EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

Rapid Collaborative Review

REMDESIVIR FOR THE TREATMENT OF COVID-19
PICO AND EVIDENCE GAPS

Project ID: PTRCR15

Version 1.0, 29 September 2020
Template version 1.0, September 2020

This Joint Assessment is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V0.1	**10/09/2020**	First draft
V0.2	**25/09/2020**	Input from the PICO survey and Dedicated Reviewers has been processed
V1.0	**29/09/2020**	Final Rapid Collaborative Review

Disclaimer

The content of this Rapid Collaborative Review Report represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Assessment team

Author(s)	National Authority of Medicines and Health Products (INFARMED), Portugal
Co-Author(s)	National Centre for Pharmacoeconomics (NCPE), Ireland
Dedicated Reviewer(s)	Austrian Institute for Health Technology Assessment (AIHTA), Austria Regione Emilia-Romagna (RER), Italy HTA Department SEC Ministry of Health Ukraine, Ukraine

For further information on the work distribution and further contributors, please see section 8.1.

Conflict of interest

All authors, co-authors, dedicated reviewers, observers, external experts (health care professionals, patients or patient representatives) involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

Copyright

How to cite this assessment

Please cite this Rapid Collaborative Report as follows:

EUnetHTA PTRCR15. Authoring Team. Rapid Collaborative Review: Evidence Gaps & Recommendations for Future Research. Remdesivir for treatment of adults (aged > 18 years) and adolescents (aged 12 years and older with body weight at least 40 kg) hospitalized with confirmed COVID-19 pneumonia. Rapid Collaborative Review. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 35 pages. Report No.: PTRCR15. Available from: https //www.eunethta.eu

Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
CDSR	Cochrane Database of Systematic Reviews
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorization
CSR	Clinical Study Reports
DOI	Declaration of Interest
DR	Dedicated Reviewers
COVID-19	Coronavirus Disease 2019
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal Membrane Oxygenation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EEA	European Economic Area
EUnetHTA	European Network of Health Technology Assessment
EuroMOMO	European Mortality Monitoring
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
PICO	Population, intervention, control, outcome
MAH	Marketing Authorisation Holder
MEDLINE	Medical Literature Analysis and Retrieval System Online
MERS-CoV	Middle East respiratory syndrome coronavirus
MEURI	Monitored Emergency Use of Unregistered Interventions Framework
NEWS	National Early Warning Score
PTJA	Pharmaceutical Joint Assessment
RCT	Randomised Control Trials
REA	Relative Effectiveness Assessment
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SLR	Systematic Literature Review
UK	United Kingdom
WHO	World Health Organization
WP4	Work Package 4

1 INTRODUCTION

In June 2020, EUnetHTA prioritized its activities around COVID-19 to respond to the public health emergency.

The MAH was invited to submit evidence for the assessment of remdesivir for the treatment of adults (aged > 18 years) and adolescents (aged 12 years and older with body weight at least 40 kg) hospitalized with confirmed COVID-19 pneumonia. The MAH informed EunetHTA that it would not be providing an evidence submission for this assessment.

Due the lack of data transparency required to conduct a Joint Relativeness Assessment, EUnetHTA proceeded with the development of a collaborative review. The report outlines the EUnetHTA PICO definition, a rapid search for published literature and a summary of the available evidence and a summary of key evidence gaps and requirements. It is envisaged that the PICO definition and the overview of the evidence and reviews can be used by national agencies to in their own national assessments. .

The target patient population and relevant comparators (based on the requirements of EUnetHTA Partners) are defined in the project scope below.

1.1 Background

A novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first identified in December of 2019 in Wuhan, China as causing a respiratory illness designated as Coronavirus disease 2019, or COVID-19 (1,2). On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern. Since then, there has been rapid spread of the virus, leading to a global pandemic of COVID-19 (1).

According to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes. Human-to-human transmission is occurring extensively. Hence, precautions to prevent human-to-human transmission are appropriate for both suspected and confirmed cases (1). Individuals of all ages are at risk for infection and severe disease. Although most coronavirus infections cause only mild respiratory symptoms, infection with SARS-CoV, MERS-CoV (Middle East respiratory syndrome coronavirus), and SARS-CoV-2 can be lethal (1).

Through September 18, 2020, there have been more than 30 million confirmed cases of COVID-19 worldwide and more than 940,000 deaths, reported to WHO. In Europe, at the same date (September 18, 2020) there have been more than 5 million confirmed cases of COVID-19 and more than 200,000 deaths (1).

According to COVID-19 surveillance report, week 37, 2020, from European Centre for Disease Prevention and Control (ECDC), 22% (country range: 3-60%) of reported COVID-19 cases in the EU/EEA and the UK to date have been hospitalised (reported by 22 countries). Data from 17 countries show that 9% (country range: 0-62%) of hospitalised patients required ICU and/or respiratory support although these proportions vary considerably by age and sex and may be influenced by national policies and practices (3).

In the same report, ECDC estimate that 14-day COVID-19 death notification rate for the EU/EEA and the UK was five (country range: 0–31) per million population. As stated by the European mortality monitoring activity collaborative network (EuroMOMO) pooled estimates of all-cause mortality have reached normal levels, following a period of a substantial excess mortality. In some countries, however, there seems to be a recent small excess mortality (3).

1.2 The technology

Remdesivir is a novel antiviral drug which received conditional marketing authorisation (CMA) in the EU on 03/07/20, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. Remdesivir is a nucleotide prodrug that is intracellularly metabolized to form a pharmacologically active nucleoside triphosphate metabolite that inhibits viral RNA polymerases (4). Remdesivir has broad-spectrum activity against coronaviruses (including SARS-CoV-2, SARS-CoV, and MERS-CoV, Ebola virus and other viruses (4–6). The currently available data on antiviral effects of remdesivir are limited. Remdesivir has shown effective inhibition of SARS-CoV-2 in vitro in human airways epithelial cells and other cell lines, and in preclinical in vivo in non-human primate studies (7,8). Efficacy was previously shown in MERS and SARS-CoV-1 animal models (5,6). Remdesivir was investigated for the treatment of Ebola virus but was shown to be less effective than alternative agents (9).

The recommended dosage of remdesivir is a single loading dose of remdesivir 200 mg given by intravenous infusion on Day 1, followed by 100mg given once daily be intravenous infusion from Day 2 onwards (10,11). The total duration of treatment should be at least 5 days and not more than 10 days. Remdesivir should not be used in patients with eGFR <30 mL/min, or initiated in patients with Alanine Aminotransferase (ALT) ≥5 times the upper limit of normal at baseline. Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended. An extensive clinical safety database exists from its investigational use in trials for the Ebola virus (9,12,13). The most common adverse reaction in healthy volunteers is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%) (10,11).

CMA was granted in the EU in the absence of comprehensive data, in the context of the public health emergency and the urgent need for effective treatments for COVID-19 (11). Clinical study reports were not provided for the EMA assessment. Both the Cochrane Collaboration and the European Ombudsman highlighted the need for data transparency in COVID-19 clinical trials (14,15). Only top line results were available from the pivotal trial and the evaluation of all-cause mortality was hampered by incomplete follow-up of patients. An integrated summary of safety data was not presented and the understanding of patient factors that may impact tolerability of remdesivir is incomplete. The optimal duration of therapy is also unclear. A review of the clinical evidence supporting the CMA is provided in Section 4.1. In order to confirm the efficacy and safety of remdesivir, and address quality issues, the EMA requires the provision of additional quality, efficacy and safety data by August 2020, and final study reports by December 2020 (10,11). Specific obligations that need to be fulfilled are outlined in European Public Assessment Report (10,11).

1.3 Current clinical management

Evidence for the optimal management of COVID-19 is evolving. Standard-of-care for COVID-19 is currently guided by disease-severity and reflects a dynamic approach to disease management, informed by growing clinical experience and evidence emerging from clinical trials. While disease severity in most people with COVID-19 is mild (40%) or moderate (40%), severe disease requiring oxygen support develops in approximately 15% and critical disease can develop in 5% of patients giving rise to complications, notably including acute respiratory distress syndrome (ARDS) that requires mechanical ventilation (16). Other complications include neurological manifestations, sepsis and septic shock, thromboembolism, multi-organ failure, including acute kidney injury and cardiovascular injury. A number of risk-factors have been associated with severe disease and COVID-19 related death including being male, older age, deprivation, diabetes, smoking, obesity, chronic heart disease, chronic lung disease and cancer (17).

For severe disease, standard-of-care is based on supportive measures including supplemental oxygen, thromboprophylaxis and management of comorbidities and nosocomial complications, including empiric antimicrobial therapy if indicated (16). The management of patients with critical illness is broadly in line with other life-threatening conditions, including consideration of ventilatory support, haemodynamic support, renal replacement therapy and other interventions aimed at the prevention and management of complications (18). The anti-inflammatory and immunosuppressive corticosteroid dexamethasone has been adopted by clinical guidelines as part of standard-of-care in severe and critical COVID-19 patient populations (19–21) . WHO living guidance on corticosteroids for COVID-19 makes a strong recommendation for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19, and a conditional recommendation not to use corticosteroid therapy in patients with non-severe COVID-19 (18). This recommendation was based on a review of meta-analyses of efficacy and safety of systemic corticosteroids in COVID-19 and relevant patient populations, which suggested that systemic corticosteroids probably reduce 28-day mortality in patients with critical COVID-19 and also in those with severe disease. In contrast, systemic corticosteroids were found to potentially increase the risk of death when administered to patients with non-severe COVID-19 (22).

A number of investigational agents for COVID-19 are in clinical trials, some of which are approved for other indications facilitating their use outside of clinical trials also e.g. tocilizumab, interferon beta-1a, baricitinib, convalescent plasma and others. EUnetHTA Rolling Collaborative Reviews present the comparative data on effectiveness and safety of potential therapies for COVID-19, including dexamethasone, and are updated on a monthly basis (23).

Currently, no other antiviral therapies are approved specifically for COVID-19. Emerging randomised control trials (RCTs) and observational cohort studies on the efficacy of antiviral treatments for COVID-19 have provided inconsistent results. However, many of these studies have been of very low quality; limited by small sample sizes, unclear methods, lack of a control arm or lack of blinding or randomisation where control arms are present, unadjusted analyses, and sub-optimal reporting. High-quality, methodologically robust transparent clinical trials, in large numbers of patients are essential to provide credible evidence on the efficacy and safety of investigational antiviral agents for COVID-19. Emerging evidence from large, well-conducted randomised control trials and observational cohort studies is increasingly showing a lack of benefit from investigational antivirals for COVID-19, including hydroxychloroquine (with/without azithromycin) and lopinavir/ritonavir (24–29). International guidelines for the management of COVID-19 generally recommend against the use of these agents, with some exceptions in the clinical trial setting. Remdesivir has been recommended for use, within its licence, in many international guidelines, though some recommendations have been described as weak/moderate/conditional due to uncertainty of the evidence (21,30,31). Prioritisation of use in patients with severe COVID-19 on supplemental oxygen but not on high-flow oxygen or more intense forms of ventilation, and limitation of treatment duration to 5 days have also been included in some recommendations (21).

2 RESEARCH QUESTION AND SCOPE

The first aim of this report is to define a PICO considered relevant by the EUnetHTA partners. To this end, a PICO survey was set up and shared among all EUnetHTA partners from July 28st 2020 – August 31st 2020. Based on the input received, the PICO in this Report was finalized. The target patient populations and relevant comparators (based on the requirements of the EUnetHTA partners) are defined in the project scope below.

The following table provides the scope identified for the assessment of remdesivir.

Table 2.1. Assessment scope: relevant PICO(s) identified for the planned assessment.

Description	Assessment scope		
PICO			
Population	Adults (aged > 18 years) and adolescents (aged 12 years and older with body weight at least 40 kg) hospitalized with confirmed COVID-19 pneumonia		
Intervention	Remdesivir plus standard of care/supportive treatment[a] (may include other drugs that potentially also change the course of the disease, such as dexamethasone)		
Comparison	Standard of care/supportive treatment* (may include other drugs that potentially also change the course of the disease, such as dexamethasone)		
Outcomes	**Clinical effectiveness**	**Rate**	**Relative importance**
	All-cause mortality	9	critical
	Time to recovery (using an Ordinal Scale for Clinical Improvement, e.g. WHO)	6	important
	Clinical improvement; using difference of stage on Ordinal Scale for Clinical Improvement, e.g. WHO)	6	important
	Additional need for non-invasive ventilation or high-flow oxygen	8	critical
	Duration of non-invasive ventilation or high-flow oxygen, in patients requiring it	7	critical
	Additional need for invasive mechanical ventilation or ECMO	8	critical
	Duration of invasive mechanical ventilation or ECMO, in patients requiring it	7	critical
	Length of stay (hospital and critical care unit)	5	important
	Safety		
	Adverse events	6	important
	Serious adverse events	8	critical
	Adverse events leading to treatment discontinuation	7	critical
	Treatment-related mortality	9	critical

[a] Standard of care may include, but is not limited to, supplemental oxygen or ventilatory support, dexamethasone, pharmacological thromboprophylaxis, empiric/targeted antimicrobial therapy, hemodynamic support, renal replacement therapy, investigational agents, other supportive measures.

3 METHODS

The MAH was invited to submit evidence for the assessment of remdesivir for the treatment of adults (aged > 18 years) and adolescents (aged 12 years and older with body weight at least 40 kg) hospitalized with confirmed COVID-19 pneumonia.

However, the MAH informed EUnetHTA that it would not be providing an evidence submission for this assessment.

Following the MAH's decision not to submit a dossier, EUnetHTA decided to carry out a rapid review of the literature and a summary of the available evidence and its limitations. Because of time constraints, the Authoring Team decided that this rapid review of the literature would be based on a meta-review that is a Systematic Literature Review of systematic reviews of randomised trials supplemented by a hand search of HTA reports.

Noteworthy, the aim of this rapid review of the literature is not to conduct a formal REA or Rolling REA, but to summarize the available evidence from published RCTs identified from the above sources (and any existing meta-analyses), to discuss its limitations, and to identify evidence gaps and make recommendations for research.

3.1 Data sources and searches

The rapid review was based on a Systematic Literature Review (SLR) carried out by the Authoring Team. The search looked for systematic literature reviews, and included MEDLINE-PubMed, Cochrane Library and the Health Technology Assessment (HTA) database (York) for articles published as of 31 August 2020. Additionally, the website of national HTA organizations was hand searched (Appendix 1).

The list of HTA organizations searched can be found in Appendix 1. The summary protocol used by the Authoring Team for the Systematic Literature Review is shown in Table 3.1.

Table 3.1. Summary protocol

Review question	
Primary study question/objective	Identify systematic literature reviews on the clinical effectiveness, safety and tolerability of remdesivir for patients with COVID-19 disease
Studies to include	
Population	Patients hospitalized with confirmed COVID-19 pneumonia
Interventions	Remdesivir
Comparator	Any intervention listed
Outcomes	All-cause mortality; Additional need for non-invasive ventilation or high-flow oxygen; Duration of non-invasive ventilation or high-flow oxygen, in patients requiring it; Additional need for invasive mechanical ventilation or ECMO; Duration of invasive mechanical ventilation or ECMO, in patients requiring it; Length of stay (hospital and critical care unit); Duration of treatment; Adverse events; Serious adverse events; Adverse events leading to treatment discontinuation; Treatment-related mortality.
Study designs	Systematic review
Language	English, French, Spanish, Italian, German
Search timeframe	Database inception to present
Country	No limit
Other specific inclusion/exclusion criteria	- Systematic reviews assessing clinical effectiveness, safety or tolerability of remdesivir in patients with COVID-19 - HTA Reports

Data sources	
Databases	MEDLINE including Epub Ahead of Print; Cochrane Central Register of Controlled Trials (CENTRAL);Health Technology Assessment Database (HTA).
Bibliographic search	Reference lists of retrieved reviews will be screened for any additional relevant studies

Abbreviations: CDSR=Cochrane Database of Systematic Reviews

4 RESULTS

4.1 Existing Evidence

The flow of published SLRs through the systematic review process is depicted in Appendix 2.

The SLR of reviews retrieved fourteen published systematic literature reviews on the use of remdesivir for the treatment of moderate or severe COVID-19 (Appendix 3). Four unique RCTs were identified from these reviews as well as a meta-analysis of two of these studies. The hand search identified seven reports from national HTA agencies, from which no additional RCT was identified. The studies identified were the following:

1. Beigel JH et al (32) (2020). NCT04280705. http://doi.org/10.1056/NEJMa2007764 **[ACTT-1]**;
2. Wang Y et al (33) (2020). NCT04257656. http://doi.org/10.1016/S0140-6736(20)31022-9;
3. Cochrane (2020). Living mapping and living systematic review of Covid-19 studies: Pharmacologic treatments for COVID-19 patient – Remdesivir vs placebo (34);
4. Goldman JD et al (35) (2020). NCT04292899. http://doi.org/ 10.1056/NEJMoa2015301 **[GS-US-540-5773 - Part A]**;
5. Spinner CD et al (36) (2020). NCT04292730. http://doi.org/ 10.1001/jama.2020.16349 **[GS-US-540-5774]**.

4.2 Summary of identified studies and results

The literature search identified two studies in patients with severe COVID-19 (ACTT-1 (32) and Wang et al (33)) comparing remdesivir vs placebo, a meta-analysis of these two studies (Cochrane 2020 (34)), a study that compared two dose regimens of remdesivir, 5 days vs 10 days, in patients with severe COVID-19 (GS-US-540-5773 - Part A (35)), and a study in patients with moderate COVID-19 (GS-US-540-5774 (36)), comparing remdesivir up to 5 days vs up to 10 days vs standard care. As study GS-US-540-5773 - Part A did not include a control group, the relative efficacy results of the study are not interpretable. Therefore, the other four studies were the focus of this review.

4.2.1 ACTT-1 study (NCT04280705) (32)

The ACTT-1 study (32) was a randomised, double-blind, placebo-controlled trial, which was ongoing at the time of the report, conducted at 60 centres in 10 countries for 29 days. The study included 1063 patients aged 18 years or older, hospitalized with confirmed COVID-19 pneumonia requiring supplemental oxygen, who were randomly assigned in a 1:1 ratio to receive either remdesivir 200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days (n= 541) or placebo (n= 522). The primary endpoint was initially defined as the difference in clinical status, defined by the eight-category ordinal scale, among patients treated with remdesivir as compared with placebo at day 15, but was subsequently changed to the time to recovery. The change was proposed on 22 March 2020 by trial statisticians who were unaware of treatment assignments, and was made in response to information indicating that COVID-19 infection may have a more protracted course than previously appreciated.

The secondary endpoints included patient's clinical status on an eight-category ordinal scale assessed daily while hospitalized and on day 15, the National Early Warning Score (NEWS) assessed daily while hospitalized and on day 15, duration of supplemental oxygen in the first 28 days (if applicable), duration of mechanical ventilation in the first 28 days (if applicable), duration of hospitalization, and 28-day mortality.

The eight-category ordinal scale included the following categories: 1- not hospitalized, no limitations of activities; 2- not hospitalized, limitations of activities; 3- hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care; 4- hospitalized, not requiring supplemental oxygen but requiring ongoing medical care; 5- hospitalized, requiring any supplemental oxygen; 6- hospitalized, requiring non-invasive ventilation or use of high-flow oxygen; 7- hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 8- death.

If the hospital had a written policy for use of other treatments for COVID-19 (whether experimental or off-label use of specific treatments for COVID-19), patients could receive those treatments during the study period.

Patients were randomised to receive remdesivir or placebo. However, a normal saline was used as a 'placebo' at the European sites and at some non-European sites due to a shortage of placebo. Although efforts were made to maintain the blinding by giving the infusions masked by the use of an opaque bag and tubing covers, it is unclear whether blinding was sufficiently maintained.

The secondary analysis was not corrected for multiplicity and therefore results were reported as point estimates and 95% confidence intervals, and the intervals could not be used to infer treatment effects for secondary endpoints. As the secondary endpoints were the most clinically relevant (mortality, duration of mechanical ventilation, duration of supplemental oxygen, duration of hospitalisation), the study was not powered to detect differences in any of the relevant outcomes.

The study had a planned interim efficacy analysis. The review occurred on 27 April 2020 (data cutoff 22 April 2020) after completion of enrolment, when a total of 482 recoveries (the number of recoveries needed for the trial was 400) had already occurred, and the data and safety monitoring board recommended that a preliminary analysis of the data should be carried out. The publication available (32) reports the early analysis of the study.

In the remdesivir arm, 103 participants did not have ordinal scale scores for the day 15 visit at the time of the data freeze and in the placebo arm, 109 participants did not have ordinal scale scores for the day 15 visit at the time of the data freeze. Therefore, the participant's worst ordinal scale score during the previous day was used as the ordinal scale at day 15 visit.

A total of 89% of the patients were classified as having severe disease at baseline (defined as participants meeting one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an $SpO_2 \leq 94\%$ on room air, or tachypnoea [respiratory rate ≥ 24 breaths per minute]), with no significant differences between groups. However, more patients in the placebo group required mechanical invasive ventilation (28.2% vs 23.1%), suggesting that, using a different definition, patients in the placebo group might suffer from more severe disease than patients in the remdesivir group. Median time from symptom onset to randomisation was 9 days in each group.

Patients in the remdesivir group had a median of 11 days to recovery while patients in the placebo group had a median of 15 days to recovery, and this difference was statistically significant (rate ratio 1.32; 95%CI 1.12 to 1.55; p<0,001). Noteworthy, time to recovery was not classified as a critical outcome for the current assessment (please see PICO).

All-cause mortality was numerically lower in the remdesivir group than in the placebo group, but the difference was not statistically significant (hazard ratio 0.70; 95%CI 0.47 to 1.04). Again, the study was not powered to detect a difference in mortality between groups.

The odds of improvement in the ordinal scale at day 15 were higher in the remdesivir group (odds ratio 1.50; 95%CI 1.18 to 1.91). However, as the secondary analysis was not corrected for multiplicity the confidence intervals could not be used to infer treatment effects for secondary endpoints.

Although the study protocol of the ACTT-1 study defined as an objective to evaluate the treatment effect on the duration of mechanical ventilation, duration of supplemental oxygen, all-cause mortality and duration of hospitalisation, the safety monitoring board decided to report only the treatment effect on mortality at this early analysis, raising the possibility of selective outcome reporting.

The proportion of patients with adverse events was not reported. More patients in the placebo group reported serious adverse events (27% vs 21.1%). The proportion of patients with grade 3 or 4 adverse events was 28.8% in the remdesivir group and 33.0% in the placebo group.

4.2.2 Wang et al study (NCT04257656) (33)

The **Wang et al study** (33) was a randomised, double-blind, placebo-controlled trial, conducted at 10 hospitals in Hubei, China, for 28 days. The study included 237 patients aged 18 years or older, hospitalized with confirmed COVID-19 pneumonia, who were randomly assigned in a 2:1 ratio to receive either remdesivir 200 mg loading dose on day 1, followed by 100 mg daily for 9 additional days (n= 158) or placebo (n= 79). The primary endpoint was time to clinical improvement within 28 days. Clinical improvement was defined as a two-point reduction in a six-point ordinal scale.

The secondary endpoints included the proportions of patients in each category of the six-point scale, all-cause mortality, frequency of invasive mechanical ventilation, duration of oxygen therapy, duration of hospital admission, and proportion of patients with nosocomial infection.

The six-category ordinal scale included the following categories: 1- discharged or having reached discharge criteria; 2- hospitalized, not requiring supplemental oxygen; 3- hospitalized, requiring supplemental oxygen; 4- hospitalized, requiring non-invasive ventilation or use of high-flow oxygen; 5- hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 6- death.

The statistical plan estimated that, assuming a dropout rate of 10%, the study needed to include 453 patients and 325 events across both groups, to provide 80% power with a type I error of 2.5% (one-sided) if the hazard ratio comparing remdesivir with placebo was 1.4. However, because of the control of the outbreak in Wuhan, no patients were enrolled after March 12, following which the data safety and monitoring board recommended that the study be terminated when only 236 patients were enrolled. Therefore, the study was underpowered to detect differences between groups (the study had a power of 58% for the primary outcome).

Remdesivir showed a smaller than anticipated treatment effect (hazard ratio 1.23; 95%CI 0.87 to 1.75), and there was no statistically significant difference in time to clinical improvement between treatment groups. The median time to clinical improvement was 21 days (95%CI 13.0 to 28) in the remdesivir group, and 23.0 days (95%CI 15.0 to 28.0) in the placebo group. Noteworthy, the study showed no difference between groups in treatment effect on any of the efficacy outcomes defined in the PICO for this report.

There was no difference between groups in the proportion of patients with adverse events (remdesivir: 66%; placebo: 64%). More patients in the placebo group reported serious adverse events (26% vs 18%), and more patients in the remdesivir group discontinued treatment due to adverse events (12% vs 5%).

4.2.3 Cochrane meta-analysis (34)

The Cochrane meta-analysis (34) pooled the data from ACTT-1 and Wang et al. The two studies included only two comparable outcomes: all-cause mortality and the incidence of WHO progression score level 6/7. The meta-analysis found no statistically significant difference in all-cause mortality between treatment groups (relative risk 0.74; 95%CI 0.40 to 1.37). There was a statistically significant reduction in the incidence of WHO progression score level 6/7 between remdesivir and placebo (relative risk 0.76; 95%CI 0.62 to 0.93). However, the treatment effect on the outcomes was assessed at different time points in those studies. While the ACTT-1 study assessed treatment effect at day 14, the study of Wang et al assessed the treatment effect at day 28. Due to the heterogeneity in outcomes combined in the meta-analysis, the authoring team did not consider the findings to be robust

A summary of the baseline characteristics of patients included in severe COVID studies is depicted in Appendix 7.

A summary of the results of severe COVID studies is shown in Appendix 8.

4.2.4 GS-US-540-5774 study (NCT04292730) (36)

The GS-US-540-5774 (36) study was a randomised, open-label trial, conducted at 105 centres in 12 countries (France, Germany, Hong Kong, Italy, Republic of Korea, The Netherlands, Singapore, Spain, Switzerland, Taiwan, United Kingdom, United States) for 28 days. The study included 596 patients aged 12 years or older, hospitalized with moderate COVID-19 pneumonia, defined by the presence of confirmed COVID-19 pneumonia and room-air oxygen saturation >94%, who were randomly assigned in a 1:1:1 ratio to receive either remdesivir 200 mg loading dose on day 1, followed by 100 mg daily for up to 5 additional days (n= 199), remdesivir 200 mg loading dose on day 1, followed by 100 mg daily for up to 10 additional days (n= 197),or to continue standard care (n= 200). Patients were randomised through an interactive web response system.

Patients were enrolled between 15 March 2020 and 18 April 2020. The primary endpoint was initially defined as the proportion of patients discharged by day 14, but was subsequently changed to assessment of clinical status on a 7-point ordinal scale by day 11. The change took place on 15 March 2020 'on the basis of emerging understanding of the clinical presentation and assessment of COVID-19'. The amendment also included a reduction of the age limit for eligibility from 18 to 12 years old, and the minimum temperature requirement for inclusion was eliminated. The Authoring Team was unable to determine the reasoning behind the change, and considers that the rationale for the change in the primary endpoint was not sufficiently justified. The proportion of patients discharged at day 14 (the initial primary endpoint) was 76% (146/193) in the remdesivir 10-day group, 76% (146/191) in the remdesivir 5-day group, and 67% (134/200) in the standard of care group, but the statistical significance of the differences was not assessed.

The secondary endpoint was the proportion of patients with adverse events during the study. Exploratory endpoints included time to recovery, defined as 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, time to modified recovery, time to clinical improvement defined as an improvement from baseline of at least 2 points on the 7-point ordinal scale, time to at least 1-point improvement, and time to discontinuation of oxygen support. The study included other exploratory endpoints as the duration of hospitalization, duration of different modes of respiratory support, and all-cause mortality.

The seven-category ordinal scale included the following categories: 1- death; 2- hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3- hospitalized, requiring non-invasive ventilation or use of high-flow oxygen; 4- hospitalized, requiring low flow supplemental oxygen; 5- hospitalized, not requiring supplemental oxygen but requiring ongoing medical care; 6- hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care;7- not hospitalized.

If, in the opinion of the investigator, patients had sufficiently improved, they could be discharged from the hospital before finishing their experimental treatment.

If the hospital used other treatments for COVID-19 as the local standard, their concurrent use was allowed. Although a subsequent amendment disallowed this practice, some patients had already received these therapies. However, the proportion of patients that has received those therapies in each treatment arm during the study period, as well as the potential impact of those treatments on the outcomes, was not reported.

The study had an open-label design, because the sponsor had an insufficient number of placebo vials. No efforts were made to minimize bias.

The effect size for the primary endpoint was calculated as an odds ratio, where an odds ratio greater than 1 indicated changes in clinical status across all categories toward category 7 (not hospitalized), favouring remdesivir. In case of missing values, the most recent assessment that was available, was imputed.

The secondary and exploratory analyses were not corrected for multiplicity and therefore results could not be used to infer treatment effects for these endpoints. As the exploratory endpoints were the most clinically relevant (mortality, duration of mechanical ventilation, duration of supplemental oxygen, duration of hospitalisation), the study was not powered to detect differences in any of the relevant outcomes defined in the PICO for this report.

At baseline, there were slight differences in the proportion of patients requiring low-flow supplemental oxygen, with a greater proportion in the standard of care group requiring this therapy (standard of care 18%; remdesivir 5-day 15%; remdesivir 10-day 12%). At baseline, there were significant differences between groups in the level of concomitant medications use. More patients in the standard of care group received steroids (SC 19%; remdesivir 5-day 17%; remdesivir 10-day 15%), hydroxychloroquine/chloroquine (SC 45%; remdesivir 5-day 8%; remdesivir 10-day 11%), lopinavir-ritonavir (SC 22%; remdesivir 5-day 5%; remdesivir 10-day 6%), and azithromycin (SC 31%; remdesivir 5-day 18%; remdesivir 10-day 21%). Additionally, the proportion of patients that continued to receive concurrent therapies for COVID-19 during the study was not reported.

Of 199 patients randomised to receive remdesivir 5-day, 191 patients (96%) received the medication and were included in the primary analysis, and 145 (72,9%) completed the treatment duration. Reasons for discontinuation were hospital discharge (18%), withdrawal of consent (3%), and adverse events (2%). Of 197 patients randomised to receive remdesivir 10-day, 193 patients (98%) received the study drug and were included in the primary analysis, and 73 patients (37,1%) completed the treatment duration. Reasons for discontinuation included hospital discharge (51%), adverse events (4%), and withdrawal of consent (3%). Of 200 patients randomised to continue standard of care, 200 patients (100%) received this treatment regimen and were included in the primary analysis. The main reason for not completing the treatment was, therefore, hospital discharge (18% in remdesivir 5-day, 51% for remdesivir 10-day, and 0% for standard of care), which could be influenced by the open-label design of the study.

The median duration of symptoms was 9 days (IQR 6-11) for the standard care group, and 8 days (IQR 5-11) for both remdesivir groups.

Median length of treatment was 5 days in the remdesivir 5-day group, and 6 days in the remdesivir 10-day group.

On day 11, patients in the remdesivir 5-day group had higher odds of a better clinical status distribution on a 7-point ordinal scale than those receiving standard care (odds ratio 1.65; 95%CI 1.09 to 2.48; p= 0.02). However, the clinical status distribution on day 11 was not significantly different between remdesivir 10-day and standard care groups (p= 0.18).

There were no significant differences between the remdesivir 5-day group or remdesivir 10-day group and standard care for any of the exploratory endpoints and, namely, duration of oxygen therapy, duration of hospitalization, or all-cause mortality. Noteworthy, the study was not powered to detect a difference between groups in any of these outcomes.

The proportion of patients with adverse events was 51% in the remdesivir 5-day group, 59% in the remdesivir 10-day group, and 47% in the standard care group. The difference between the remdesivir 5-day and standard care was not statistically significant (p= 0.36). However, the difference between the remdesivir 10-day and standard care was statistically significant (p= 0.02). Serious adverse events were reported in 5% of patients in the remdesivir 10-day group, 5% of patients in the remdesivir 5-day group, and 9% of patients in the standard care group. Discontinuation of treatment due to adverse events were reported in 4% of patients in the remdesivir 10-day group, 2% of patients in the remdesivir 5-day group, and 0% of patients in the standard care group.

A summary of the baseline characteristics of patients included in the moderate COVID study is depicted in Appendix 9.

A summary of the results of the moderate COVID study is shown in Appendix 10.

4.3 Risk of bias / quality of evidence

The risk of bias of the studies identified by SLR was assessed using the risk of bias tool of the Cochrane collaboration (37). This tool includes the following five domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. This involves answering a specific question (e.g. was the allocation sequence adequately generated?) for each domain. An answer 'Yes' indicates a low risk of bias, and an answer 'No' indicates high risk of bias.

The risk of bias was evaluated by two independent assessors. Differences in the judgment about risk of bias was solved by a third party. The risk of bias was considered high for all three studies. Table 4.1 shows a summary of the assessment of risk of bias.

Table 4.1. Risk of bias

Studies	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
ACTT-1	Yes	Yes	Not clear[1]	Not clear[1]	NA	No[2]	Not clear[3]	No[4]
Wang et al	Yes	Not clear[5]	Yes	Yes	NA	Yes	Yes	No[6]
GS-US-540-5774	Yes	Yes	No[7]	No[7]	NA	No[8]	Yes	No[9]

Note: The observations that underlie the judgements are shown in Appendix 5.

5 DISCUSSION (LIMITATIONS)

The evidence of efficacy in COVID-19 is inconsistent and comes from two double-blind placebo-controlled RCTs (severe COVID), one open-label RCT (moderate COVID) and one dose-comparison trial. All trials were judged to be at high risk of bias.

The largest of the placebo-controlled studies (ACTT-1) was stopped early, following interim analysis showing benefit in time to recovery. The available publication reports the early analysis of the study; however this early analysis may have overestimated the treatment effect. The primary endpoint was initially defined as the difference in clinical status using an ordinal scale, but was subsequently changed to the time to recovery. However, as the treatment effect on the ordinal scale (the initial primary endpoint) was statistically significant, the change in the definition of the primary endpoint appears not to be a threat to the internal validity of the study. The secondary analysis was not corrected for multiplicity and therefore results were reported as point estimates and 95% confidence intervals, and the intervals could not be used to infer treatment effects for secondary endpoints. As the secondary endpoints were the most clinically relevant (mortality, duration of mechanical ventilation, duration of supplemental oxygen, duration of hospitalisation), the study was not powered to detect differences in any of the relevant outcomes of greatest relevance to this report. The interpretation of mortality data from this study is further limited by the large number of patients yet to complete the study. Even with complete follow-up, the ability of the trial to demonstrate a mortality benefit from treatment is hampered by the early unblinding of treatment assignment and the facility to discontinue placebo. A normal saline was used as a ‘placebo’ at the European sites and at some non-European sites due to a shortage of placebo. Although efforts were made to maintain the blinding by giving the infusions masked by the use of an opaque bag and tubing covers, it is unclear whether blinding was sufficiently maintained. The proportion of patients who received other therapies for COVID-19 in each treatment arm, as well as the potential impact of those treatments on the outcomes was not reported. This lack of information threatens the internal validity of the study. A total of 89% of the patients were classified as having severe disease at baseline (defined as participants meeting one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an $SpO_2 \leq 94\%$ on room air, or tachypnoea [respiratory rate ≥ 24 breaths per minute]), with no significant differences between groups. However, more patients in the placebo group required mechanical invasive ventilation (28.2% vs 23.1%), suggesting that, using a different definition, patients in the placebo group might suffer from more severe disease than patients in the remdesivir group.

A smaller study (Wang et al) reported no evidence of benefit compared with placebo, though it was under-powered to detect a significant effect. Neither trial was powered to detect a difference in mortality between treatment groups.

One open-label RCT in moderate COVID-19 (GS-US-540-5774) suggests greater clinical improvement versus treatment with standard of care alone, though the clinical significance of this improvement is unclear. Various categories on the ordinal scale used for the primary endpoint do not have the same clinical significance, leading to uncertainty in the clinical relevance of a “better clinical status distribution”. In this study, if, in the opinion of the investigator, patients had sufficiently improved, they could be discharged from the hospital before finishing their experimental treatment. This procedure, in a study with an open-label design, may bias in favour of the experimental treatment. If the hospital used other treatments for COVID-19 as the local standard, their concurrent use was allowed. However, the proportion of patients that has received those therapies in each treatment arm during the study period, as well as the potential impact of those treatments on the outcomes, was not reported. This lack of information threatens the internal validity of the study. As with the ACTT-1 study this study was not powered to detect differences in any of the outcomes of greatest relevance to this report. Taken together, the inconsistency in these results makes interpretation difficult, and may be influenced by the open label nature of the study and other biases discussed in Section 4.3 of this report.

The optimal duration of remdesivir treatment is also uncertain. Studies have shown no incremental benefit of 10 days of treatment over 5 days. In the GS-US-540-5774 study, patients in the remdesivir 5-day group had a higher odds of clinical improvement (assessed by the 7-point ordinal scale) than those receiving standard care (odds ratio 1.65; 95%CI 1.09 to 2.48; p= 0.02). However, the clinical status distribution was not significantly different between remdesivir 10-day and standard care groups (p= 0.18). Taken together, the inconsistency in these results makes interpretation difficult, and may be influenced by the open-label nature of the study and other biases discussed in Section 4.3 of this report.

Therefore, the reported difference between remdesivir 5-day and standard care may be considered as of uncertain clinical importance.

Small, retrospective, observational studies have been published for many investigational treatments for COVID-19, including for remdesivir (38). Such studies are at high risk of bias due to selection bias, low patient numbers which render methods of minimising confounding ineffective, and other limitations and were therefore not included as part of this review.

6 CONCLUSION

The evidence of efficacy in COVID-19 is inconsistent and comes from two double-blind placebo-controlled RCTs (severe COVID), one open-label RCT (moderate COVID) and one dose-comparison trial. None of the clinical trial reports have been made available for the four RCTs for remdesivir.

The primary endpoints in three identified RCTs did not include those of critical importance identified in the PICO of this report. The studies were not powered to detect differences in secondary endpoints which included the most clinically relevant endpoints such as mortality, duration of mechanical ventilation, duration of supplemental oxygen, duration of hospitalisation. Interpretation of results is further hampered in some cases by early study termination/unblinding, ambiguous blinding methods or lack of blinding, mid-trial protocol changes, selective reporting and lack of clarity in concomitant medications received. All studies were judged to be at high risk of bias.

The studies identified in this review suggest some benefit with remdesivir, reducing time to recovery in severe COVID-19. Greater clinical improvement on a 7-point ordinal scale, with remdesivir 5-day versus treatment with standard of care alone is suggested in patients with moderate COVID-19, though the inconsistency in results across the remdesivir 5 day and 10 day groups limit the interpretation of this finding. The clinical significance of both of these findings is unclear.

Clear evidence of benefit in key clinical outcomes of most relevance for patients, including mortality and the need for intubation/mechanical ventilation, is lacking. Further evidence from large RCTs are urgently needed to address uncertainties.

As the MAH did not provide an evidence submission, the Authoring Team could only assess evidence in the public domain.

7 EVIDENCE GAPS

The evidence gaps detected following the SLR are shown in Appendix 6. There is a need for credible adequately powered randomised controlled trials in patients with COVID and pneumonia, comparing the effect of remdesivir with alternative treatments on clinically relevant outcomes, such as mortality, the additional need for and duration of mechanical ventilation, additional need for and duration of supplemental oxygen, duration of hospitalisation (please also see PICO). Further the availability of full clinical study reports for completed trials to allow open and robust scrutiny of the trials is imperative.

8 PROJECT ORGANISATION

8.1 Participants

Table 8.1. Project participants

Role in the project	Agency	Country	Distribution of work
Assessment Team			
Author	National Authority of Medicines and Health Products (INFARMED)	Portugal	Author will draft the report. Author will review and comment the sections drafted by the co-author. All important milestones will be discussed in advance with the co-author.
Co-Author	National Centre for Pharmacoeconomics (NCPE)	Ireland	Co-author will support drafting the report. Co-author will review and comment on all parts of the report.
Dedicated Reviewer	Austrian Institute for Health Technology Assessment (AIHTA)	Austria	Review of first draft
Dedicated Reviewer	Regione Emilia-Romagna (RER)	Italy	Review of first draft
Dedicated Reviewer	HTA Department SEC Ministry of Health Ukraine	Ukraine	Review of first draft
Contributors			
Project Manager	Zorginstituut Nederland (ZIN)	Netherlands	Coordination between involved parties throughout the assessment period

8.2 Project stakeholders

Table 8.2. Project stakeholders

Organisation	Role in the project
Gilead	Manufacturer [MAH]; However, Gilead declined to collaborate with EUnetHTA during the production of this report.

8.3 Milestones and deliverables

Table 8.3. Milestones and deliverables

Milestones/Deliverables	Start date	End date
CHMP opinion	*25/06/2020*	
EPAR	*06/07/2020*	
Project duration	**17/07/2020**	**29/09/2020**
Scoping PICO	17/07/2020	24/07/2020
PICO survey – request relevant PICO from Member States	25/07/2020	31/08/2020
Draft Rapid Collaborative Review report based on PICO survey	01/09/2020	09/09/2020
Review of first draft report	10/09/2020	16/09/2020
Development of 2nd draft report & answers to DR comments	17/09/2020	28/09/2020
Finalize RCR report	28/09/2020	
Publication final version of Report	29/09/2020	

9 REFERENCES

1. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. [cited 2020 Sep 9]. Available from: https://covid19.who.int/
2. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. [Internet]. Available from: https://www.covid19treatmentguidelines.nih.gov/. Accessed 18/09/2020
3. ECDC COVID-19 surveillance report [Internet]. [cited 2020 Sep 18]. Available from: https://covid19-surveillance-report.ecdc.europa.eu/
4. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. MBio. 2018;9(2):1–15.
5. Brown AJ, Won JJ, Graham RL, Dinnon KH, Sims AC, Feng JY, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information . 2020;(January).
6. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9(396).
7. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. bioRxiv.
8. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.
9. Mulangu S, Dodd LE, Davey RT, Mbaya OT, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293–303.
10. EMA. Veklury EPAR Information - EMEA/H/C/005622 [Internet]. [cited 2020 Sep 22]. Available from: https://www.ema.europa.eu/documents/overview/veklury-epar-medicine-overview_en.pdf
11. EMA. Veklury Public Assessment Report [Internet]. [cited 2020 Sep 22]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/veklury-epar-public-assessment-report_en.pdf
12. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02818582, GS-5734 to Assess the Antiviral Activity, Longer-Term Clearance of Ebola Virus, and Safety in Male Ebola Survivors With Evidence of Ebola Virus Persis [Internet]. [cited 2020 Jul 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT02818582.
13. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03719586, Investigational Therapeutics for the Treatment of People With Ebola Virus Disease. [Internet]. ClinicalTrials.gov [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT03719586
14. Cochrane Centres call for transparency of COVID-19 clinical studies [Internet]. [cited 2020 Sep 22]. Available from: https://www.cochrane.org/news/cochrane-centres-call-transparency-covid-19-clinical-studies
15. Letter to the European Medicines Agency (EMA) concerning the transparency and independence of the work of the EMA in supporting the development and evaluation of COVID-19 medicines [Internet]. [cited 2020 Sep 22]. Available from: https://www.ombudsman.europa.eu/en/correspondence/en/130852
16. World Health Organization. Clinical management of COVID-19. Interim Guidance 27 May 2020 . WHO/2019-nCoV/clinical/2020. [Internet]. [cited 2020 Jun 2]. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
17. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature [Internet]. 2020;584(7821):430–6. Available from: http://dx.doi.org/10.1038/s41586-020-2521-4
18. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) [Internet]. Vol. 46, Intensive Care Medicine. Springer Berlin Heidelberg; 2020. 854–887 p. Available from: https://doi.org/10.1007/s00134-020-06022-5
19. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. N Engl J Med. 2020;1–11.
20. COVID-19 Therapeutic Alert 24 June 2020. Dexamethasone in the treatment of COVID-19. [Internet]. [cited 2020 Jul 23]. Available from:

https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103054
21. National Institutes of Health (US). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. [Internet]. [cited 2020 Jul 23]. Available from: https://covid19treatmentguidelines.nih.gov/
22. Organization WH. Corticosteroids for COVID-19: living guidance, 2 September 2020 [Internet]. Geneva PP - Geneva: World Health Organization; Available from: https://apps.who.int/iris/handle/10665/334125
23. EUnetHTA Joint Action 3 (2016-2021) Covid-19 Rolling Collaborative Review [Internet]. [cited 2020 Sep 22]. Available from: https://eunethta.eu/rcr01-rcrxx/
24. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med. 2020;382(19):1787–99.
25. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med. 2020;
26. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv [Internet]. 2020;2020.07.15.20151852. Available from: https://doi.org/10.1101/2020.07.15.20151852
27. Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, et al. Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. Clin Infect Dis [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32674126
28. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19. Ann Intern Med. 2020;
29. Randomised Evaluation of COVID-19 Therapy [Internet]. [cited 2020 Jul 24]. Available from: https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19
30. Bhimraj A, Morgan RL, Hirsch Shumaker A LV et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19.
31. Rochwerg B, Agarwal A, Zeng L, Leo Y-S, Appiah JA, Agoritsas T et al. Remdesivir for severe covid-19: a clinical practice guideline. BMJ. :2020;370:m2924.
32. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. N Engl J Med. 2020;
33. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet [Internet]. 2020;395(10236):1569–78. Available from: http://dx.doi.org/10.1016/S0140-6736(20)31022-9
34. Cochrane (2020). Living mapping and living systematic review of Covid-19 studies: Pharmacologic treatments for COVID-19 patient – Remdesivir vs placebo [Internet]. [cited 2020 Sep 9]. Available from: https://covid-nma.com/living_data/
35. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020;1–11.
36. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. Jama. 2020;94404.
37. Editors Julian PT Higgins and Sally Green, editor. Cochrane Handbook for Systematic Reviews of Interventions. In Reprinted August 2012. Wiley-Blackwell;
38. Pasquini Z, Montalti R, Temperoni C, Canovari B, Mancini M, Tempesta M, et al. Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU. Journal of Antimicrobial Chemotherapy. 2020.

APPENDIX 1: SLR SEARCH STRATEGIES

#	**PUBMED (31/08/2020)**
1	"remdesivir"[All Fields] OR "remdesivir"[Supplementary Concept]: 535
2	"severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019-nCoV"[All Fields] OR "COVID-19"[All Fields] OR "SARS-CoV-2"[All Fields] OR ((coronavirus[All Fields] OR "cov"[All Fields]) : 66128
3	"systematic review"[Publication Type] .or. "systematic reviews as topic"[MeSH Terms] .or. "systematic review"[All Fields]: 187139
4	#1 AND #2 AND #3: 15

#	**CENTRAL (31/08/2020)**
1	Coronavirus Infections (limits: in Cochrane Reviews and Cochrane Protocols): 34
2	remdesivir (limits: in Cochrane Reviews): 1
3	#1 AND #2: 1

#	**Health Technology Assessment Database (University of York) (31/08/2020)**
1	((Coronavirus infection)) and ((Systematic review:ZDT and Bibliographic:ZPS) OR (Systematic review:ZDT and Abstract:ZPS) OR (Cochrane review:ZDT) OR (Cochrane related review record:ZDT) OR (Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS) OR Project record:ZDT OR Full publication record:ZDT) IN DARE, NHSEED, HTA: 0

#	National HTA searches for the SLR
1	UCSC Gemelli – Italy
2	HAS - France
3	MIZ - Croatia
4	NICE – UK
5	AEMPS - Spain
6	DVSV - Austria
7	ZIN - Netherlands
8	FIMEA – Finland
9	SEC MoH - Ukraine
10	GOEG - Austria
11	Government – Hungary
12	NVD - Latvia
13	GBA - Germany
14	SESCS - Spain
15	IQWIG - Germany
16	RER – Italy
17	CADTH – Canada
18	INFARMED - Portugal

APPENDIX 2: FLOW OF PUBLISHED SLRS THROUGH THE SYSTEMATIC REVIEW PROCESS

The search of specified biomedical databases yielded 16 citations. Twelve additional studies/HTA reports were retrieved from reference lists of key papers and after consultation of HTA agencies. None of the citations was found to be duplicated. Following the first pass of citations, 27 potentially relevant references were identified. Full-text reports of these citations were obtained for further detailed evaluation.

Following detailed examination of the reports, 6 citations were excluded. In total, 21 references met the inclusion/exclusion criteria for this review (14 SLR and 7 HTA reports). Figure A 1 depicts the flow of records through the systematic review process.

Four unique RCTs were identified from the reference lists of these 14 reviews as well as a meta-analysis of two of these studies. The hand search identified seven reports from national HTA agencies, from which no additional RCT was identified.

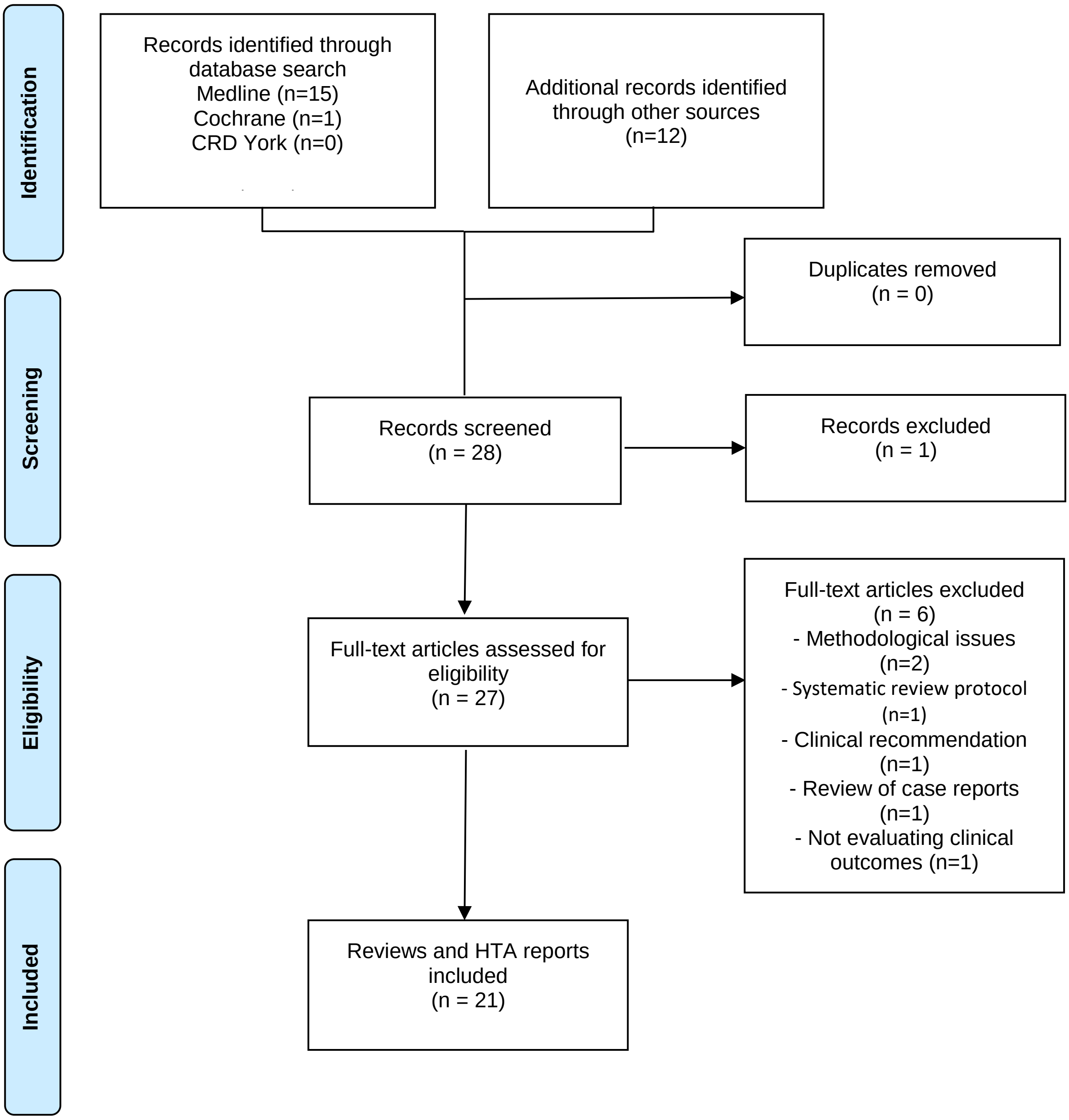

Figure A 1. Flow of published SLRs through the systematic review process

APPENDIX 3: PUBLISHED SLRS AND REPORTS FROM NATIONAL HTA AGENCIES INCLUDED, FOLLOWING FULL-TEXT REVIEW

#	Reports from National HTA agencies
1	NICE. National Institute for Health and Excellence. Evidence review. Remdesivir for treating hospitalised patients with suspected or confirmed COVID-19. Publication date: June 2020. Available at https://www.nice.org.uk/advice/es27/resources/covid-19-rapid-evidence-summary-remdesivir-for-treating-hospitalised-patients-with-suspected-or-confirmed-covid19-pdf-1158180847045
2	NCPE. National Centre for Pharmacoeconomics. Rapid Evidence Review. Clinical evidence for the use of antivirals in the treatment of COVID-19. Version 11, 22nd July 2020. Available at http://www.ncpe.ie/wp-content/uploads/2020/07/Antivirals-for-treatment-of-COVID-19-A-Rapid-Evidence-Review_V11.pdf
3	CADTH. Canadian Agency for Drugs and Technologies in Health. Remdesivir: Evidence Review and Appraisal. Version 3.0. June 2020. Available at https://cadth.ca/sites/default/files/covid-19/hc0003-remdesivir-update3.pdf
4	INFARMED. Autoridade Nacional do Medicamento e Produtos de Saúde. Remdesivir for the treatment of adults (aged > 18 years) and adolescents (aged 12 years and older with body weight at least 40 kg) hospitalized with confirmed COVID-19 pneumonia requiring supplemental oxygen. Version 1.0. 4th August 2020 (Portuguese version). Not yet published
5	FIMEA. Evaluation summary (published 8/2020) Intended use: Remdesivir is indicated for the treatment of coronavirus disease (COVID-19) in adults and adolescents (12 years of age and older and weighing 40 kg or more) with pneumonia who require supplemental oxygen (Finnish version). Available at www.fimea.fi/documents/160140/1454401/Remdesiviiri_arviointikooste_200807.pdf/bde619f4-dd9b-f9d7-c6fd-cc19d7e4056b?t=1596788063048
6	SEC MoH. The use of drugs in COVID-19 (Ukrainian version). Available at http://covid19.dec.gov.ua
7	SESCS. Recommendations for treatment of with remdesivir (Spanish version). Available at https://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/2020/NI-MUH-20-2020-remdesivir.pdf?x42065

#	Published SLRs
1	Teoh SL, Lim YH, Lai NM, Lee SWH (2020) Directly Acting Antivirals for COVID-19: Where Do We Stand? Front. Microbiol. 11:1857. doi: 10.3389/fmicb.2020.01857
2	Siordia JA Jr, Bernaba M, Yoshino K, et al. Systematic and Statistical Review of Coronavirus Disease 19 Treatment Trials [published online ahead of print, 2020 Jul 15]. SN Compr Clin Med. 2020;1-12. doi:10.1007/s42399-020-00399-6
3	Frediansyah A, Nainu F, Dhama K, Mudatsir M, Harapan H. Remdesivir and its antiviral activity against COVID-19: A systematic review [published online ahead of print, 2020 Aug 7]. Clin Epidemiol Glob Health. 2020;10.1016/j.cegh.2020.07.011. doi:10.1016/j.cegh.2020.07.011
4	Misra S, Nath M, Hadda V, Vibha D. Efficacy of various treatment modalities for nCOV-2019: a systematic review and meta-analysis [published online ahead of print, 2020 Aug 18]. Eur J Clin Invest. 2020;e13383. doi:10.1111/eci.13383
5	Subramanian K, Nalli A, Senthil V, Jain S, Nayak A, Bhat A. Perspectives on the Early Quality of Evidence Guiding the Therapeutic Management of SARS-CoV-2: A Systematic Literature Review [published online ahead of print, 2020 Aug 18]. Adv Ther. 2020;1-25. doi:10.1007/s12325-020-01460-5
6	Siemieniuk Reed AC, Bartoszko Jessica J, Ge Long, Zeraatkar Dena, Izcovich Ariel, Pardo-Hernandez Hector et al. Drug treatments for covid-19: living systematic review and network meta-analysis BMJ 2020;370:m2980
7	Davies M, Osborne V, Lane S, et al. Remdesivir in Treatment of COVID-19: A Systematic Benefit-Risk Assessment. Drug Saf. 2020;43(7):645-656. doi:10.1007/s40264-020-00952-1
8	Musa A, Pendi K, Hashemi A, et al. Remdesivir for the Treatment of COVID-19: A Systematic Review of the Literature. West J Emerg Med. 2020;21(4):737-741. Published 2020 May 20. doi:10.5811/westjem.2020.5.47658
9	Nasir M, Talha KA, Islam T, Saha SK, Selina F, Parveen RA. Use of Remdesivir in the Management of COVID-19: A Systematic Review on Current Evidences. Mymensingh Med J. 2020;29(2):481-487
10	Vijayvargiya P, Garrigos EG, Almeida NEC, et al. Treatment considerations for COVID-19: a critical review of the evidence (or lack thereof). Mayo Clin Proc 2020; 95(7): 1454-1466
11	Eastmen RT, Roth JS, Brimacombe KR et al. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Cent Sci 2020; 6: 672-683
12	Azevedo TCP, Azevedo PCP, Filho RNS, et al. Use of remdesivir for patients with Covid-19: a review article. Rev Ass Med Bras 2020; 66(6): 838-841
13	Singh AK, Singh A, Singh R, Misra A. Remdesivir in COVID-19: A critical review of pharmacology, pre-clinical and clinical studies. Diabetes Metab Syndr. 2020;14(4):641-648. doi:10.1016/j.dsx.2020.05.018
14	Cochrane (2020). Living mapping and living systematic review of Covid-19 studies: Pharmacologic treatments for COVID-19 patient – Remdesivir vs standard care/placebo

APPENDIX 4: LIST OF PUBLISHED SLRS EXCLUDED FROM THE SYSTEMATIC REVIEW OF REVIEWS

#	Medline	Reason for exclusion
1	Rochwerg B, Agarwal A, Zeng L, et al. Remdesivir for severe covid-19: a clinical practice guideline. BMJ. 2020;370:m2924. Published 2020 Jul 30. doi:10.1136/bmj.m2924	Clinical recommendation
2	Musa A, Warbasse E, Baron DA, et al. Addendum to Systematic Review of Remdesivir for the Treatment of COVID-19. West J Emerg Med. 2020;21(4):742-743. Published 2020 May 22. doi:10.5811/westjem.2020.5.48121	Addendum to previously included systematic review
3	Marouf BH, Dizaye K. Re-tasking the use of pre-existing medications and potential therapeutic options for coronavirus disease (COVID-19): systematic review of clinical studies. Drug Discov Ther. 2020;14(3):109-116. doi:10.5582/ddt.2020.03035	Narrative review
4	Kouzy R, Abi Jaoude J, Garcia Garcia CJ, El Alam MB, Taniguchi CM, Ludmir EB. Characteristics of the Multiplicity of Randomized Clinical Trials for Coronavirus Disease 2019 Launched During the Pandemic. JAMA Netw Open. 2020;3(7):e2015100. Published 2020 Jul 1. doi:10.1001/jamanetworkopen.2020.15100	No information collected on the clinical effectiveness, safety and tolerability of treatments
5	Patel RS, Patel N, Baksh M, Zaidi A, Patel J. Clinical Perspective on 2019 Novel Coronavirus Pneumonia: A Systematic Review of Published Case Reports. Cureus. 2020;12(6):e8488. Published 2020 Jun 7. doi:10.7759/cureus.8488	Inappropriate study design (case reports)
6	Gebrie D, Getnet D, Manyazewal T. Efficacy of remdesivir in patients with COVID-19: a protocol for systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2020;10(6):e039159. Published 2020 Jun 4. doi:10.1136/bmjopen-2020-039159	Systematic review protocol

APPENDIX 5: ASSESSMENT OF RISK OF BIAS

Table A 1. Risk of bias

Studies	Sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
ACTT-1	Yes	Yes	Not clear[1]	Not clear[1]	NA	No[2]	Not clear[3]	No[4]
Wang et al	Yes	Not clear[5]	Yes	Yes	NA	Yes	Yes	No[6]
GS-US-540-5774	Yes	Yes	No[7]	No[7]	NA	No[8]	Yes	No[9]

1. Patients were randomised to receive remdesivir or placebo. However, a normal saline was used as a 'placebo' at the European sites and at some non-European sites due to a shortage of placebo. Although efforts were made to maintain the blinding by giving the infusions masked by the use of an opaque bag and tubing covers, it is unclear whether blinding was sufficiently maintained.

2. In the remdesivir arm, 103 participants did not have ordinal scale scores for the day 15 visit at the time of the data freeze and in the placebo arm, 109 participants did not have ordinal scale scores for the day 15 visit at the time of the data freeze. Therefore, the participant's worst ordinal scale score during the previous day was used as the ordinal scale at day 15 visit.

3. The primary endpoint was initially defined as the difference in clinical status, but was subsequently changed to the time to recovery. The change was proposed on 22 March 2020 by trial statistician who were unaware of treatment assignments, and was made in response to information indicating that COVID-19 infection may have a more protracted course than previously appreciated. The Authoring Team was unable to understand the reasoning behind the change, and considers that the motive for the change in the primary endpoint was not sufficiently justified. However, as the treatment effect on the ordinal scale (the initial primary endpoint) was statistically significant, the change in the definition of the primary endpoint appears not to be a threat to the internal validity of the study.

4. The study had a planned interim efficacy analysis. The review occurred on 27 April 2020 (data cutoff 22 April 2020) after completion of enrolment, when a total of 482 recoveries (the number of recoveries needed for the trial was 400) had already occurred, and the data and safety monitoring board recommended that a preliminary analysis of the data should be carried out. The publication available, reports the early analysis of the study; however this this early analysis may have overestimated the treatment effect. If the hospital had a written policy for use of other treatments for COVID-19 (whether experimental or off-label use of specific treatments for COVID-19), patients could receive those treatments during the study period. However, the proportion of patients who received these therapies in each treatment arm, as well as the potential impact of those treatments on the outcomes was not reported. This lack of information threatens the internal validity of the study.

5. The method of allocation concealment is not reported

6. The study was stopped early because of the control of the outbreak in Wuhan (there were no patients available for inclusion).

7. Study with an open-label design

8. The main reason for not completing the treatment was hospital discharge (18% in remdesivir 5-day, 51% for remdesivir 10-day, and 0% for standard of care), which could be influenced by the open-label design of the study, making incomplete outcome data a serious issue that may threat the internal validity of the study.

9. If the hospital used other treatments for COVID-19 as the local standard, their concurrent use was allowed. Although a subsequent amendment disallowed this practice, some patients had already received these therapies. However, the proportion of patients that has received those therapies in each treatment arm during the study period, as well as the potential impact of those treatments on the outcomes, was not reported. This lack of information threatens the internal validity of the study.

APPENDIX 6: EVIDENCE GAPS

Table A 2. Recommendations for research

Research question: What is the relative clinical effectiveness and safety of remdesivir compared with other interventions, in patients with COVID-19 pneumonia? **Rationale:** No credible evidence comparing the effect of remdesivir with standard care or active treatment, assessing the effect on relevant outcomes, is available.	
Evidence	Adequately powered RCTs are needed. Clinical study reports of all completed trials should be made available.
Population	Patients with COVID-19 pneumonia
Intervention	Remdesivir
Comparator	Standard care and active treatments
Outcomes	mortality; additional need for mechanical ventilation; duration of mechanical ventilation; additional need for mechanical ventilation; duration of mechanical ventilation; additional need for supplemental oxygen; duration of supplemental oxygen; duration of hospitalisation.
Time stamp	Beyond one month
Study design	Adequately powered RCTs

APPENDIX 7: BASELINE CHARACTERISTICS OF THE POPULATIONS INCLUDED IN THE RCTS OF SEVERE COVID-19

Table A 3. Baseline characteristics of the populations included in the RCTs of severe COVID-19

	Beigel 2020, ACTT-1 (NCT04280705)		**Wang et al (NCT04257656)**	
	Remdesivir (n= 541)	**Placebo (n= 522)**	**Remdesivir (n= 158)**	**Placebo (n= 78)**
Follow up time, days	14	14	28	28
Age, years (range)	58,6±14,6	59,2±15,4	66 (57-73)	64 (53-70)
Male sex, n (%)	352 (65,1)	332 (63,6)	89 (56)	51 (65)
Median time from symptom onset, days	9 (6-12)	9 (7-13)	11 (9-12)	10 (9-12)
Hypertension, n (%)	231/469 (49,3)	229/459 (49,9)	72/158 (46)	30 (38%)
Type 2 diabetes	144/470 (30,6)	131/457 (28,7)	40/158 (25)	16/78 (21)
Not requiring supplemental oxygen, n (%)	67 (12,4)	60 (11,5)	0	3 (4,0)
Requiring supplemental oxygen, n (%)	222 (41,0)	199 (38,1)	129 (82)	65 (83)
Receiving noninvasive venti-lation or high-flow oxygen, n (%)	98 (18,1)	99 (19,0)	28 (18,0)	9 (12,0)
Receiving invasive mechanical ventilation or ECMO, n (%)	125 (23,1)	147 (28,2)	1 (1%)	0
Disease severity				
Mild/moderate, n (%)	63 (11,6)	57 (10,9)	0	0
Severe	478 (88,4)	465 (89,1)	158 (100)	78 (100)

Source: Modified from Refs 32 and 33

APPENDIX 8: MAIN OUTCOMES IN THE RCTS ON SEVERE COVID-19

Table A 4. Summary of the main outcomes in trials on severe COVID-19

	Beigel 2020, ACTT-1 (NCT04280705)			Wang et al (NCT04257656)		
	Remdesivir (n= 541)	**Placebo (n= 522)**	**Rate ratio* / hazard ratio****	**Remdesivir (n= 158)**	**Placebo (n= 78)**	**Difference**
Median time to clinical improvement, days (95%CI)	------	------		21.0 (13.0 to 28.0)	23.0 (15.0 to 28.0)	1.23 (0.87 to 1.75)
Median time to recovery, days (95%CI)	11.0 (9.0 to 12.0)	15.0 (13.0 to 19.0)	1.32 (1.12-1.55)*	------	------	------
Day 14 mortality, n (%)	32 (7.4)	54 (13.2)	0.70 (0.47 to 1.04)**	42 (27)	18 (23)	3.5% (-8.1 to 15.1)
Day 28 mortality, n (%)	------	------	------	103 (65)	45 (58)	7.5% (-5.7 to 20.7)
Duration of invasive mechanical ventilation, days (range)	------	------	------	7.0 (4.0 to 16.0)	15.5 (6.0 to 21.0)	-4.0 (-14.0 to 2.0)
Duration of oxygen support, days (range)	------	------	------	19.0 (11.0 to 30.0)	21.0 (14.0 to 30.5)	-2.0 (-6.0 to 1.0)
Duration of hospital stay, days (range)	------	------	------	25.0 (16.0 to 38.0)	24.0 (18.0 to 36.0)	0.0 (-4.0 to 4.0)

Source: Modified from Refs 32 and 33

APPENDIX 9: BASELINE CHARACTERISTICS OF THE POPULATIONS INCLUDED IN THE TRIAL OF MODERATE COVID-19

Table A 5. Baseline characteristics of the populations included in the RCTs of moderate COVID-19

	Spinner 2020, GS-US-540-5774 (NCT04292730)		
	10-day remdesivir (n= 193)	**5-day remdesivir (n= 191)**	**Standard care (n= 200)**
Follow up time, days	11	11	11
Median age, years (IQR)	56 (45-66)	58 (48-66)	57 (45-66)
Male sex, n (%)	118 (61)	114 (60)	125 (63)
Median time from symptom onset, days (IQR)	8 (5-11)	8 (5-11)	9 (6-11)
Hypertension, n (%)	85 (44)	82 (43)	81 (41)
Type 2 diabetes, n (%)	85 (44)	71 (37)	76 (38)
Cardiovascular disease, n (%)	111 (58)	111 (58)	107 (54)
Not requiring supplemental oxygen, n (%)	169 (87)	160 (84)	162 (81)
Requiring supplemental oxygen, n (%)	23 (12)	29 (15)	36 (18)
Receiving noninvasive venti-lation or high-flow oxygen, n (%)	1 (1)	2 (1)	2 (1)
Receiving invasive mechanical ventilation or ECMO, n (%)	0 (0)	0 (0)	0 (0)
Concomitant therapy, n (%)			
Steroids	29 (15)	33 (17)	38 (19)
Hydroxychloroquine/chloroquine	22 (11)	16 (8)	89 (45)
Tocilizumab	1 (1)	1 (1)	10 (5)
Lopinavir-ritonavir	11 (6)	10 (5)	43 (22)

Source: Modified from Ref 36

APPENDIX 10: MAIN OUTCOMES IN THE TRIAL ON MODERATE COVID-19, AT DAY 11

Table A 6. Summary of the main outcomes in the trial on moderate COVID-19

	Spinner 2020, GS-US-540-5774 (NCT04292730)		
	10-day remdesivir (n= 193)	**5-day remdesivir (n= 191)**	**Standard care (n= 200)**
Difference in clinical status distribution vs standard care, odds ratio (95%CI)	NR	1.65 (1.09 to 2.48)	1 (reference)
Mortality, n (%)	2 (1)	0 (0)	4 (2)
Requiring invasive mechanical ventilation or ECMO, n (%)	1 (1)	0 (0)	4 (2)
Receiving noninvasive ventilation or high-flow oxygen, n (%)	0 (0)	5 (3)	7 (4)
Requiring supplemental oxygen, n (%)	12 (6)	7 (4)	11 (6)
Not requiring supplemental oxygen, n (%)	53 (28)	45 (24)	54 (27)

Source: Modified from Ref 36