2.7)
	Respiratory distress	6 (1.1)	11 (2.1)
	Acute respiratory distress syndrome	7 (1.3)	5 (1.0)
	Pneumothorax	5 (0.9)	5 (1.0)
	Pulmonary embolism	5 (0.9)	4 (0.8)
	Hypoxia	4 (0.8)	4 (0.8)
	Pneumonia aspiration	4 (0.8)	2 (0.4)
Vascular disorders	Hypotension	4 (0.8)	7 (1.4)
	Shock	5 (0.9)	4 (0.8)

ACTT = Adaptive COVID-19 Treatment Trial; PBO = placebo; RDV = remdesivir.

[a] Number of patients reporting at least one event.

Table 25: Harms Outcomes for GS-US-540-5773

	GS-US-540-5773[2]	
	RDV 5 days N = 200	RDV 10 days N = 197
All adverse events, n (%)		
Any adverse events	141 (70)	145 (74)
Grade 3 or higher	60 (30)	85 (43)
Most common adverse events[a]		
Nausea	20 (10)	17 (9)
Acute respiratory failure	12 (6)	21 (11)
ALT increased	11 (6)	15 (8)
Constipation	13 (6)	13 (7)
AST increased	10 (5)	13 (7)
Hypokalemia	10 (5)	12 (6)
Hypotension	9 (4)	12 (6)
Respiratory failure	7 (4)	14 (7)
Insomnia	10 (5)	11 (6)
Acute kidney injury	4 (2)	15 (8)
Serious adverse events, n (%)[b]		
Any serious adverse event	42 (21)	68 (35)
Most common serious adverse events		
Acute respiratory failure	10 (5)	18 (9)
Respiratory failure	5 (2)	10 (5)
Septic shock	2 (1)	5 (3)
Acute respiratory distress syndrome	1 (<1)	5 (3)
Hypoxia	2 (1)	4 (2)
Respiratory distress	3 (2)	4 (2)
Dyspnea	4 (2)	1 (1)
Pneumothorax	2 (1)	3 (2)
Viral pneumonia	3 (2)	2 (1)
Aminotransferase levels increased	3 (2)	2 (1)
Any grade ≥ 3 laboratory abnormality	53/195 (27)	64/191 (34)
Selected grade ≥ 3 laboratory abnormality		
Creatinine clearance decreased		
Grade 3	13/193 (7)	13/188 (7)
Grade 4	5/193 (3)	23/198 (12)
ALT elevation		
Grade 3	8/194 (4)	11/191 (3)
Grade 4	4/194 (2)	5/191 (3)
AST elevation		
Grade 3	11/194 (6)	7/190 (4)
Grade 4	3/194 (2)	4/190 (2)
Bilirubin increased		

	GS-US-540-5773[2]	
	RDV 5 days N = 200	RDV 10 days N = 197
Grade 3	1/193 (1)	3/190 (2)
Grade 4	0	1/190 (1)
Events leading to drug discontinuation, n (%)		
Any event leading to drug discontinuation	9 (4)	20 (10)
Most common events leading to drug discontinuation	NR	NR

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported; RDV = remdesivir.

[a] Adverse events occurring in at least 5% of patients in either treatment group.

[b] Serious adverse events listed occurring in five or more patients.

Table 26: Harms Outcomes for GS-US-540-5774 — Part A

	GS-US-540-5774[4]		
	RDV 5 days N = 191	RDV 10 days N = 193	SOC N = 200
All adverse events, n (%)			
Any adverse events	98 (51)	113 (59)	93 (47)
Difference vs. SOC, % (95% CI)	4.8 (–5.2 to 14.7), P = 0.36	12.0 (1.6 to 21.8), P = 0.02	Reference
Grade 3 or 4 adverse events	20 (10)	24 (12)	24 (12)
Adverse events occurring in > 5% of patients in any treatment group			
Nausea	19 (10)	18 (9)	6 (3)
Diarrhea	12 (6)	10 (5)	14 (7)
Hypokalemia	10 (5)	13 (7)	4 (2)
Headache	10 (5)	10 (5)	5 (3)
Laboratory abnormalities, n/N (%)			
Any	131/180 (73)	128/179 (72)	136/186 (73)
Grade 3	18/180 (10)	25/179 (14)	25/186 (13)
Grade 4	5/180 (3)	4/179 (2)	9/186 (5)
ALT increase, n/N (%)			
Any	61/179 (34)	57/177 (32)	71/182 (39)
Grade 3[a]	4/179 (2)	6/177 (3)	11/182 (6)
Grade 4[b]	0	0	3 (2)
AST increase, n/N (%)			
Any	56/177 (32)	56/175 (32)	60/182 (33)
Grade 3[a]	3/177 (2)	2/175 (1)	6/182 (3)
Grade 4[b]	1/177 (1)	0	5/182 (3)
Total bilirubin increase, n (%)			
Grade 3	1/177 (< 1)	3/176 (2)	1/181 (< 1)
Grade 4	0	1/176 (< 1)	1/181 (< 1)
CrCl decrease, n/N (%)			
Any	26/178 (15)	45/176 (26)	55/183 (30)
Grade 3[c]	4/178 (2)	7/176 (4)	9/183 (5)

	GS-US-540-5774[4]		
	RDV 5 days N = 191	RDV 10 days N = 193	SOC N = 200
Grade 4[d]	0	2/176 (1)	5/183 (3)
Serious adverse events, n (%)			
Any serious adverse event	9 (5)	10 (5)	18 (9)
Difference vs. SOC, % (95% CI)	–4.3 (–9.7 to 0.9), P = 0.11	–3.8 (–9.3 to 1.4), P = 0.17	Reference
Adverse events leading to drug discontinuation, n (%)			
Any adverse event leading to drug discontinuation	4 (2)	8 (4)	NA

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CrCl = creatinine clearance; NA = not applicable; NR = not reported; RDV = remdesivir, SOC = standard of care.

[a] > 5 to 10 times upper limits of normal.

[b] > 10 times upper limits of normal.

[c] 30 to < 60 mL/min or 30% to < 50% decrease from baseline.

[d] < 30 mL/min, ≥50% decrease from baseline, or dialysis needed.

Appendix 7: Modifications to Trial Design

Table 27: Modifications to Trial Design After Initial Registration

	Original	Modification
Wang et al.		
Dates	February 3, 2020	April 13, 2020
Sample size, number of patients	452 anticipated	237 actual (terminated; no eligible patients can be enrolled)
Primary end point	TTCI (censored at day 28) TTCI is defined as the time (in days) from initiation of study treatment (active or placebo) until a decline of two categories from admission status on a six-category ordinal scale of clinical status which ranges from 1 (discharged) to 6 (death). Six-category ordinal scale: 6. Death 5. ICU, requiring ECMO and/or IMV 4. ICU/hospitalization, requiring NIV/ HFNC therapy 3. Hospitalization, requiring supplemental oxygen (but not NIV/ HFNC) 2. Hospitalization, not requiring supplemental oxygen 1. Hospital discharge	TTCI (censored at day 28) The primary end point is time to clinical improvement (censored at day 28), defined as the time (in days) from randomization of study treatment (remdesivir or placebo) until a decline of two categories on a six-category ordinal scale of clinical status (1 = discharged; 6 = death) **or live discharge from hospital.** Six-category ordinal scale: 6. Death 5. ICU, requiring ECMO and/or IMV 4. ICU/hospitalization, requiring NIV/ HFNC therapy 3. Hospitalization, requiring supplemental oxygen (but not NIV/ HFNC) 2. Hospitalization, not requiring supplemental oxygen 1. Hospital discharge **or meet discharge criteria (discharge criteria are defined as clinical recovery; i.e., fever, respiratory rate, oxygen saturation return to normal, and cough relief)**
ACTT		
Dates	February 20, 2020	April 16, 2020
Study phase	Phase II	Phase III
Number of sites	Approximately 50	Approximately 100
Estimated enrolment	394	800
Treatment arms	Experimental: Remdesivir 200 mg of Remdesivir administered intravenously on day 1, followed by a 100 mg once-daily maintenance dose of remdesivir for the **duration of the hospitalization** up to a 10 days total course. Placebo 200 mg of remdesivir placebo administered intravenously on day 1, followed by a 100 mg once-daily maintenance dose of remdesivir placebo for **the duration of the hospitalization** up to a 10 days total course.	Experimental: Remdesivir 200 mg of remdesivir administered intravenously on day 1, followed by a 100 mg once-daily maintenance dose of remdesivir **while hospitalized** for up to a 10 days total course. Placebo 200 mg of remdesivir placebo administered intravenously on day 1, followed by a 100 mg once-daily maintenance dose of remdesivir placebo **while hospitalized** for up to a 10 days total course.
Placebo comparator	The supplied matching placebo lyophilized formulation is identical in physical appearance to	The supplied placebo lyophilized formulation is identical in physical appearance to the active lyophilized formulation and contains the same

	Original	Modification
	the active lyophilized formulation and contains the same inactive ingredients.	inactive ingredients. **Alternatively, a placebo of normal saline of equal volume may be given if there are limitations on matching placebo supplies.**
Primary end point	Percentage of subjects reporting each severity rating on **the seven-point ordinal scale** (day 15) The scale is as follows: 1) Death 2) Hospitalized, on invasive mechanical ventilation or ECMO 3) Hospitalized, on non-invasive ventilation or high-flow oxygen devices 4) Hospitalized, requiring supplemental oxygen 5) Hospitalized, not requiring supplemental oxygen 6) Not hospitalized, limitation on activities 7) Not hospitalized, no limitations on activities	Time to recovery (day 1 through day 29) Day of recovery is defined as the first day on which the subject satisfies one of the following **three categories from the ordinal scale:** 1) Hospitalized, not requiring supplemental oxygen; no longer requires ongoing medical care 2) Not hospitalized, limitation on activities and/or requiring home oxygen 3) Not hospitalized, no limitations on activities

Inclusion and exclusion criteria modifications	Key inclusion criteria:
	• Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 72 hours before randomization.
	• Illness of any duration, and at least one of the following:
	  ○ radiographic infiltrates by imaging (chest X-ray, CT scan)
	  ○ clinical assessment (evidence of rales/crackles on exam) AND SpO2 < / = 94% on room air
	  ○ requiring mechanical ventilation and/or supplemental oxygen.
		Key inclusion criteria:
		• Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either or the following:
		  ○ PCR positive in sample collected < 72 hours before randomization; OR
		  ○ PCR positive in sample collected >/= 72 hours before randomization, documented inability to obtain a repeat sample (e.g., due to lack of testing supplies, limited testing capacity, results taking > 24 hours) AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
		• Agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through day 29.
		• Illness of any duration, and at least one of the following:
		  ○ radiographic infiltrates by imaging (chest X-ray, CT scan), OR
		  ○ SpO2 < / = 94% on room air, OR
		  ○ requiring supplemental oxygen, OR
		  ○ requiring mechanical ventilation.

Adverse events	Cumulative incidence of SAEs (day 1 to 29) An SAE is defined as an AE or suspected adverse reaction and is considered serious if, in the view of either the investigator or the sponsor, it results in death, a life-threatening AE, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect.	Cumulative incidence of grade 3 and 4 clinical and/or laboratory AEs (day 1 to 29) Grade 3 AEs are defined as events that interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating. Grade 4 AEs are defined as events that are potentially life threatening.

	Original	Modification
	Cumulative incidence of severe AEs (day 1 to 29) Severe AEs include grade 3 and 4 AEs. Grade 3 AEs are defined as events that interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating. Grade 4 AEs are defined as events that are potentially life threatening.	Cumulative incidence of SAEs (day 1 to 29) An SAE is defined as an AE or suspected adverse reaction and is considered serious if, in the view of either the investigator or the sponsor, it results in death, a life-threatening AE, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect.
Other secondary end points	There were 22 secondary efficacy outcome measures initially specified for the trial, a number of which were modified after initial trial registration. The May 6, 2020, modification specifies 26 secondary efficacy outcomes.	
GS-US-540-5773		
Dates	February 28, 2020	April 20, 2020
Estimated enrolment	400	6,000
Treatment arms	Experimental: Remdesivir, 10 days Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10. Experimental: Remdesivir, 10 days Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10.	Experimental: Part A: Remdesivir, 5 days (Not mechanically ventilated) Participants who are not mechanically ventilated will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, and 5. Experimental: Part A: Remdesivir, 10 days (not mechanically ventilated) Participants who are not mechanically ventilated will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10. Experimental: Part B: Remdesivir, 5 or 10 days (extension) Part B (extension) will enroll participants after enrolment to Part A is complete. Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2 to 10. Experimental: Part B: Remdesivir 10 days (mechanically ventilated) Participants on mechanical ventilation will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2 to 10
Definition of standard of care	Standard of care therapy **per local written policies or guidelines**	Standard of care treatment for COVID-19 infection
Inclusion and exclusion criteria modified	**Minimum age: 18** Key inclusion criteria: • Currently hospitalized with fever defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, or ≥ 37.8 °C rectal	**Minimum age: 12** Key inclusion criteria: • Currently hospitalized • SpO2 ≤ 94% or requiring supplemental oxygen at screening

	Original	Modification
	• Peripheral capillary oxygen saturation (SpO2) ≤ 94% on room air at screening Key exclusion criteria: • Requiring mechanical ventilation at screening	Key exclusion criteria: • Mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO.
Primary end point	Proportion of participants with normalization of fever and oxygen saturation through day 14 This is a composite outcome measure. Criteria for fever normalization: Temperature < 36.6 °C armpit, < 37.2 °C oral, or < 37.8 °C rectal sustained for at least 24 hours. Criteria for oxygen normalization: Sp02 > 94% sustained for at least 24 hours.	The odds of ratio for improvement on a seven-point ordinal scale on day 14. The scale is as follows: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on non-invasive ventilation or high-flow oxygen devices 4. Hospitalized, requiring low-flow supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise) 6. Hospitalized, not requiring supplemental oxygen; no longer required ongoing medical care (other than per-protocol remdesivir administration) 7. Not hospitalized
Adverse effects	Proportion of participants with treatment-emergent adverse events leading to study drug discontinuation (from first dose date up to 10 days)	Proportion of participants experiencing treatment-emergent adverse events (from first dose date up to 10 days plus 30 days)
GS-US-540-5774		
Dates	February 28, 2020	April 6, 2020
Estimated enrolment	600	1,600
Treatment arms	Experimental: Remdesivir, 5 days Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, and 5. Experimental: Remdesivir, 10 days Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10. Active Comparator: Continued standard of care therapy participants will receive continued standard of care therapy.	Experimental: Part A: Remdesivir, 5 days Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, and 5. Experimental: Part A: Remdesivir, 10 days Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10. Active Comparator: Part A: Continued standard of care therapy. Participants will receive continued standard of care therapy. Experimental: Part B: Extension treatment, Remdesivir 5 or 10 days Participants will receive continued standard of care therapy together with remdesivir 200 mg on day 1 followed by remdesivir 100 mg on days 2, 3, 4, 5, 6, 7, 8, 9, and 10.

	Original	Modification
Definition of standard of care	Standard of care therapy **per local written policies or guidelines**	Standard of care treatment for COVID-19 infection
Inclusion and exclusion criteria modified	**Minimum age: 18** Key inclusion criteria: Currently hospitalized with fever defined as temperature ≥ 36.6 °C armpit, ≥ 37.2 °C oral, or ≥ 37.8 °C rectal	**Minimum age: 12** Key inclusion criteria: Currently hospitalized and requiring medical care for COVID-19
Primary end point	Proportion of participants discharged by day 14	The odds of ratio for improvement on a seven-point ordinal scale on day 11 The scale is as follows: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on non-invasive ventilation or high-flow oxygen devices 4. Hospitalized, requiring low-flow supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19 related or otherwise) 6. Hospitalized, not requiring supplemental oxygen; no longer required ongoing medical care (other than per-protocol remdesivir administration) 7. Not hospitalized

ACTT = Adaptive COVID-19 Treatment Trial; AEs = adverse events; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; ICU = intensive care unit; IMV = intermittent mandatory ventilation; NIV = non-invasive ventilation; PCR = polymerase chain reaction; SAEs = serious adverse events; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SpO2 = peripheral capillary oxygen saturation; TTCI = time to clinical improvement; V-A ECMO - veno-arterial extracorporeal membrane oxygenation; V-V ECMO = veno-venous extracorporeal membrane oxygenation.

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