National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[O] Evidence review for early remdesivir

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Guideline version (Final)

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Objective

This evidence review aims to review and evaluate the evidence on the effectiveness and safety of early remdesivir (7 days or less since symptom onset) for the treatment of adults, young people and children with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of early remdesivir for adults, young people and children with COVID-19?

Note that this review is separate from the NICE evidence review on the use of remdesivir for the treatment of people with COVID-19 who are in hospital and needing low-flow supplemental oxygen.

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Included studies

The searches for evidence were run on 6 January 2022. The search was intended to be rapid and focussed, making efficient use of prior NICE work on remdesivir as far as possible. The search made efficient use of the NICE COVID-19 Surveillance process for NICE guideline 191 and Evidence Summary 27. The methods are described in Appendix B.

The following databases were searched using clinical trial identity numbers: MEDLINE (Ovid) and Embase (Ovd). There was also a search of the NICE Evidence Search Medicines Awareness Daily content (via https://www.evidence.nhs.uk). Full search strategies are provided in Appendix B.

NICE information specialists conducted the searches. The Surveillance strategy was quality assured by a trained NICE information specialist with procedures adapted from the 2016 PRESS Checklist.

A total of 459 studies were screened at title and abstract against the PICO and 48 full text references were obtained and assessed for relevance.

46 studies were excluded. Details of excluded studies are in appendix E.

2 studies are included in this evidence review. A summary of the included studies is shown in Table 1.

Table 1: Summary of included studies

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Gottleib et al 2021 ["PINETREE"] Early Remdesivir to Prevent Progression to Severe COVID-19 in Outpatients Countries: USA (94.5% study participants), EU, Japan	RCT	Non-hospitalised No respiratory support	562 people with confirmed SARS-CoV-2 infection who did not require hospitalisation or respiratory support Median age 50 47% Female At least one ongoing symptom of COVID-19, and symptom onset within 7 days All participants had at least one risk factor for disease progression: age over 60, obesity or other comorbidity [incl. diabetes mellitus, hypertension, cardiovascular or cerebrovascular disease, chronic lung, liver or kidney disease, immune compromise, current cancer, or sickle cell disease] Key exclusions: people previously hospitalised or treated for COVID-19, or vaccinated against COVID-19	Remdesivir (200mg on day 1, 100 mg on day 2 and 3)	Placebo	COVID-19-related hospitalisation or death (at day 14 and 28) COVID-19- related medical visit or death (at day 14 and 28) Hospitalisation (all causes, at day 28) Symptom resolution (patient-reported) Viral load Adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Abd-Elsalam 2021 Remdesivir Efficacy in COVID-19 Treatment: a Randomised Controlled Trial Country: Egypt	RCT	Mild to moderate COVID-19	200 adults with confirmed SARS-CoV-2 infection who were hospitalised 3 days after symptom onset Key exclusions: severe COVID, history of renal impairment, pregnant or lactating mothers	Remdesivir (200mg on day 1, 100 mg on day 2 through to day 10] plus standard care	Standard care composed of zinc, acetyl cysteine, lactoferrin, and vitamin C	Duration of hospital stay Need for mechanical ventilation Mortality

See appendix F for full evidence tables.

Results

What is the effectiveness and safety of early remdesivir for adults, young people and children with COVID-19?

Key results

Among people with COVID-19, the evidence suggests that early use of remdesivir (7 days or less from symptom onset) may reduce the need for further medical care and hospitalisation in people who are unvaccinated and have at least one risk factor for developing severe COVID-19 disease, compared to placebo.

What is the evidence informing this conclusion?

Evidence comes from 2 randomised controlled trials in unvaccinated people that compared remdesivir with placebo or standard care in 762 participants with confirmed SARS-COV-2 infection (Abd-Elsalam 2021; Gottleib 2021). Most data are from the PINETREE trial [Gottleib 2021] which included 562 people with COVID-19. In this study, participants were randomised to remdesivir or placebo within 7 days of symptom onset. Participants in the PINETREE study had at least one ongoing COVID-19 symptom and had at least one risk factor for progression (age 60 and over or a comorbidity). In the Abd-Elsalam study, participants were randomised to remdesivir or standard care within 3 days of symptom onset, and severe COVID-19 patients were excluded. The PINETREE trial took place in outpatient settings while participants in the Abd-Elsalam 2021 study were treated in hospital.

Publication status

Both studies included in this review have been peer-reviewed.

Study characteristics

The severity of COVID across both studies was mild-to-moderate: severe COVID patients did not meet eligibility criteria in either study. The PINETREE study excluded patients requiring supplemental oxygen; the Abd-Elsalam study did not specify whether people requiring supplemental oxygen were excluded. Both studies took place prior to the emergence of the Delta and Omicron variants of COVID-19 and before the availability of vaccination against COVID-19.

Broadly speaking, the remdesivir and control arms in the PINETREE study are similar to one another while in the Abd-Elsalam study, there are meaningful differences in key patient characteristics across the different study arms. Those differences are noted below.

Eligibility criteria for age were similar in both studies: the PINETREE study was open to participants aged 12 and over, the Abd-Elsalam was open to participants aged 18-80. The mean age in the PINETREE study was 50 years, and the mean ages in the Abd-Elsalam study were 55 (remdesivir arm) and 52 (standard care arm). Note that the PINETREE study only enrolled 8 adolescent patients.

The proportion of males in the PINETREE trial was 53%, whereas in the Abd-Elsalam study, men comprised 66% of those in the remdesivir arm and 53% of those in the control arm.

The PINETREE study enrolled participants who were at elevated risk of disease progression due to at least one of the following factors: age 60 and over, obesity, or another comorbidity [incl. diabetes mellitus, hypertension, chronic lung disease among others]. The presence of these comorbidities was balanced across the treatment arms. Participants in the PINETREE study had normal blood tests at baseline. In the Abd-Elsalam study, the presence of diabetes mellitus was significantly higher in the remdesivir arm (39%) than in the placebo arm (27%). Aside from diabetes and hypertension, other comorbid conditions are not specified in the Abd-Elsalam study.

The starting dose and maintenance of intravenous (IV) remdesivir was the same in both studies (200 mg starting dose) followed by 100 mg on subsequent days, but the duration of treatment differed between the studies: 3 days in the PINETREE and 10 days in the Abd-Elsalam study. The cumulative dosage of remdesivir was higher in the Abd-Elsalam study.

Outcomes presented in both studies aimed to measure the differences in risk of disease progression between those treated with remdesivir vs. standard care. The PINETREE study also provided adverse event frequency as a measure of safety.

The PINETREE study was funded by Gilead Sciences; funding source is not disclosed for the Abd-Elsalam study.

What are the main results?

Overall, COVID-19-related medical visits and hospitalisation, as well as serious adverse events, were significantly lower with remdesivir than standard care. Meta-analysis was not conducted for this evidence review. This is because the study populations were too heterogeneous to combine in a meta-analysis, and because there were serious concerns about the risk of bias from the Abd-Elsalam study. See appendix H for full GRADE profiles.

COVID-19-related hospitalisation or death (at day 14 and 28)

The PINETREE trial found a statistically significant reduction in the composite outcome of hospitalisation or death in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

Subgroup analyses presented based on several patient risk factors [age 60 and over male sex, obesity, hypertension, and diabetes] were consistent with the overall finding. For the subgroups of patients with chronic lung disease, cardiovascular or cerebrovascular disease, and cancer, the differences between remdesivir and placebo were not statistically significant. Differences between remdesivir and placebo were also not statistically significant for ethnic subgroups represented in the PINETREE study.

COVID-19-related medical visit or death (at day 14 and 28)

The PINETREE trial found a statistically significant reduction in the composite outcome of medically attended visit or death in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo. Note that this outcome was only reported for 88% of patients in the PINETREE study.

Death

No patients in either arm of the PINETREE study had died at day 28.

The Abd-Elsalam study found no statistically significant difference in mortality in people hospitalised with mild-to-moderate COVID-19 3 days after symptom onset who were treated with remdesivir compared to standard care.

Due to differences in study populations, these outcomes were not combined into meta-analysis.

Hospitalisation (all causes, at day 28)

The PINETREE trial found a statistically significant reduction in all-cause hospitalisation in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

Duration of hospital stay

The Abd-Elsalam study found a statistically significant reduction in the duration of hospital stay in people hospitalised with mild-to-moderate COVID-19 3 days after symptom onset who were treated with remdesivir compared to standard care.

Need for mechanical ventilation

The Abd-Elsalam study found no statistically significant difference in need for mechanical ventilation in people hospitalised with mild-to-moderate COVID-19 3 days after symptom onset who were treated with remdesivir compared to standard care.

Adverse events (any)

The PINETREE trial found no statistically significant difference in the frequency of any adverse event in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo. Adverse events that were determined by the investigators to be related to the trial regimen occurred in 34 of 279 patients (12.2%) in the remdesivir group and in 25 of 283 (8.8%) in the placebo group.

Adverse events measured in the study included (from most to least frequent): nausea, headache, cough, diarrhea, dyspnea, fatigue, ageusia, anosmia, dizziness, chills, pyrexia, and COVID-19 pneumonia.

Serious adverse events

The PINETREE trial found a statistically significant reduction in the frequency of serious adverse events in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

Note that severity grades were defined according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

Discontinuation of trial regimen due to adverse events

The PINETREE trial found no statistically significant difference in the frequency of discontinuation due to adverse events in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

Symptom resolution

The PINETREE trial found no statistically significant difference in the reduction of baseline COVID-19 symptoms among those treated with remdesivir compared to placebo. Note that this outcome is based on patient-reported symptoms in the FLU-PRO plus questionnaire and that data was not available for all patients in the PINETREE study.

Viral load

The PINETREE trial found no statistically significant change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 in people with at least one risk factor for COVID-19 who were treated with remdesivir compared to placebo.

Our confidence in the results

Since both studies cited in this review took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the populations measured in the study may not be directly relevant or comparable to current populations in the UK, where the Delta and Omicron variants are dominant and many people have been vaccinated against COVID-19. As a result, the certainty in all outcomes presented was downgraded due to indirectness.

Altogether, we have moderate confidence in results from the PINETREE study but very low confidence in results from the Abd-Elsalam study.

Most outcomes from the PINETREE study were assessed as being at low risk of bias, and the certainty of the evidence was moderate to high due to large n-size (n>300), appropriate analysis methods used and sufficient information provided to assess the methods. There were some notable exceptions: certainty of evidence presented for two outcomes (COVID-19-related medical visits and patient-reported symptom alleviation) were downgraded due to risk of bias, since this data were only available for an unspecified subgroup of the study population.

All outcomes from the Abd-Elsalam study were assessed as being at high risk of bias, due to significant differences in baseline patient characteristics of those allocated to remdesivir vs. standard care. Evidence from the Abd-Elsalam study was imprecise as the total study n-size was 200 patients (n<300).

Evidence to decision

Benefits and harms

Two randomised controlled trials were included as part of the evidence review for remdesivir in people who do not need supplementary oxygen and are within 7 days of symptom onset, Abd-Elsalam (2021) and PINETREE. Because of serious concerns about risk of bias for Abd-Elsalam and concerns about the comparability of the 2 study populations, the panel focused on PINETREE when making recommendations.

The primary outcome of PINETREE was the composite outcome of COVID-19-related hospitalisation or death from any cause within 28 days. A secondary outcome was the composite outcome of COVID-19-related medical visits or death from any cause within 28 days. Both of these composite outcomes included 'death from any cause within 28 days'. But the panel noted that there were no deaths reported in either arm of the study. So, they considered the frequency of hospitalisations and medical visits in the study to inform the recommendations.

The panel noted that PINETREE enrolled people who had not been vaccinated against COVID-19 and who had at least 1 risk factor for progression to severe COVID-19 (including being over 60, or having a body mass index of 30 or more, hypertension, diabetes, chronic lung disease or other comorbidities). The panel agreed that the evidence in this population suggests there is a reduction in COVID-19-related hospitalisation and COVID-19-related medical visits within 28 days with remdesivir compared with placebo. They also agreed that the results were consistent across the subgroup analyses presented. However, the panel noted that the difference in the absolute number of events between the remdesivir and placebo groups was modest. There were 2 hospitalisations within 28 days with remdesivir compared with 15 hospitalisations within 28 days with placebo. The panel considered that the absolute benefit of remdesivir would potentially be smaller among people who have been vaccinated against COVID-19.

The panel noted that the eligibility criteria for PINETREE included being 12 years and over. However, of the 562 people in the trial, only 8 were between 12 and 18

years, and outcomes were not presented for this group. The panel also noted that the indication for remdesivir for people with COVID-19 who do not need supplemental oxygen and who are at increased risk of progressing to severe COVID-19 includes children and young people weighing 40kg and over as well as adults .

The panel noted that there were no statistically significant differences in the frequency of adverse events:

- among people having remdesivir compared with those having placebo, or
- leading to treatment being stopped.

They noted that people in PINETREE had normal baseline renal function and blood tests. They also noted that serious adverse events were statistically significantly less frequent with remdesivir. Based on this evidence, the panel concluded that there were no serious safety concerns associated with remdesivir in the study.

The panel also discussed the potential benefits and harms of combination treatment with an antiviral drug and a neutralising monoclonal antibody or another antiviral drug in people who do not need supplemental oxygen for COVID-19 and who are at high risk of progression to severe disease.

Certainty of the evidence

The certainty of all outcomes from the PINETREE study was downgraded because of indirectness. This was because it took place before the emergence of the Delta and Omicron variants of COVID-19 and because no one in the study had been vaccinated against COVID-19. The panel agreed that these factors meant that the evidence from PINETREE was not directly relevant to the COVID-19 situation in the UK in early 2022, when the Omicron variant was dominant and many people had been vaccinated against COVID-19. So, the certainty of the evidence for the key outcome that the panel referenced in their decision making (COVID-19-related hospitalisation or death from any cause within 28 days) was rated as moderate.

Some outcomes from PINETREE were downgraded further because of imprecision. This applied to the outcomes for ‘any adverse event’ and ‘adverse event leading to

trial discontinuation', which were graded as low certainty because of imprecision. This was because the confidence interval crossed the line of no effect.

One outcome from PINETREE was downgraded further because of risk of bias. The study authors did not provide data for everyone in the study for 'COVID-19-related medical visit or death from any cause within 28 days'. Also, they did not specify the reasons for the exclusion of people from this outcome, so the certainty in this outcome was rated as low.

The panel noted that the evidence was from people with COVID-19 who were not in hospital. But, they agreed that the results could be generalised to people in hospital for reasons other than COVID-19 who meet the criteria set out in the recommendation.

Values and preferences

The panel were not aware of any systematically collected data on peoples' preferences and values. But, they noted that remdesivir's intravenous mode of delivery is likely to influence patient preference, particularly because it would mean people would need to travel to an infusion site on 3 consecutive days for treatment. The panel discussed that the time involved in the infusion process may affect people's preferences because they would need to set aside time to travel to and from the infusion site. It could also mean they may need to take time away from caring responsibilities or work to have remdesivir. The panel were also aware that some people have a fear of needles or injections.

Resources

The recommendations were not informed by a cost-effectiveness analysis. The panel had concerns about the opportunity costs associated with using remdesivir, including drug costs, costs associated with running outpatient infusion facilities and NHS staff time, and the importance of not diverting resources away from hospital care.

Equity

The panel raised several concerns about potential inequities that may result from this recommendation. Primarily, the panel were concerned that the intravenous mode of delivery for remdesivir could make it inaccessible to subgroups with lower

socioeconomic status. This was because they may not be able to access transport to an infusion facility or take time away from work on consecutive days to complete their treatment. The panel noted that people who use public transport to access their remdesivir infusion might also risk exposing others to COVID-19 throughout their transit. The panel were aware that some trusts provide transport to help people with COVID-19 safely attend infusion appointments, but noted that this may be difficult to access. The panel also noted that people with mobility issues, people with caring responsibilities who need to arrange care cover over consecutive days and people who are homeless or from Traveller communities could face additional barriers in accessing remdesivir treatment.

When discussing the evidence, the panel noted that underrepresentation of several groups in PINETREE could result in inequities. The panel noted that only 8 young people aged 12 to 17, and no one younger than this, were included. It also noted that only 4% of the study population were immunocompromised. Also, the study authors did not specify whether anyone in the study was pregnant.

The panel also noted that people from a minority ethnic family background were underrepresented in the study, including people from a Black or Asian family background. This underrepresentation presented an important inequity issue because COVID-19 incidence and severity in the UK are higher in these groups. The panel were concerned that inequitable access to treatment could exacerbate existing health inequalities. They emphasised that the underrepresentation of these groups in PINETREE, and the subsequent lack of evidence, should not prevent people from these groups, who are otherwise eligible for treatment, from being offered remdesivir.

The panel acknowledged that additional information is needed to understand how potential inequities may arise from this recommendation and how those inequities might be minimised. So, they proposed a research recommendation on remdesivir that includes pregnant women, people from minority ethnic family backgrounds, and children and young people as subgroups of particular interest.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. However, they noted that an intravenous treatment needing 3 consecutive days of infusion may not be acceptable to all people who are eligible for treatment. They noted that alternative treatments may be preferred. The panel thought that it was likely that some people who would qualify for and benefit from treatment with remdesivir to prevent progression to severe COVID-19 may elect not to have treatment. They might instead see if their symptoms resolve without remdesivir treatment.

Feasibility

The panel discussed the availability and feasibility of administering remdesivir in different areas in the UK. They were concerned that some NHS trusts may struggle to accommodate people wanting remdesivir infusions. They noted that COVID-19 Medicine Delivery Units (CMDUs) or similar units in the devolved administrations will be the main hub for people to have these treatments. But they were aware that travel to a CMDU for 3 consecutive days of remdesivir infusions may not be feasible for some people. The panel concluded that there are significant barriers to using remdesivir for people with COVID-19 in the community.

Appendices

Appendix A: PICO table

PICO and eligibility criteria

Question 1:

What is the effectiveness and safety of early remdesivir for adults, young people and children with COVID-19?

Criteria	**Notes**
Population	Adults, young people and children with COVID-19 with symptom onset within the previous 7 days who do not need supplementary oxygen.
Interventions	Remdesivir
Comparators	• Standard care alone, standard care plus placebo, placebo or active comparator Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as corticosteroids, antivirals, and neutralising monoclonal antibodies).
Outcomes	Effectiveness outcomes • Mortality • Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration) • Hospitalisation (requirement and duration) • Supplemental oxygen (requirement and duration) • High-flow oxygen, continuous positive airway pressure or non-invasive respiratory support (requirement and duration) • Symptom resolution or clinical recovery (number and time until) • Clinical worsening / deterioration (number and time until) • Sustained recovery (absence of long-term effects of COVID measured at least 4 weeks from onset of acute COVID-19) • Virological clearance (negative PCR) / viral load Safety outcomes

	• Adverse events • Discontinuation due to adverse events The definitions of mechanical ventilation, non-invasive respiratory support and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive respiratory support:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. **Supplemental oxygen:** includes oxygen via (low flow) nasal cannulae or face mask.
Settings	All settings
Subgroups	• Community vs enhanced medical supervision outside a hospital setting (e.g. oximetry at home or virtual ward) vs hospital • Vaccination status • PCR confirmed COVID-19 vs. not confirmed • COVID-19 variants • Time from symptom onset • Adults > 50 years • Children <12 years of age • Disease severity (mild/moderate) • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • People who are immunocompromised
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs)

	• RCTs If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, and migrant workers.

Appendix B: Literature search strategy/Data source

Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.
A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 6 January 2022. This search report is compliant with the requirements of PRISMA-S.
The search was intended to be rapid and focussed, making efficient use of prior NICE work on remdesivir as far as possible. The search made efficient use of the NICE COVID-19 Surveillance process.

Review management

RIS files were downloaded from each of the steps described below. The search results were then managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The NICE COVID-19 Surveillance process began on 30 March 2020 to cover new journal articles, reports, policy, guidelines, pre-prints and other documents on COVID-19 and SARS-CoV-2 published since 16 March 2020. Weekly and monthly searches are performed of MEDLINE, Embase, bioRxiv and medRxiv, other pre-print sources, BMJ Best Practice, NICE Evidence Search, TRIP database, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL). A number of websites are checked manually (listed in "COVID-19 rapid guideline: Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT): Search strategies. NICE guideline 200").
The search is limited to items published in English. Animal studies, letters, comments, editorial, case reports and conference reports are also excluded.
The MEDLINE and Embase strategies are based on The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines (medRxiv, doi: 10.1101/2021.06.11.21258749). The Information Services team at NICE peer reviewed the principal database strategies according to the standard NICE checklist that was adapted from the 2016 Peer review of electronic search strategies (PRESS) checklist.
The results of these Surveillance searches are processed on a weekly basis using a combination of automated and manual processes. The references that are of potential relevance to NICE are marked and placed into a group for the guidelines or other products to which they relate. These groups use the codeset function in EPPI-R5. By the end of 2021, the Surveillance master EPPI review contained over 250,000 unique records.
NICE published an Evidence Summary (ES27) on remdesivir on 5 June 2020 COVID-19 rapid evidence summary: Remdesivir for treating hospitalised patients with suspected or confirmed COVID-19.

Main search

Method	Date searched	No. of results downloaded
Surveillance of remdesivir for NG191	6 January 2022	296
Surveillance search from 6 January 2022	6 January 2022	29
Surveillance of Evidence Summary 27	6 January 2022	74
References included in Evidence Summary 27	6 January 2022	9
MEDLINE search for clinical trial IDs Ovid MEDLINE(R) ALL 1946 to January 05, 2022	6 January 2022	31
Embase search for clinical trial IDs Embase 1974 to 2022 January 05	6 January 2022	99
Check of the RAPID C19 remdesivir set	6 January 2022	17
Medicines Current Awareness	6 January 2022	3

Total downloaded	558
Duplicates removed	99
Total for screening	459

Search history

Surveillance of remdesivir for NG191

The Surveillance process started to monitor remdesivir in relation to NICE guideline 191 COVID-19 rapid guideline 191: managing COVID-19 from 23 March 2021. Any items of potential relevance were added to a set in EPPI Reviewer. This process was still operating on 6 January 2022. The whole of this set containing 296 items was downloaded on 6 January 2022.

Surveillance search from 6 January 2022

The latest searches for Surveillance used in the step above had been completed on 23 December 2021. The next Surveillance searches were conducted on 6 January 2022 but had not yet been processed for Surveillance. In order to check them for this review, the weekly results were searched within EPPI Reviewer on 6 January 2022 using the terms:

Remdesivir* or GS5734 or Veklury* or "GS-5734"

Clinical trial registry entries were removed manually from the search results in EPPI Reviewer. This produced a total of 29 items.

Surveillance of Evidence Summary 27

The Surveillance process monitored remdesivir in relation to Evidence Summary 27 from 28 May 2020 to 14 April 2021 (when it was replaced by NG191). Any items of potential relevance were added to a set in EPPI Reviewer. The whole of this set, containing 74 items was downloaded on 6 January 2022.

References included in Evidence Summary 27

The steps above using Surveillance meant that items retrieved since 28 May 2020 had been reviewed. The references included in ES27 were used to find references from before that date. This resulted in 9 items being added to the current review on 6 January 2022.

The searches for ES27 were done on 26-27 May 2020 and date limited to 2019-current. During development of ES 27, 328 unique records were processed, of which 17 were reviewed in full text, with 3 being included and 14 being excluded. It was not felt necessary to screen all 328 records again, as they had already been reviewed by NICE.

The 3 trials included in ES27 were added to the current review. The 14 papers that had been excluded were reviewed and a further 6 were added to the current review. Therefore 9 items cited in ES27 were made available in the current review.

The following table, adapted from "Table 1 Summary of included studies" in ES27, shows how the 4 included studies have been processed for the current review.

Study reference	Action taken on 6 January 2022
Beigel et al. 2020 **(Adaptive COVID-19 Treatment Trial-1 study [ACTT])** 10.1056/NEJMoa2007764	Added to the current review. Note that the Final Report has now been published in NEJM and was already available via Surveillance.
Cochrane 2020 **Meta-analysis of Beigel et al. 2020 and Wang et al. 2020**	No action. A later Cochrane Review had been published and was already available via Surveillance. 10.1002/14651858.cd014962.

Grein et al. 2020 10.1056/NEJMoa2007016	Added to the current review.
Wang et al. 2020 10.1016/s0140-6736(20)31022-9	Added to the current review.

The following table from Appendix 3 of ES27 shows how the 14 excluded papers were processed for the current review.

Study reference	Action taken on 6 January 2022
Blasiak A et al (2020). Artificial Intelligence Pinpoints Remdesivir in Combination with Ritonavir and Lopinavir as an Optimal Regimen Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) medrxiv preprint	Added to the current review
Davies M et al (2020). Remdesivir in treatment of COVID-19: A systematic benefit-risk assessment medrxiv	No action – full article has now been published and is already in EPPI from the Surveillance searches.
Gebrie D et al (2020). Efficacy of remdesivir versus placebo for the treatment of COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials medrxiv preprint	No action – full article has now been published and is already via Surveillance.
Goldman JD et al (2020). Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 New England Journal of Medicine	Added to the current review
Grein Jonathan; Myers, Robert P; Brainard, Diana Compassionate Use of Remdesivir in Covid-19. Reply. New England Journal of Medicine 382	No action
Hillaker E et al (2020). Delayed Initiation of Remdesivir in a COVID-19-Positive Patient. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy	No action
Holshue ML et al (2020). First Case of 2019 Novel Coronavirus in the United States New England Journal of Medicine, 382, 10, 929-936	No action
Hsu, C-Y et al (2020). Efficacy of remdesivir in COVID-19 patients with a simulated two-arm controlled study medrxiv	Added to the current review
Kujawski SA et al (2020). First 12 patients with coronavirus disease 2019 (COVID-19) in the United States medRxiv, 2020030920032896	Added to the current review – added the full article rather than this preprint.
Lin, Ting-Yu et al. Impacts of remdesivir on dynamics and efficacy stratified by the severity of COVID-19: a simulated two-arm controlled study medrxiv	Added to the current review
Paul AE et al (2020). Remdesivir use in patients with coronavirus COVID-19 disease: a systematic review and meta-analysis medrxiv preprint	Added to the current review
Spinello A et al (2020). 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. Pharmacological research 104899	No action
Wang Y et al (2020). Evaluation of the efficacy and safety of intravenous remdesivir in adult	No action

patients with severe COVID-19: study protocol for a phase 3 randomized, double-blind, placebo-controlled, multicentre trial. Trials, 21, 1, 422	
Wu J et al (2020). Compassionate Use of Remdesivir in Covid-19. The New England Journal of Medicine 382	No action

Clinical trial searches

In order to ensure that no relevant published clinical trial reports had been missed, a top up search was undertaken on MEDLINE and Embase for the key clinical trials. This was done by obtaining the clinical trial ID numbers from the National Institute for Health Research Innovation Observatory (NIHRIO) Covid-19 Therapeutics and Vaccines in Clinical Development Scan list prepared for NICE. This was last updated on 16 December 2021.
Two lists were obtained, one for remdesivir pivotal trials and the other for remdesivir non-pivotal trials. There were 74 trials in total (27 pivotal; 47 non-pivotal). All trials were used, they were not reviewed for relevance to the current review.
There were 31 items from MEDLINE (24 from the first search and 7 from the second search). There were 99 items from Embase (57 and 42). They were both searched on 6 January 2022.

MEDLINE search for clinical trial IDs

MEDLINE – pivotal trials

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 05, 2022
Search Strategy:

#	Searches	Results
1	(NCT04988035 or NCT04978259 or NCT04843761 or NCT04391309 or NCT04745351 or NCT04640168 or NCT04593940 or NCT04583956 or NCT04583969 or NCT04546581 or NCT04501978 or NCT04492475 or NCT04488081 or NCT04575064 or NCT04349410 or NCT04401579 or NCT04409262 or "JPRN-jRCT2031190264" or JPRNjRCT2031190264 or jRCT2031190264 or NCT04351724 or "2020-001366-11" or "202000136611" or NCT04330690 or "2020-000982-18" or "202000098218" or NCT04321616 or NCT04315948 or NCT04280705 or NCT04292730 or NCT04292899).af.	24

MEDLINE – non-pivotal trials

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 05, 2022
Search Strategy:

#	Searches	Results
1	(IRCT20200426047212N2 or IRCT20151227025726N28 or IRCT20200721048159N4 or NCT05041907 or "CTRI 2021 08 035537" or CTRI202108035537 or NCT05024006 or NCT04970719 or NCT04944082 or IRCT20201229049872N1 or IRCT20200329046892N2 or IRCT20210324050760N1 or NCT04871633 or NCT04853901 or "CTRI 2021 02 031430" or CTRI202102031430 or NCT04779047 or NCT04738045 or NCT04727775 or "CTRI 2020 12	7

	029615" or CTRI202012029615 or NCT04713176 or NCT04596839 or IRCT20161206031255N4 or NCT04678739 or NCT04693026 or NCT04694612 or NCT04647669 or NCT04647695 or IRCT20200404046937N5 or NCT04610541 or "2020-004928-42" or "202000492842" or NCT04560231 or NCT04539262 or NCT04501952 or NCT04492501 or NCT04480333 or "2020-002060-31" or "202000206031" or LBCTR2020043495 or NCT04431453 or NCT04410354 or IRCT20171122037571N2 or IRCT20200405046953N1 or "PER-010-20" or PER01020 or ISRCTN83971151 or NCT04345419 or NCT04323761 or NCT04252664 or NCT04257656 or NCT04302766).af.	

Embase search for clinical trial IDs

Embase was searched in two ways. The clinical trial IDs were searched in the title, abstract, keyword and keyword headings field. Secondly, the IDs were searched in the clinical trial number (.cn) field and then the results were limited to remove letters, editorials and unique MEDLINE content, before being combined with the standard RCT filter that NICE uses from Wong et al. (2006). This was to focus on papers about the remdesivir trials and to exclude the papers where the trials are briefly mentioned.

Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Embase – pivotal trials

Database(s): **Embase** 1974 to 2022 January 05
Search Strategy:

#	Searches	Results
1	(NCT04988035 or NCT04978259 or NCT04843761 or NCT04391309 or NCT04745351 or NCT04640168 or NCT04593940 or NCT04583956 or NCT04583969 or NCT04546581 or NCT04501978 or NCT04492475 or NCT04488081 or NCT04575064 or NCT04349410 or NCT04401579 or NCT04409262 or "JPRN-jRCT2031190264" or JPRNjRCT2031190264 or jRCT2031190264 or NCT04351724 or "2020-001366-11" or "202000136611" or NCT04330690 or "2020-000982-18" or "202000098218" or NCT04321616 or NCT04315948 or NCT04280705 or NCT04292730 or NCT04292899).cn.	363
2	(Remdesivir* or "GS-5734" or GS5734 or Veklury*).tw,kw,kf.	2679
3	1 and 2	113
4	3 not (letter or editorial).pt.	112
5	4 not medline.db.	110
6	random:.tw.	1739103
7	placebo:.mp.	486848
8	double-blind:.tw.	226317
9	or/6-8	2004171

10	5 and 9	48
11	(NCT04988035 or NCT04978259 or NCT04843761 or NCT04391309 or NCT04745351 or NCT04640168 or NCT04593940 or NCT04583956 or NCT04583969 or NCT04546581 or NCT04501978 or NCT04492475 or NCT04488081 or NCT04575064 or NCT04349410 or NCT04401579 or NCT04409262 or "JPRN-jRCT2031190264" or JPRNjRCT2031190264 or jRCT2031190264 or NCT04351724 or "2020-001366-11" or "202000136611" or NCT04330690 or "2020-000982-18" or "202000098218" or NCT04321616 or NCT04315948 or NCT04280705 or NCT04292730 or NCT04292899).ti,ab,kf,kw.	12
12	10 or 11	57

Embase – non-pivotal trials

Database(s): **Embase** 1974 to 2022 January 05
Search Strategy:

#	Searches	Results
1	(IRCT20200426047212N2 or IRCT20151227025726N28 or IRCT20200721048159N4 or NCT05041907 or "CTRI 2021 08 035537" or CTRI202108035537 or NCT05024006 or NCT04970719 or NCT04944082 or IRCT20201229049872N1 or IRCT20200329046892N2 or IRCT20210324050760N1 or NCT04871633 or NCT04853901 or "CTRI 2021 02 031430" or CTRI202102031430 or NCT04779047 or NCT04738045 or NCT04727775 or "CTRI 2020 12 029615" or CTRI202012029615 or NCT04713176 or NCT04596839 or IRCT20161206031255N4 or NCT04678739 or NCT04693026 or NCT04694612 or NCT04647669 or NCT04647695 or IRCT20200404046937N5 or NCT04610541 or "2020-004928-42" or "202000492842" or NCT04560231 or NCT04539262 or NCT04501952 or NCT04492501 or NCT04480333 or "2020-002060-31" or "202000206031" or LBCTR2020043495 or NCT04431453 or NCT04410354 or IRCT20171122037571N2 or IRCT20200405046953N1 or "PER-010-20" or PER01020 or ISRCTN83971151 or NCT04345419 or NCT04323761 or NCT04252664 or NCT04257656 or NCT04302766).cn.	242
2	(Remdesivir* or "GS-5734" or GS5734 or Veklury*).tw,kw,kf.	2679
3	1 and 2	96
4	3 not (letter or editorial).pt.	94
5	4 not medline.db.	94
6	random:.tw.	1739103
7	placebo:.mp.	486848
8	double-blind:.tw.	226317
9	or/6-8	2004171
10	5 and 9	36

11	(IRCT20200426047212N2 or IRCT20151227025726N28 or IRCT20200721048159N4 or NCT05041907 or "CTRI 2021 08 035537" or CTRI202108035537 or NCT05024006 or NCT04970719 or NCT04944082 or IRCT20201229049872N1 or IRCT20200329046892N2 or IRCT20210324050760N1 or NCT04871633 or NCT04853901 or "CTRI 2021 02 031430" or CTRI202102031430 or NCT04779047 or NCT04738045 or NCT04727775 or "CTRI 2020 12 029615" or CTRI202012029615 or NCT04713176 or NCT04596839 or IRCT20161206031255N4 or NCT04678739 or NCT04693026 or NCT04694612 or NCT04647669 or NCT04647695 or IRCT20200404046937N5 or NCT04610541 or "2020-004928-42" or "202000492842" or NCT04560231 or NCT04539262 or NCT04501952 or NCT04492501 or NCT04480333 or "2020-002060-31" or "202000206031" or LBCTR2020043495 or NCT04431453 or NCT04410354 or IRCT20171122037571N2 or IRCT20200405046953N1 or "PER-010-20" or PER01020 or ISRCTN83971151 or NCT04345419 or NCT04323761 or NCT04252664 or NCT04257656 or NCT04302766).ti,ab,kf,kw.	9
12	10 or 11	42

Check of the RAPID-C19 remdesivir set

The NICE programme Research to access pathway for investigational drugs for COVID-19 (RAPID C-19) monitor remdesivir using different selection criteria to NG191 and ES27. The RAPID C-19 set had last been updated on 24 December 2021 and was accessed on 6 January 2022. 17 items were selected from the 104 items in the set, after excluding clinical trial registry entries, trial protocols, commissioning policies and treatment guidelines.

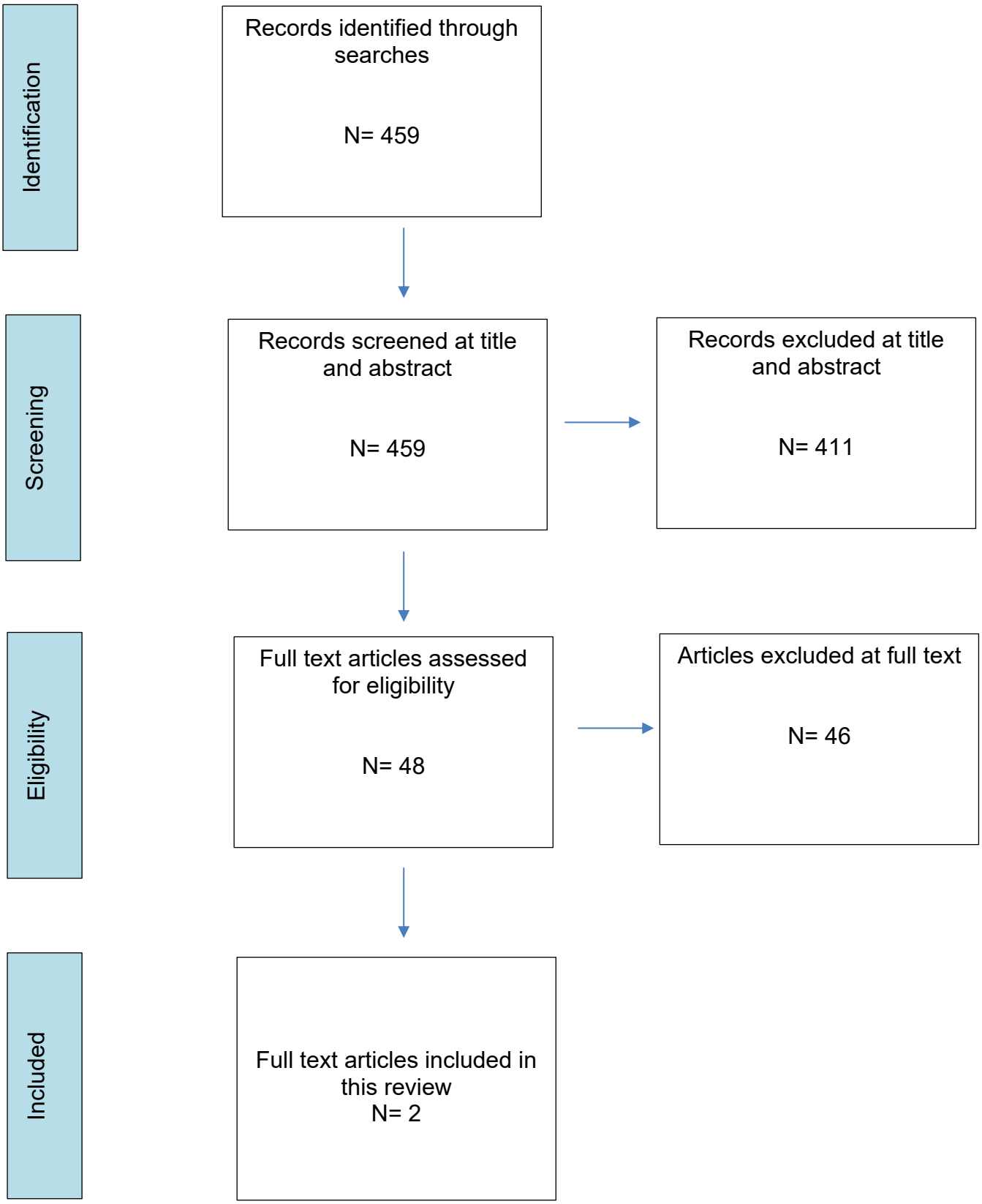
Medicines Current Awareness

The NICE Evidence Search Medicines Awareness Daily content was searched on 6 January 2022 via https://www.evidence.nhs.uk. The following search terms were used:

(coronavirus or covid19 or sarscov2) and (remdesivir or veklury)

The filter Evidence Type>Medicines Current Awareness was applied. No date limits were applied as only MCA content from the last 3 months is available to search. There were 4 results and 3 were relevant to this search and downloaded.

Appendix C: PRISMA diagram



Appendix D: Included studies

Abd-Elsalam, S, Ahmed, OA, Mansour, NO et al. (2021) remdesivir Efficacy in COVID-19 Treatment: a Randomised Controlled Trial. American journal of tropical medicine and hygiene.

Gottlieb, Robert L, Vaca, Carlos E, Paredes, Roger et al. (2021) Early remdesivir to Prevent Progression to Severe COVID-19 in Outpatients. The New England journal of medicine.

Appendix E: Excluded studies at full text screening

Study reference	Reason for exclusion
Bansal, Vikas, Kashyap, Rahul, Mahapure, Kiran S. et al. (2020) Mortality Benefit of remdesivir in COVID-19: A Systematic Review and Meta-Analysis. Frontiers in Medicine 7: 606429	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Criner, Gerard J., Ahn, Mi Young, Huhn, Gregory et al. (2020) Safety of remdesivir vs standard care in patients with moderate COVID-19. Open Forum Infectious Diseases 7(suppl1): 345-s346	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Davies, Miranda, Osborne, Vicki, Lane, Samantha et al. (2020) remdesivir in Treatment of COVID-19: A Systematic Benefit-Risk Assessment. Drug safety	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Jiang, Yawen, Chen, Daqin, Cai, Dan et al. (2020) Effectiveness of remdesivir for the treatment of hospitalized COVID-19 persons: a network meta-analysis. Journal of medical virology	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Piscoya, Alejandro, Ng-Sueng, Luis F., del Riego, Angela Parra et al. (2020) Efficacy and harms of remdesivir for the treatment of COVID-19: A systematic review and meta-analysis. PLoS ONE 15(12december): e0243705	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Shrestha, Dhan Bahadur, Budhathoki, Pravash, Syed, Nawazish-I-Husain et al. (2020) remdesivir: A potential game-changer or just a myth? A systematic review and meta-analysis. Life sciences: 118663	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Siemieniuk, Reed Ac, Bartoszko, Jessica J, Zeraatkar, Dena et al. (2020) Drug treatments for covid-19: Living systematic review and network meta-Analysis. The BMJ 370: m2980	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Thiruchelvam, Kaeshaelya, Kow, Chia Siang, Hadi, Muhammad et al. (2021) The use of remdesivir for the management of patients with moderate-to-severe COVID-19: A systematic review. Expert review of anti-infective therapy	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Verdugo-Paiva, Francisca, Acuna, Maria Paz, Sola, Ivan et al. (2020) remdesivir for the treatment of COVID-19: a living systematic review. Medwave 20(11): e8080	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Wilt, Timothy J., Kaka, Anjum S., MacDonald, Roderick et al. (2020) remdesivir for Adults With COVID-19. Annals of Internal Medicine	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Yokoyama, Y., Briasoulis, A., Takagi, H. et al. (2020) Effect of remdesivir on patients with COVID-19: A network meta-analysis of	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs

randomized control trials. Virus Research 288: 198137	
Zhao, Gang, Cheng, Qinglin, Chen, Junfang et al. (2021) Efficacy and safety of current treatment interventions for patients with severe COVID-19 infection: a network meta-analysis of randomised controlled trials. Journal of medical virology	Systematic review - Out of date (prior to Jan 2021) and will therefore not include the most recent RCTs
Panda Prateek, Kumar, Sharawat Indar, Kumar, Natarajan, Vivekanand et al. (2021) COVID-19 treatment in children: A systematic review and meta-analysis. Journal of family medicine and primary care 10(9): 3292-3302	Systematic review - Non-RCTs [SR; Exclude: SR of case studies only]
De Crescenzo, Franco, Amato, Laura, Cruciani, Fabio et al. (2021) Comparative Effectiveness of Pharmacological Interventions for COVID-19: A Systematic Review and Network Meta-Analysis. Frontiers in pharmacology 12: 649472	Systematic review - Network meta analysis [SR; RCTs [remdesivir]: Beigel 2020, Wang 2020, Spinner 2020, SOLIDARITY; Exclude - Included RCTs not relevant to this review]
Zhang, Chenyang, Jin, Huaqing, Wen, Yifeng et al. A Systematic Review and Network Meta-Analysis for COVID-19 Treatments. medrxiv preprint	Systematic review - Network meta analysis [NMA; Exclude: does not specify which studies contribute to remdesivir endpoints]
Okoli George, N, Copstein, Leslie, Al-Juboori, Amenah et al. (2021) remdesivir for coronavirus disease 2019 (COVID-19): a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials. Infectious Diseases 53(9): 691-699	Systematic review - Included studies not relevant to this review [SR. RCTs included: Beigel 2020, Goldman 2020, Spinner 2020, Wang 2020, SOLIDARITY Exclude - Included RCTs not relevant to this review]
Alexander Paul, E, Piticaru, Joshua, Lewis, Kim et al. remdesivir use in patients with coronavirus COVID-19 disease: a systematic review and meta-analysis. medrxiv preprint	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Wang 2020; Exclude - Included RCTs not relevant to this review]
Zhu, Yun, Teng, Zhaowei, Yang, Lirong et al. Efficacy and Safety of remdesivir for COVID-19 Treatment: An Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. medrxiv preprint	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Wang 2020; Exclude - Included RCTs not relevant to this review]
Enoki, Y., Igarashi, Y., Watabe, Y. et al. remdesivir for the treatment of coronavirus COVID-19: A meta-analysis of randomised controlled trials. Journal of Global Antimicrobial Resistance 24: 81-82	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Spinner 2020, Wang 2020; Exclude - Included RCTs not relevant to this review]
Al-Abdouh, Ahmad, Bizanti, Anas, Barbarawi, Mahmoud et al. (2021) remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. Contemporary clinical trials: 106272	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Spinner 2020, Wang 2020, SOLIDARITY; Exclude - Included RCTs not relevant to this review]
Robinson, Robert, Prakash, Vidhya, Tamimi Raad, Al et al. Impact of remdesivir on 28 day	Systematic review - Included studies not relevant to this review

mortality in hospitalized patients with COVID-19: February 2021 Meta-analysis. medrxiv preprint	[SR; RCTs included: Beigel 2020, Spinner 2020, Wang 2020, SOLIDARITY; Exclude - Included RCTs not relevant to this review]
Tasavon Gholamhoseini, Mohammad, Yazdi-Feyzabadi, Vahid, Goudarzi, Reza et al. (2021) Safety and Efficacy of remdesivir for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques 24: 237-245	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Spinner 2020, Wang 2020, Olender 2020, SOLIDARITY; Exclude - Included RCTs not relevant to this review]
Sarfraz, Azza, Sanchez-Gonzalez, Marcos, Michel, Jack et al. (2021) Randomized controlled trials of remdesivir in hospitalized coronavirus disease 2019 patients: A meta-analysis. Turkish Journal of Emergency Medicine 21(2): 43-50	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Spinner 2020, Wang 2020, Olender 2020 ; Exclude: RCTs evaluated independently and found not to be relevant to this review]
NA Lixiang Lou, Sr., NA Hui Zhang, Sr., NA Zeqing Li, Sr. et al. The efficacy and safety of remdesivir in the treatment of patients with COVID-19: a systematic review and meta-analysis. medrxiv preprint	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Goldman 2020, Wang 2020Non-randomised studies: Grein 2020, Antinori 2020; Exclude: RCTs evaluated independently and found not to be relevant to this review]
Lai, Chih-Cheng; Chao, Chien-Ming; Hsueh, Po-Ren (2021) Clinical efficacy of antiviral agents against coronavirus disease 2019: A systematic review of randomized controlled trials. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Goldman 2020, Wang 2020, Spinner 2020, SOLIDARITY, Kalil 2021 [Baricitinib]; Exclude: RCTs evaluated independently and found not to be relevant to this review]
Tao, Jun, Aristotelidis, Rebecca, Zanowick-Marr, Alexandra et al. (2021) Evaluation of the Treatment Efficacy and Safety of remdesivir for COVID-19: a Meta-analysis. SN comprehensive clinical medicine: 1-12	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Goldman 2020, Wang 2020, Spinner 2020, SOLIDARITY, Kalil 2021 [Baricitinib] Non-randomised studies: Grein 2020, Antinori 2020, Pasquini 2020, Lee 2020, Lapadula 2020, Rivera 2020, Falcao 2021; Exclude: RCTs evaluated independently and found not to be relevant to this review]

Elsokary, Mohamed Ahmed, Elsawah, Hozaifa Khalil, Abdallah, Mahmoud Samy et al. (2021) Efficacy and safety of remdesivir in hospitalized COVID-19 patients: Systematic review and meta-analysis including network meta-analysis. Reviews in Medical Virology 31(4): e2187	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Goldman 2020, Spinner 2020, Wang 2020Non-randomised studies: Grein 2020; Exclude: RCTs evaluated independently and found not to be relevant to this review; non-randomized studies not relevant]
Lai, Chih-Cheng, Chen, Chao-Hsien, Wang, Cheng-Yi et al. (2021) Clinical efficacy and safety of remdesivir in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials. The Journal of antimicrobial chemotherapy	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Goldman 2020, Spinner 2020, Wang 2020, SOLIDARITY; Exclude: RCTs evaluated independently and found not to be relevant to this review]
Singh, Surjit, Khera, Daisy, Chugh, Ankita et al. (2021) Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis. BMJ open 11(6): e048416	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Goldman 2020, Spinner 2020, Wang 2020, SOLIDARITY; Exclude: RCTs evaluated independently and found not to be relevant to this review]
Rezagholizadeh, Afra, Khiali, Sajad, Sarbakhsh, Parvin et al. (2021) remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis. European Journal of Pharmacology 897: 173926	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Goldman 2020, Spinner 2020, Wang 2020, SOLIDARITY Non-randomised studies (n=5); Exclude: RCTs evaluated independently and found not to be relevant to this review; non-randomized studies not relevant]
Zuniga Roberto Ariel, Abeldano, Coca, Silvia, Abeldano, Giuliana et al. Clinical effectiveness of drugs in hospitalized patients with COVID-19 infection: a systematic review and meta-analysis. medrxiv preprint	Systematic review - Included studies not relevant to this review [SR; RCTs [remdesivir]: Wang 2020, Spinner 2020; Exclude: RCTs evaluated independently and found not to be relevant to this review]
Reddy Vegivinti, C.T., Pederson, J.M., Saravu, K. et al. (2021) remdesivir therapy in patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. Annals of Medicine and Surgery 62: 43-48	Systematic review - Included studies not relevant to this review [SR; RCTs included: Beigel 2020, Spinner 2020, Wang 2020, SOLIDARITY; Exclude: RCTs evaluated independently and found not to be relevant to this review]
Crichton Megan, L, Goeminne Pieter, C, Tuand, Krizia et al. (2021) The impact of therapeutics on mortality in hospitalised patients with COVID-19: systematic review	Systematic review - Included studies not relevant to this review

and meta-analyses informing the European Respiratory Society living guideline. European respiratory review : an official journal of the European Respiratory Society 30(162)	[Guideline; RCTs included: Beigel 2020, Goldman 2020, Wang 2020, Spinner 2020, SOLIDARITY; Exclude: Guideline]
Shih, W.J., Shen, X., Zhang, P. et al. (2020) remdesivir is effective for moderately severe patients: A re-analysis of the first double-blind, placebo-controlled, randomized trial on remdesivir for treatment of severe covid-19 patients conducted in wuhan city. Open Access Journal of Clinical Trials 12: 15-21	Post-hoc analysis [Post-hoc analysis based on incomplete study data]
Hosseini, Hamed, Sadeghi, Anahita, Tabarsi, Payam et al. Another step toward final call on remdesivir efficacy as a treatment for hospitalized COVID-19 patients: a multicenter open-label trial. medrxiv preprint	Population not relevant (severe COVID) [Inclusion criteria requires O2 supplementation for at least 72 hours]
Wang, Yeming, Zhang, Dingyu, Du, Guanhua et al. (2020) remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England) 395(10236): 1569-1578	Population not relevant (severe COVID) [Focused on 'severe COVID', all patients in remdesivir arm were on supplemental oxygen. Inclusion criteria: oxygen saturation of 94% or lower, within 12 days of symptom onset]
Ader, Florence, Bouscambert-Duchamp, Maude, Hites, Maya et al. (2021) remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. The Lancet. Infectious diseases	Population not relevant (severe COVID) [All study participants require oxygen supplementation]
Goldman, Jason D, Lye, David C B, Hui, David S et al. (2020) remdesivir for 5 or 10 Days in Patients with Severe COVID-19. The New England journal of medicine 383(19): 1827-1837	Population not relevant (severe COVID)
Sarfraz, Azza, Sarfraz, Zouina, Gonalez Marcos A., Sanchez-Gonalez et al. Randomized placebo-controlled trials of remdesivir in severe COVID-19 patients: A Systematic Review and Meta-analysis. medrxiv preprint	Population not relevant (severe COVID)
Zhao, Gang, Chen, Junfang, Jia, Qingjun et al. (2021) Efficacy and safety of current treatment interventions for patients with severe COVID-19 infection: A network meta-analysis of randomized controlled trials. Journal of Medical Virology	Population not relevant (severe COVID)
Ansems, Kelly, Grundeis, Felicitas, Dahms, Karolina et al. (2021) remdesivir for the treatment of COVID-19. The Cochrane database of systematic reviews 8: cd014962	Population not relevant (other) SR; RCTs included: Beigel 2020, Spinner 2020, Wang 2020, SOLIDARITY;

	While RCTs are already included in review, this study has a specific subgroup analysis for no oxygen at baseline. However, the studies that are cited in that subgroup analysis do not specify whether the patients who had no oxygen at baseline were early in the course of their disease [eg, <10 days between symptom onset and randomisation]
Beigel, John H, Tomashek, Kay M, Dodd, Lori E et al. (2020) remdesivir for the Treatment of COVID-19 - Final Report. The New England journal of medicine 383(19): 1813-1826	Population not relevant (other) ACTT-1 Study Population includes n=138 patients not on supplemental oxygen Median 9 days from symptom onset to randomisation Study results available for no-oxygen subgroup. However, study authors do not specify the median time from symptom presentation to randomisation for the no-oxygen subgroup
Spinner, Christoph D, Gottlieb, Robert L, Criner, Gerard J et al. (2020) Effect of remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 324(11): 1048-1057	Population not relevant (other) 80-84% in each study arm (remdesivir 5/ remdesivir 10/ control) did not require supplemental oxygen but did require medical care. Median 2 days hospitalisation before first remdesivir dose Median duration of symptoms before first dose was 8 days in remdesivir groups (IQR 5-11 days) and 9 days in SoC group (IQR, 6-11). Outcomes not available for the subgroup that did not require supplemental oxygen and was early in their course of disease
WHO Solidarity Trial, Consortium, Pan, Hongchao, Peto, Richard et al. (2021) Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results. The New England journal of medicine 384(6): 497-511	Population not relevant (other) 36% (1325) in remdesivir arm had no supplemental oxygen at entry. Outcomes not available for the subgroup that did not require supplemental oxygen and was early in their course of disease
Marty, Francisco M., Malhotra, Prashant, Gottlieb, Robert L. et al. (2020) remdesivir vs standard care in patients with moderate	Population not relevant (moderate COVID) [Interim study results from Spinner et al 2021]

COVID-19. Open Forum Infectious Diseases 7(suppl1): 166-s167	
Hariyanto, Timotius Ivan, Kwenandar, Felix, Japar, Karunia Valeriani et al. (2021) The effectiveness and safety of remdesivir for the treatment of patients with covid-19: A systematic review and meta-analysis. Anti-Infective Agents 19(3): 333-340	Systematic review - Included studies not relevant to this review [SR; RCTs [remdesivir]: Beigel 2020, Wang 2020, Spinner 2020 Pan 2020, non-RCTs Maffei 2020, Olender 2020; Exclude: RCTs evaluated independently and found not to be relevant to this review]

Appendix F: Evidence tables

Abd-Elsalam, 2021

Bibliographic Reference	Abd-Elsalam, S; Ahmed, OA; Mansour, NO; Abdelaziz, DH; Salama, M; Fouad, MHA; Soliman, S; Naguib, AM; Hantera, MS; Ibrahim, IS; et, al; remdesivir Efficacy in COVID-19 Treatment: a Randomized Controlled Trial; American journal of tropical medicine and hygiene; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04345419
Study start date	16-Jun-2020
Study end date	19-Dec-2020
Aim of the study	Assess the efficacy of remdesivir in hospitalised adult Egyptian patients with COVID-19
Country/geographical location	Egypt: two major hospitals; Tanta University Hospital and Ain-shams University Hospital
Study setting	Hospital
Population description	• All patients admitted to the two hospitals 3 days after the onset of symptoms with PCR–confirmed COVID-19 infection
Inclusion criteria	• Mild or moderate symptoms • Age 18-80

Exclusion criteria	• Exclusion
	  ○ Severe COVID symptoms
	  ○ Dialysis/ renal impairment
	  ○ ALT/ AST levels > 5x normal
	  ○ Contraindication or allergy to remdesivir
	  ○ Pregnant or breastfeeding

Intervention dosage (loading)	200mg (Day 1)
Intervention dosage (maintenance)	100mg (Day 2-10)
Intervention scheduled duration	10 days
Intervention actual duration	10 days
Intervention route of administration	IV

Comparator (where applicable)	Standard care: composed of zinc, acetyl cysteine, lactoferrin, and vitamin C. Paracetamol and a prophylactic anticoagulant were prescribed when indicated.
Methods for population selection/allocation	Randomised
Methods of data analysis	Logistic regression
Attrition/loss to follow-up	N=5 patients in the intervention [remdesivir] group were lost to follow up because they transferred to another hospital N=4 patients in the control [standard care] group were lost to follow up because they transferred to another hospital
Source of funding	Not stated/ Academic
Study limitations (Author)	• Included mild/moderate patients only - may limit generalisability to severe cases • Open-label design • Small sample size • Limited ethnic diversity
Study limitations (Reviewer)	• 'Mild/moderate' symptoms not defined • Small sample size (n=100 in each group) • Patients not vaccinated- may not be generalisable to vaccinated population • Course of treatment is 10 days
Other details	

Study arms

remdesivir (N = 100)
remdesivir + standard care, 200mg remdesivir on day 1 + 100 mg on day 2-10

Standard Care (N = 100)
The standard care was composed of zinc, acetyl cysteine, lactoferrin, and vitamin C

Characteristics

Arm-level characteristics

Characteristic	remdesivir (N = 100)	Standard Care (N = 100)
Age (years) Mean (SD)	55.04 (14.15)	52.02 (16.25)
Gender Male No of events	n = 66 ; % = 66	n = 53 ; % = 53
Diabetes mellitus	n = 39 ; % = 39	n = 27 ; % = 27

Characteristic	remdesivir (N = 100)	Standard Care (N = 100)
No of events		
Hypertension No of events	n = 33 ; % = 33	n = 35 ; % = 35
Smoking No of events	n = 24 ; % = 24	n = 26 ; % = 26
Oxygen saturation (%) Mean (SD)	87.27 (11.43)	89.89 (8.09)

Outcomes

Clinical outcomes of remdesivir vs. control arm

Outcome	remdesivir, , N = 100	Standard Care, , N = 100
Duration of hospital stay (days) Standardised Mean (SD)	12.37 (8.96)	16.72 (5.78)
Duration of hospital stay (days) Median (IQR)	10 (8 to 13.75)	16 (12 to 21)
Need for mechanical ventilation No of events	n = 11 ; % = 11	n = 8 ; % = 8
Deaths No of events	n = 9 ; % = 9	n = 7 ; % = 7

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Parallel RCT

Duration of hospital stay

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes (Treatment allocation was concealed from outcome assessors and patients using sequentially numbered opaque sealed envelopes kept by the hospital pharmacist. Envelopes were opened sequentially only after participant details were written on the envelope.)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes (There are notable differences in baseline characteristics of those treated with remdesivir than in the placebo arm- such that those in the remdesivir arm are more likely to have characteristics associated with poorer outcomes from COVID-19 [the remdesivir arm has a higher proportion of male participants and participants with DM], although this was not significant at p=0.061)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (While study authors state that treatment allocation was random, there are differences between the remdesivir and control arms that suggest potential bias in the randomisation process)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes (*Open label trial*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable

Section	Question	Answer
intended interventions (effect of assignment to intervention)		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended	2.4. Could failures in implementing the intervention have affected the outcome?	No

Section	Question	Answer
interventions (effect of adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes (It is not stated if there were any patients that did not complete the full 10-day course of treatment but this is unlikely as the trial took place in a hospital setting where adherence to therapy is generally high)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes (9 patients in total were lost to follow-up after randomisation because they transferred to another hospital (n=5 from the remdesivir arm, n=4 from the control arm))
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Not applicable
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (There are some serious concerns about the bias in this study due to the differences in key patient characteristics [gender + key comorbidities] between the treatment and control groups. Also, the study did not specify whether people requiring supplemental oxygen were excluded.)
Overall bias and Directness	Overall Directness	Indirectly applicable (Days in hospital is an appropriate proxy for measuring whether early administration of remdesivir prevents progression to severe disease or death. However, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK.)

Need for mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes (Treatment allocation was concealed from outcome assessors and patients using sequentially numbered opaque sealed envelopes kept by the hospital pharmacist. Envelopes were opened sequentially only after participant details were written on the envelope.)
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes (There are notable differences in baseline characteristics of those treated with remdesivir than in the placebo arm- such that those in the remdesivir arm are more likely to have characteristics associated with poorer outcomes from COVID-19 [the remdesivir arm has a higher proportion of male participants and participants with DM])
Domain 1: Bias arising from the	Risk of bias judgement for the randomisation process	Some concerns (While study authors state that treatment allocation was random,

Section	Question	Answer
randomisation process		there are differences between the remdesivir and control arms that suggest potential bias in the randomisation process)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes – open label study
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis)
Domain 2a: Risk of bias due to deviations from the intended	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to	Not applicable

Section	Question	Answer
interventions (effect of assignment to intervention)	analyse participants in the group to which they were randomised?	
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes – open label
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes – open label
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes (It is not stated if there were any patients that did not complete the full 10-day course of treatment but this is unlikely as the trial took place in a hospital setting where adherence to therapy is generally high)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable

Section	Question	Answer
of adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes (9 patients in total were lost to follow-up after randomisation because they transferred to another hospital (n=5 from the remdesivir arm, n=4 from the control arm))
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Not applicable

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (There are some serious concerns about the bias in this study due to the differences in key patient characteristics [gender + key comorbidities] between the treatment and control groups)
Overall bias and Directness	Overall Directness	Indirectly applicable (Need for mechanical ventilation is an appropriate proxy for measuring whether early administration of remdesivir prevents progression to severe disease or death, and it is applicable to the outcome of interest.

Section	Question	Answer
		However, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK)

Deaths

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes (Treatment allocation was concealed from outcome assessors and patients using sequentially numbered opaque sealed envelopes kept by the hospital pharmacist. Envelopes were opened sequentially only after participant details were written on the envelope.)
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes (There are notable differences in baseline characteristics of those treated with remdesivir than in the placebo arm- such that those in the remdesivir arm are more likely to have characteristics associated with poorer outcomes from COVID-19 [the remdesivir arm has a higher proportion of male participants and participants with DM])
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns (While study authors state that treatment allocation was random, there are differences between the remdesivir and control arms that suggest potential bias in the randomisation process)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the	2.2. Were carers and people delivering the interventions aware of participants'	No (Treatment allocation was concealed from outcome assessors and patients

Section	Question	Answer
intended interventions (effect of assignment to intervention)	assigned intervention during the trial?	using sequentially numbered opaque sealed envelopes kept by the hospital pharmacist. Envelopes were opened sequentially only after participant details were written on the envelope.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
intended interventions (effect of adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes (It is not stated if there were any patients that did not complete the full 10-day course of treatment but this is unlikely as the trial took place in a hospital setting where adherence to therapy is generally high)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes (9 patients in total were lost to follow-up after randomisation because they transferred to another hospital (n=5

Section	Question	Answer
		from the remdesivir arm, n=4 from the control arm))
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Not applicable
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (There are some serious concerns about the bias in this study due to the differences in key patient characteristics [gender + key comorbidities] between the treatment and control groups)
Overall bias and Directness	Overall Directness	Indirectly applicable (Deaths is an appropriate proxy for measuring whether early administration of remdesivir prevents progression to severe disease or death, and it is an outcome of interest. However, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK)

Gottlieb, 2021

Bibliographic Reference	Gottlieb, Robert L; Vaca, Carlos E; Paredes, Roger; Mera, Jorge; Webb, Brandon J; Perez, Gilberto; Oguchi, Godson; Ryan, Pablo; Nielsen, Bibi U; Brown, Michael; Hidalgo, Ausberto; Sachdeva, Yessica; Mittal, Shilpi; Osiyemi, Olayemi; Skarbinski, Jacek; Juneja, Kavita; Hyland, Robert H; Osinusi, Anu; Chen, Shuguang; Camus, Gregory; Abdelghany, Mazin; Davies, Santosh; Behenna-Renton, Nicole; Duff, Frank; Marty, Francisco M; Katz, Morgan J; Ginde, Adit A; Brown, Samuel M; Schiffer, Joshua T; Hill, Joshua A; GS-US-540-9012 (PINETREE), Investigators; Early remdesivir to Prevent Progression to Severe COVID-19 in Outpatients.; The New England journal of medicine; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	
Study start date	18-Sep-2020
Study end date	08-Apr-2021
Aim of the study	Evaluate treatment with IV-administered remdesivir (remdesivir) in an outpatient setting in participants with confirmed COVID-19 who are at risk for disease progression.
Country/geographical location	64 sites in the United States, Spain, Denmark, and the United Kingdom. 94.5% of all study participants were from the US.
Study setting	Primary care/Community
Population description	Trial sites included outpatient infusion facilities and skilled nursing facilities, and some participants received infusions at home.

Inclusion criteria	• Eligibility
	  ○ COVID
	  ○ Age >12 eligible;
	  ○ At least one risk factor for progression [Age > 60 OR comorbidity]
	  ○ O2 > 94% on room air
	  ○ Symptom onset within 7 days

Exclusion criteria	• Exclusion
	  ○ Receiving or expected to receive supplemental oxygen or hospital care
	  ○ Previous hospitalisation/ treatment for COVID
	  ○ Vaccinated

Intervention dosage (loading)	Day 1: 200 mg remdesivir
Intervention dosage (maintenance)	Day 2 & Day 3: 100 mg remdesivir
Intervention scheduled duration	3 days

Intervention actual duration	3 days
Intervention route of administration	IV
Comparator (where applicable)	Placebo
Methods for population selection/allocation	Randomised
Methods of data analysis	Kaplan-Meier estimate of the time to hospitalisation related to coronavirus disease 2019 (COVID-19) or death from any cause by day 28 (the primary efficacy end point). Hazard ratio of COVID-19–Related Hospitalisation or Death from Any Cause at Day 28
Attrition/loss to follow-up	2 patients in remdesivir arm and 5 patients in the placebo arm experienced an adverse event leading to discontinuation of trial regimen. Otherwise LTF/ attrition not stated.
Source of funding	Funded by Gilead Sciences; PINETREE ClinicalTrials.gov number, NCT04501952; EudraCT number, 2020-003510-12.
Study limitations (Author)	Our trial has several limitations. • Several risk factors underrepresented: Black or Asian race, chronic liver disease, chronic kidney disease, immunocompromised status, and cancer • Trial was conducted primarily in the United States (94.5% of patients lived in the United States), • Only 8 patients (1.4%) were adolescents. • Excluded vaccinated patients • Conducted before the emergence of the B.1.617.2 (delta) variant of SARS-CoV-2 as the dominant circulating strain. • The trial was stopped for administrative reasons, and less than half of the planned enrolment was achieved. Nonetheless, we observed significantly better clinical outcomes among patients who received remdesivir than among those who received placebo. The discontinuation of the trial because of administrative reasons was unlikely to have introduced bias because no interim statistical analyses were performed, and double blinding was maintained until the data were finalised.
Study limitations (Reviewer)	• Vaccinated patients excluded - given high vaccination rates in the UK, this study may not be helpful in understanding

	the effectiveness of remdesivir as a treatment for people who have been vaccinated and have COVID-19 • Variants of COVID-19 - study does not address remdesivir efficacy against different strains of COVID-19 that are dominant in the UK [Omicron and Delta]
Other details	• Note: aim was to enroll 1230 pts (615 in each group). On April 6 2021, an orderly closure of trial enrollment was announced by the sponsor because of administrative reasons related to a decrease in the incidence of SARS-CoV-2 infections, ethical concerns regarding assigning patients to placebo in the context of increased access to emergency-use–authorised treatments such as monoclonal antibodies, and increasing vaccination rates among high-risk persons

Study arms

remdesivir (N = 279)
200mg day 1; 100 mg day 2 and day 3

Placebo (N = 283)

Characteristics

Arm-level characteristics

Characteristic	remdesivir (N = 279)	Placebo (N = 283)
Age (years (mean)) Mean (SD)	50 (15)	51 (15)
Gender (number) Female No of events	n = 131 ; % = 47	n = 138 ; % = 48.8
White No of events	n = 228 ; % = 81.7	n = 224 ; % = 79.2
Black No of events	n = 20 ; % = 7.2	n = 22 ; % = 7.8
American Indian or Alaska Native No of events	n = 15 ; % = 5.4	n = 21 ; % = 7.4
Asian, Native Hawaiian or Pacific Islander No of events	n = 7 ; % = 2.5	n = 7 ; % = 2.5

Characteristic	remdesivir (N = 279)	Placebo (N = 283)
Hispanic or Latinx No of events	n = 123 ; % = 44.1	n = 112 ; % = 39.6
Other No of events	n = 3 ; % = 1.1	n = 2 ; % = 0.7
Diabetes mellitus No of events	n = 173 ; % = 62	n = 173 ; % = 61.1
Obesity No of events	n = 154 ; % = 55.2	n = 156 ; % = 55.1
Hypertension No of events	n = 138 ; % = 49.5	n = 130 ; % = 45.9
Chronic lung disease No of events	n = 67 ; % = 24	n = 68 ; % = 24
Current cancer No of events	n = 12 ; % = 4.3	n = 18 ; % = 6.4
Cardiovascular or cerebrovascular disease No of events	n = 20 ; % = 7.2	n = 24 ; % = 8.5
Immune compromise No of events	n = 14 ; % = 5	n = 9 ; % = 3.2
Age: 60 years or older (number) Age >= 60 No of events	n = 83 ; % = 29.7	n = 87 ; % = 30.7
Age: under 18 (number) Age < 18 No of events	n = 3 ; % = 1.1	n = 5 ; % = 1.8
BMI Mean (SD)	31.2 (6.7)	30.8 (5.8)
Median duration of symptoms before first infusion (days) Median (IQR)	5 (3 to 6)	5 (4 to 6)
Residence in US No of events	n = 264 ; % = 94.6	n = 267 ; % = 94.3

Outcomes

COVID-19–related hospitalisation or death from any cause

Outcome	remdesivir, , N = 279	Placebo, , N = 283
COVID-19–related hospitalisation or death from any cause by day 28 Primary efficacy endpoint No of events	n = 2 ; % = 0.7	n = 15 ; % = 5.3
Residence in US Total of 264 in remdesivir arm, 267 in placebo arm No of events	n = 2 ; % = 0.8	n = 12 ; % = 4.5
Age >=60 Total of 83 in remdesivir arm, 87 in placebo arm No of events	n = 1 ; % = 1.2	n = 9 ; % = 10.3
Male sex Total of 148 in remdesivir arm, 145 in placebo arm No of events	n = 1 ; % = 0.7	n = 9 ; % = 6.2
Diabetes mellitus Total of 173 in remdesivir arm, 173 in placebo arm No of events	n = 2 ; % = 1.2	n = 14 ; % = 8.1
Obesity Total of 154 in remdesivir arm, 156 in placebo arm No of events	n = 1 ; % = 0.6	n = 9 ; % = 5.8
Hypertension Total of 138 in remdesivir arm, 130 in placebo arm No of events	n = 2 ; % = 1.4	n = 10 ; % = 7.7
Chronic lung disease Total of 67 in remdesivir arm, 68 in placebo arm No of events	n = 0 ; % = 0	n = 4 ; % = 5.9
Cardiovascular or cerebrovascular disease Total of 20 in remdesivir arm, 25 in placebo arm No of events	n = 0 ; % = 0	n = 2 ; % = 8.3
Current cancer Total of 12 in remdesivir arm, 18 in placebo arm No of events	n = 0 ; % = 0	n = 2 ; % = 11.1

Outcome	remdesivir, , N = 279	Placebo, , N = 283
COVID-19–related hospitalisation or death from any cause by day 14 Secondary efficacy endpoint No of events	n = 2 ; % = 0.7	n = 15 ; % = 5.3
Death from any cause by day 28 Secondary efficacy endpoint No of events	n = 0 ; % = 0	n = 0 ; % = 0
Time-weighted average change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 — log10 copies/ml Nominal	-1.24	-1.14
Hospitalisation for any cause by day 28 This analysis was conducted post-hoc No of events	n = 5 ; % = 1.8	n = 18 ; % = 6.4

The primary analysis set for efficacy analysis is defined as the Full Analysis Set, which will include all participants who (1) are randomised into the study, and (2) have received at least 1 dose of study treatment.

COVID-19–related medically attended visit or death from any cause

Outcome	remdesivir, , N = 246	Placebo, , N = 252
COVID-19–related medically attended visit or death from any cause by day 14 No of events	n = 2 ; % = 0.8	n = 20 ; % = 7.9
COVID-19–related medically attended visit or death from any cause by day 28 No of events	n = 4 ; % = 1.6	n = 21 ; % = 8.3

Secondary efficacy endpoint. Data are shown for patients who underwent randomisation, received at least one infusion of remdesivir or placebo, and met eligibility criteria as defined in protocol amendment 2 or later. Protocol amendment 2 added "COVID-19–related medically attended visit or death from any cause" as a secondary endpoint. The key change in eligibility criteria that was introduced in protocol amendment 2 or later was the exclusion criteria around vaccination that was introduced to the study protocol in January 2021 as part of protocol amendment 4 ["Participants who meet any of the following exclusion criteria are not eligible to be enrolled in this study... administration of any SARS-CoV-2 (or COVID-19) vaccine."] Some other inclusion/exclusion criteria were modified in protocol amendment 2.

Alleviated baseline COVID-19 symptoms, according to FLU-PRO Plus questionnaire

Outcome	remdesivir, , N = 66	Placebo, , N = 60
Questionnaire completed before infusion on day 1 No of events	n = 23 ; % = 34.8	n = 15 ; % = 25

FLU-PRO (Influenza Patient-Reported Outcome) Plus questionnaire was adapted for patients with COVID-19, alleviation of COVID-19 symptoms was defined as mild or absent symptoms

Adverse Events

Outcome	remdesivir, , N = 279	Placebo, , N = 283
Any adverse event Primary safety endpoint No of events	n = 118 ; % = 42.3	n = 131 ; % = 46.3
Nausea No of events	n = 30 ; % = 10.8	n = 21 ; % = 7.4
Headache No of events	n = 16 ; % = 5.7	n = 17 ; % = 6
Cough No of events	n = 10 ; % = 3.6	n = 18 ; % = 6.4
Diarrhoea No of events	n = 11 ; % = 3.9	n = 11 ; % = 3.9
Dyspnoea No of events	n = 7 ; % = 2.5	n = 15 ; % = 5.3
Fatigue No of events	n = 10 ; % = 3.6	n = 11 ; % = 3.9
Aguesia No of events	n = 8 ; % = 2.9	n = 7 ; % = 2.5
Anosmia No of events	n = 9 ; % = 3.2	n = 6 ; % = 2.1
Dizziness No of events	n = 5 ; % = 1.8	n = 10 ; % = 3.5
Chills	n = 6 ; % = 2.2	n = 8 ; % = 2.8

Outcome	remdesivir, , N = 279	Placebo, , N = 283
No of events		
Pyrexia No of events	n = 1 ; % = 0.4	n = 11 ; % = 3.9
COVID-19 pneumonia No of events	n = 2 ; % = 0.7	n = 8 ; % = 2.8
Adverse event related to trial regimen No of events	n = 34 ; % = 12.2	n = 25 ; % = 8.8
Serious adverse event Severity grades were defined according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1. No of events	n = 5 ; % = 1.8	n = 19 ; % = 6.7
Adverse event leading to discontinuation of trial regimen No of events	n = 2 ; % = 0.7	n = 5 ; % = 1.8

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Parallel RCT

COVID-19 related hospitalisation or death from any cause by day 14/28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2 and 3) or placebo. Randomisation was stratified according to residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States).)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (Key patient characteristics are broadly similar in both intervention and control group)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis was used)
Domain 2a: Risk of bias due to deviations from the intended	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to	Not applicable

Section	Question	Answer
interventions (effect of assignment to intervention)	analyse participants in the group to which they were randomised?	
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes (It is unclear how many in each group adhered to all 3 days of treatment, but all participants included in the primary efficacy endpoints received at least one dose)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable

Section	Question	Answer
of adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes (The primary analysis set for efficacy analysis is defined as the Full Analysis Set, which will include all participants who (1) are randomised into the study, and (2) have received at least 1 dose of study treatment.)
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low (No missing outcome data)
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No (The outcome [COVID-19 related hospitalisation or death from any cause by day 14 or 28] is an appropriate measure of the ability of early remdesivir treatment to prevent progression to severe COVID. However, there is a risk that the threshold for hospitalisation differs based on the country in which the study takes place)
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed	No

Section	Question	Answer
	between intervention groups ?	
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No (Double blind study, outcome assessors were blinded to intervention allocation)
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (The outcome [COVID-19 related hospitalisation or death from any cause by day 14 or 28] is an appropriate measure of the ability of early remdesivir treatment to prevent progression to severe COVID. However, there is a risk that the threshold for hospitalisation differs based on the country in which the study takes place)
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes (Yes, trial was analysed in accordance with the prespecified study protocol. Some amendments to the study protocol were made to further specify the relevant outcomes and inclusion criteria, but these did not have an affect on the measurement or analysis of the primary efficacy outcomes.)
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes (The outcomes measured are relevant and practical)
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from	Yes/Probably yes

Section	Question	Answer
	multiple analyses of the data?	
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low (Altogether there is a low risk of bias in the outcomes [COVID-19 related hospitalisation or death from any cause by day 14 and 28].)
Overall bias and Directness	Overall Directness	Indirectly applicable (Since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK.)

COVID-19-related medially attended visit or death from any cause by day 14/28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2 and 3) or placebo. Randomisation was stratified according to residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States).)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (Key patient characteristics are broadly similar in both intervention and control group)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
interventions (effect of assignment to intervention)		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis was used)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
of assignment to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes (It is unclear how many in each group adhered to all 3 days of treatment, but all participants included in the primary efficacy endpoints received at least one dose)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
of adhering to intervention)		
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No (This outcome only presents data for a subgroup of patients (246 of the 279 pts randomised to remdesivir and 252 of the 283 randomised to placebo). Study authors explain that "data are shown for patients who... met eligibility criteria as defined in protocol amendment 2 or later" but they do not specify which of the eligibility changes the patients excluded from this analysis failed to meet.)
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Probably no (While there is no specific analysis method or detailed explanation to compensate for the missing outcomes data, the outcomes presented for this subgroup are comparable to the study-wide outcomes [re: hospitalisation or death within 14/28 days].)
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Probably no (Missing outcome data occurred for documented reasons that are unrelated to the outcome)
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No (The outcome [COVID-19 related medically attended visit or death from any cause by day 14 or 28] is an appropriate measure of the ability of early remdesivir treatment to prevent progression to severe COVID. However, there is a risk that the threshold for a medically attended visit differs based on the country in which the study takes place)

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No (Double blind study, outcome assessors were blinded to intervention allocation)
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (The outcome [COVID-19 related medically attended visit or death from any cause by day 14 or 28] is an appropriate measure of the ability of early remdesivir treatment to prevent progression to severe COVID and is unlikely to be at risk of bias)
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes (This secondary outcome was added to the study as part of protocol amendment 2)
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes (The outcomes measured are relevant and practical)
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Yes/Probably yes

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (While this outcome is appropriate and there is a low risk of bias in the measurement, there are some concerns about the potential for bias since the outcome is measured only for a subgroup of the study population, and reasons for exclusion are not provided)
Overall bias and Directness	Overall Directness	Indirectly applicable (Since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK)

Death from any cause by day 28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2 and 3) or placebo. Randomisation was stratified according to residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States).)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (Key patient characteristics are broadly similar in both intervention and control group)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis was used)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes (It is unclear how many in each group adhered to all 3 days of treatment, but all participants included in the primary efficacy endpoints received at least one dose)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes (The primary analysis set for efficacy analysis is defined as the Full Analysis Set, which will include all participants who (1) are randomised into the study, and (2) have received at least 1 dose of study treatment.)
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low (No missing outcome data)
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No (The outcome [death from any cause by day 28] is an appropriate measure of the ability of early remdesivir treatment to prevent progression to severe COVID and death)
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No (Double blind study, outcome assessors were blinded to intervention allocation)

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (The outcome [death from any cause by day 14 or 28] is unlikely to be at risk of bias)
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes (Yes, trial was analysed in accordance with the prespecified study protocol. Some amendments to the study protocol were made to further specify the relevant outcomes and inclusion criteria, but these did not have an affect on the measurement or analysis of the primary efficacy outcomes.)
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes (The outcomes measured are relevant and practical)
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Yes/Probably yes
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low (Altogether there is a low risk of bias in the outcome [death from any cause by day 28].)
Overall bias and Directness	Overall Directness	Indirectly applicable (Since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this

Section	Question	Answer
		outcome may not be directly applicable to the current situation of COVID-19 in the UK)

Hospitalisation from any cause by day 28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2 and 3) or placebo. Randomisation was stratified according to residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States).)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (Key patient characteristics are broadly similar in both intervention and control group)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no

Section	Question	Answer
of assignment to intervention)		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis was used)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No (Double-blind study)

Section	Question	Answer
of adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes (It is unclear how many in each group adhered to all 3 days of treatment, but all participants included in the primary efficacy endpoints received at least one dose)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes (The primary analysis set for efficacy analysis is defined as the Full Analysis Set, which will include all participants who (1) are randomised into the study, and (2) have received at least 1 dose of study treatment.)
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low (No missing outcome data)
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No (The outcome is an appropriate measure of the ability of early remdesivir treatment to prevent progression to severe COVID and death)
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No (Double blind study, outcome assessors were blinded to intervention allocation)
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (The outcome is unlikely to be at risk of bias)
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes (Yes, trial was analysed in accordance with the prespecified study protocol. Some amendments to the study protocol were made to further specify the relevant outcomes and inclusion

Section	Question	Answer
		criteria, but these did not have an affect on the measurement or analysis of the primary efficacy outcomes.)
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes (The outcomes measured are relevant and practical)
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Yes/Probably yes
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low (Altogether there is a low risk of bias in the outcome.)
Overall bias and Directness	Overall Directness	Indirectly applicable (Since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK)

Symptom alleviation (based on patient-reported FLU-PRO Plus Questionnaire)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	No information

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low (There were no notable deviations from intended interventions; all analyses are on an ITT basis)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low (While deviations from intended interventions could have an impact on the outcome [patient-reported alleviation of symptoms], it is unlikely that this outcome is at risk of systematic bias.)
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No (Data was only available for 66 of the 279 participants randomised to remdesivir, and 60 of the 283 participants randomised to placebo. Study authors do not specify why this is the case, it is plausible that the FLU-PRO questionnaire was optional for participants to complete.)
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No (No evidence is provided to confirm that the outcomes are not biased by missing outcomes data)
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	No information
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	No
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Probably no
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Probably no (A standardised questionnaire, typically used to measure symptoms of the flu, was used in this study to measure participant's symptoms from COVID-19. However, patient-reported outcomes [vs. clinical outcomes] may be at risk of bias.)

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Yes (If participants were aware of the intervention [remdesivir or placebo] that they received, there could be systematic biases in their self-reported symptom alleviation in the FLU-PRO survey. However, the study was double-blind so it is unlikely that this bias influenced the outcomes.)
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Yes/Probably yes
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (There are some concerns about the risk of bias for this outcome because (1) outcome data is only available for an unspecified subset of the study population and (2) potential for bias from patient-reported outcomes)
Overall bias and Directness	Overall Directness	Indirectly applicable (This outcome is an appropriate measure of the ability of remdesivir to impact on the symptomatic presentation of COVID-19. However since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK)

Reduction in viral load

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No

Section	Question	Answer
assignment to intervention)		
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No

Section	Question	Answer
adhering to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	No
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the	Not applicable

Section	Question	Answer
	outcome depended on its true value?	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Yes
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Yes/Probably yes

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable (Viral load is a proxy for the effectiveness of remdesivir. Also, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK.)

Adverse Events (Any, serious, leading to trial discontinuation)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes (Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2 and 3) or placebo. Randomisation was stratified according to residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States).)
Domain 1: Bias arising from the randomisation process	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
Domain 1: Bias arising from the randomisation process	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No (Key patient characteristics are broadly similar in both intervention and control group)
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	No/Probably no
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes (ITT analysis was used)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No (Double-blind study)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.4. Could failures in implementing the intervention have affected the outcome?	Yes
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.5. Did study participants adhere to the assigned intervention regimen?	Yes (It is unclear how many in each group adhered to all 3 days of treatment, but all participants included in the primary efficacy endpoints received at least one dose)
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Not applicable
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes (The primary analysis set for efficacy analysis is defined as the Full Analysis Set, which will include all participants who (1) are randomised into the study, and (2) have received at least 1 dose of study treatment.)
Domain 3. Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
Domain 3. Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
Domain 3. Bias due to missing outcome data	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low (No missing outcome data)
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No (The outcome [death from any cause by day 28] is an appropriate measure of the ability of early remdesivir treatment to prevent progression to severe COVID and death)
Domain 4. Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	No
Domain 4. Bias in measurement of the outcome	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No (Double blind study, outcome assessors were blinded to intervention allocation)
Domain 4. Bias in measurement of the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
Domain 4. Bias in measurement of the outcome	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by	Not applicable

Section	Question	Answer
	knowledge of intervention received?	
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low (The outcome [death from any cause by day 14 or 28] is unlikely to be at risk of bias)
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes (Yes, trial was analysed in accordance with the prespecified study protocol. Some amendments to the study protocol were made to further specify the relevant outcomes and inclusion criteria, but these did not have an affect on the measurement or analysis of the primary efficacy outcomes.)
Domain 5. Bias in selection of the reported result	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Yes/Probably yes (The outcomes measured are relevant and practical)
Domain 5. Bias in selection of the reported result	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Yes/Probably yes
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable (Since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK)

Appendix G: Forest Plots

Forest plots were not produced as meta-analysis was not possible in this review.

Appendix H: GRADE profiles

Remdesivir compared to standard care or placebo for COVID-19 (symptom onset within the last 7 days)

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard care or placebo	With remdesivir	Relative effect (95% CI)	Risk with standard care or placebo	Risk difference with remdesivir
Covid-19–related hospitalization or death from any cause by day 28											
562 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	15/283 (5.3%)	2/279 (0.7%)	**RR 0.14** (0.03 to 0.59)	53 per 1,000	**46 fewer per 1,000** (from 51 fewer to 22 fewer)
Alleviated baseline COVID-19 symptoms [based on FLU-PRO Plus questionnaire]											
126 (1 RCT)	not serious	not serious	serious[a]	very serious[b]	none	Very low	15/60 (25.0%)	23/66 (34.8%)	**RR 1.39** (0.81 to 2.41)	250 per 1,000	**97 more per 1,000** (from 47 fewer to 353 more)
Adverse event leading to discontinuation of trial regimen											
562 (1 RCT)	not serious	not serious	serious[a]	serious[c]	none	Low	5/283 (1.8%)	2/279 (0.7%)	**RR 0.41** (0.08 to 2.07)	18 per 1,000	**10 fewer per 1,000** (from 16 fewer to 19 more)
Serious adverse event											
562 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	19/283 (6.7%)	5/279 (1.8%)	**RR 0.27** (0.10 to 0.70)	67 per 1,000	**49 fewer per 1,000** (from 60 fewer to 20 fewer)
Covid-19–related hospitalization or death from any cause by day 14											

Certainty assessment							Summary of findings				
562 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	15/283 (5.3%)	2/279 (0.7%)	**RR 0.14** (0.03 to 0.59)	53 per 1,000	**46 fewer per 1,000** (from 51 fewer to 22 fewer)
Covid-19–related medically attended visit or death from any cause by day 28											
498 (1 RCT)	serious[d]	not serious	serious[a]	not serious	none	Low	21/252 (8.3%)	4/246 (1.6%)	**RR 0.20** (0.07 to 0.56)	83 per 1,000	**67 fewer per 1,000** (from 77 fewer to 37 fewer)
Covid-19–related medically attended visit or death from any cause by day 14											
498 (1 RCT)	serious[d]	not serious	serious[a]	not serious	none	Low	20/252 (7.9%)	2/246 (0.8%)	**RR 0.10** (0.02 to 0.43)	79 per 1,000	**71 fewer per 1,000** (from 78 fewer to 45 fewer)
Death											
200 (1 RCT)	serious[e]	not serious	serious[a]	very serious[f]	none	Very low	7/100 (7.0%)	9/100 (9.0%)	**RR 1.29** (0.50 to 3.32)	70 per 1,000	**20 more per 1,000** (from 35 fewer to 162 more)
Hospitalisation from all causes by day 28											
562 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	18/283 (6.4%)	5/279 (1.8%)	**RR 0.28** (0.11 to 0.75)	64 per 1,000	**46 fewer per 1,000** (from 57 fewer to 16 fewer)
Need for mechanical ventilation											
200 (1 RCT)	serious[e]	not serious	serious[a]	very serious[f]	none	Very low	8/100 (8.0%)	11/100 (11.0%)	**RR 1.38** (0.58 to 3.27)	80 per 1,000	**30 more per 1,000** (from 34 fewer to 182 more)
Any adverse event											

Certainty assessment							Summary of findings				
562 (1 RCT)	not serious	serious[a]	serious[c]	not serious	none	Low	131/283 (46.3%)	118/279 (42.3%)	**RR 0.91** (0.76 to 1.10)	463 per 1,000	**42 fewer per 1,000** (from 111 fewer to 46 more)
Duration of hospital stay											
200 (1 RCT)	serious[e]	not serious	serious[a]	not serious	none	Low	100	100	-	The mean duration of hospital stay was **0**	MD **4.35 lower** (6.44 lower to 2.26 lower)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations
b. Certainty of this outcome was downgraded because the confidence interval includes no effect and the n-size for this outcome was <300.
c. Certainty of this outcome was downgraded because the confidence interval includes no effect.
d. Certainty of this outcome was downgraded because data were only available for a subset (88%) of the full study population, study authors did not provide a clear explanation as to why some patients were excluded from this analysis.
e. Certainty of this outcome was downgraded because of serious concerns about the randomisation approach used in the study. There were significant baseline differences between the remdesivir and placebo groups that could have biased the outcome: specifically, a higher proportion of males and greater incidence of diabetes mellitus among patients in the remdesivir arm compared to patients in the placebo arm
f. Certainty in this outcome is further downgraded due to small n-size and because the confidence interval includes no effect.