Multiple Technology Appraisal

Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Gilead
   a. Draft Guidance comments
   b. CROI 2024 paper, Mozaffari, E. *et al*: "Remdesivir+dexamethasone vs. dexamethasone for the treatment of COVID-19: real-world study in the US"
   c. CROI 2024 paper, Mozaffari, E. *et al*: "Remdesivir reduces mortality in immunocompromised patients hospitalised for COVID-19 during Omicron"
   d. CROI 2024 paper, Mozaffari, E. *et al*: "Disparities in treatment initiation by race and ethnicity among patients hospitalized for COVID-19"
   e. CROI 2024 paper, Mozaffari, E. *et al*: "Characteristics and outcomes of kidney transplant patients hospitalized for COVID-19 in the United States"
   f. CROI 2024 paper, Mozaffari, E. *et al*: "CROI 2024 Mozaffari - LFO mortality"
   g. CROI 2024 paper, Berry M. *et al*: "Effect of Remdesivir on Post-COVID Conditions Among Individuals Hospitalized with COVID-19 by Age"

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. British Infection Association
   b. Faculty of Pharmaceutical Medicine

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company response to the DG**

5. **Hospital mortality data from the OpenSAFELY - TPP database**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

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Draft Guidance comments form

Consultation on the Draft Guidance document – deadline for comments 5pm on Thursday 8 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology. • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Gilead Sciences Ltd 280 High Holborn London WC1V 7EE
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted] [redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Page 3 – **Highly restrictive patient population** **Gilead is concerned that the requirement to meet the McInnes criteria in combination with the LFO requirement will severely restrict access for patients who are most likely to benefit from remdesivir.** Patients who receive low-flow oxygen (LFO) and who do not meet the high risk (McInnes) criteria will not have access to remdesivir under the current draft guidance, even though several meta-analysis and large real-world evidence (RWE) studies have shown a clear mortality benefit for LFO patients. [1-4] Similarly, those individuals at highest risk of progression to severe COVID would not be able to access remdesivir unless they are already receiving LFO (i.e. have progressed to severe disease), This negates the benefit of remdesivir access earlier in the disease course, prior to supplemental oxygen being required. For example, a stem-cell transplant recipient requiring conditioning chemotherapy pre-transplant, who has COVID on admission to hospital (but are not receiving LFO), would be ineligible for access to any COVID antiviral under this guidance. The expert advice received by the committee confirmed that all people admitted to hospital who receive low-flow oxygen are critically unwell. This evidence should be considered by the Committee when reaching its decision on access to treatment, bearing in mind that the McInnes criteria were aimed to identify individuals at high risk of progressing to severe COVID-19 disease and the patients admitted to hospital with COVID-19 on LFO already meet that definition. It is therefore unnecessary to additionally impose the McInnes criteria on such patients and it represents an inappropriate use of such criteria.
2	Page 4 – **NICE considers remdesivir to be only cost-effective for patients who have a high risk of serious illness – this statement does not align with the cost-effectiveness results shown during the third appraisal committee meeting** All 27 cost-effectiveness scenarios presented by the evidence assessment group (EAG) indicated that remdesivir was cost-effective, with an ICER below £30,000 in each of those scenarios (Slide 29 of the committee slides shows only 25 out of 27 scenarios to be cost-effective, which is not accurate, considering the PAS price Gilead has submitted). On top of that high-efficacy scenarios for remdesivir were not shown, thus potentially introducing bias to the committee's decision making. At the third meeting and considering the cost-effectiveness results, NICE chair Stephen O'Brien, referred to the cost-effectiveness results as "a sea of green" (i.e. demonstrating cost-effectiveness). Against this background, a conclusion which recommends remdesivir only in a very narrowly defined group of high risk patients is not credible and disregards the evidence from the experts that "people having low-flow oxygen are considered to be critically unwell" (paragraph 3.4) irrespective of other risk factors.
3	Page 8 - **Committee has misrepresented Gilead's positioning of remdesivir treatment**

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	At paragraph 3.4, the ACD states that "Gilead positioned remdesivir only for adults with pneumonia needing low-flow oxygen, for adults with pneumonia needing low-flow oxygen who are immunocompromised and for children". This is incorrect. Gilead stated that remdesivir should be recommended for use in adults who are immunocompromised irrespective of whether they require low-flow oxygen.
4	Page 9 – **Committee has documented advice from experts that patients requiring low-flow oxygen (LFO) are critically unwell – yet the committee fails to acknowledge the mortality risk for those patients** The draft guidance documents advice from experts that patients who require LFO are critically unwell. The committee does not disagree with or otherwise challenge that conclusion but, nonetheless, has failed to acknowledge that those patients – should they not get active treatment with one of the treatment options recommend by NICE as part of the multiple technology appraisal (MTA) – have a high rate of mortality.
5	Page 26 – **Amstutz et al. meta-analysis: Sensitivity analysis "did not show a significant difference in relative benefit between the no oxygen and the low-flow oxygen groups" – this statement is misleading** The wording used in the draft guidance is not reflective of the actual wording used in the official publication from Amstutz et al. 2023 (page 8).[1] In their publication, Amstutz et al. use the following wording:[1] *"The sensitivity analysis, which investigated oxygenation in more detail (appendix p 36), suggested that patients who were receiving no oxygen at baseline derived a similar relative benefit (aOR 0·86, 95%\ CI 0·53–1·39 with and 0·77, 0·34–1·74 without additional WHO Solidarity data) to patients receiving low-flow oxygen (0·79, 0·68–0·92 with and 0·59, 0·43–0·82 without additional WHO Solidarity data)."* As can be seen from the quote above, the authors described the relative benefit between the no oxygen group and the LFO group as "similar". Even though the results between no oxygen and LFO were described as similar by Amstutz et al., this doesn't justify ignoring the results of the more appropriate subset of data to reflect the LFO patient population for which Gilead is seeking reimbursement.[1] Importantly, Amstutz et al. did NOT say that the results between the LFO (with SOLIDARITY) and LFO (without SOLIDARITY) group are similar.[1] In fact, results for those two groups are very different, as shown below: LFO (with SOLIDARITY): 0.79, 0.68–0.92 → this is what the EAG used in their model LFO (without SOLIDARITY): 0.59, 0.43–0.82 → this is what should have been used in the model The difference between these two estimates is rather large. Comparing these relative treatment benefits, we can see that they show a difference of 0.20 (0.79 vs. 0.59). In other words, LFO (with SOLIDARIRTY) shows a 21% reduction in the odds of mortality compared to a 41% percent reduction in odds of mortality when using the LFO (without SOLIDARITY) data. This is almost double and demonstrates a large effect difference between the two datasets. Consequently, the LFO (without SOLIDARITY) dataset should be used for decision making.
6	Page 27 – **The draft guidance states that "The committee recalled the consideration from earlier meetings that including SOLIDARITY in the NMA was important and appropriate for**

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	remdesivir" – this is seriously misleading, given that the scope of the evaluation has changed since those earlier meetings Before the appeal of the final draft guidance, Gilead highlighted the importance of the SOLIDARITY trial for the assessment of an all-hospitalised patient population with oxygen.[5] This was important at the time as NICE did not differentiate between the level of oxygenation patients were receiving. Older versions of the EAG model – which were aligned with the scope of the NICE assessment back then – only distinguished between patients with or without oxygen in hospital. However, following the successful appeal, the scope of the MTA has changed, given that the appeal panel instructed NICE to assess the benefit of remdesivir in a LFO patient population specifically, rather than in the broader hospitalised population with oxygen. As mentioned in the Amstutz et al. paper, the SOLIDARITY trial did not distinguish between level of oxygenation.[1, 5] Therefore, no conclusions can be drawn from the SOLIDARITY trial on the benefits of remdesivir in the LFO population. This also implies that the NMA results from the Amstutz paper should be used which do not include the SOLIDARITY trial, i.e. LFO (without SOLIDARITY).[1] These results demonstrate a robust mortality benefit for remdesivir, with an adjusted OR of 0.59 (0.43–0.82). Gilead is concerned that the reasons why Gilead was initially arguing for the inclusion of SOLIDARITY and – following the appeal – is now arguing for why SOLIDARITY should be excluded for the assessment of the LFO population are not fully understood by the committee and thus might have a negative impact on decision making.
7	Page 33 – **The mortality rate applied by the committee is not appropriate and does not reflect LFO mortality rates seen in current clinical practice.** The draft guidance provides a wide range for the mortality rate between 2 and 12%. As stated in the draft guidance, these estimates were informed by two clinical experts. In a phone call with NICE on the 15th of December 2023, Gilead was informed that NICE considered the mortality rate to be 7%. This value does not appear in the draft guidance, and the origin of the 7% mortality rate has not been cited by NICE. Any reliance of a figure of 7% therefore lacks transparency and there is, so far as Gilead is aware, no robust rationale for selecting this figure. Instead, the 7% mortality rate appears to be the average of the two estimates provided by the clinical experts. This 7% estimate is severely misleading given that the 2% mortality refers to an "overall population", that wasn't specified in more detail during the appraisal committee meeting. Given the lack of detail around the 2% estimate, this estimate should not be considered to calculate an average, as has presumably been done by NICE. Looking at ONS data published on the COVID-19 dashboard, a proxy mortality rate can be calculated by dividing the COVID-19 deaths by the number of COVID-19 patients admitted to hospital. Using the most recent one-year dataset (01.01.23 – 19.12.23) from UKHSA yields a mortality rate of approximately 9% (deaths: 15,021; hospitalisations: 172,984; data retrieved on 30.01.2024).[6] Given that this data does not distinguish between oxygenation status or treatment received, it is likely to represent the lower threshold for the mortality rate in the LFO population. [redacted].[7] This is likely to represent an upper estimate of the mortality rate.

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	Therefore, a more plausible range for the mortality rate is somewhere between 9 and 22%. Most published real-world evidence (RWE) of studies focused on the LFO population falls into this range. Mozaffari et al. for example report a mortality rate of 12.3% in the comparator arm, summarizing data for over 65,000 LFO patients.[4] Similarly, a study which evaluated more than 1.6 million hospitalisations for COVID-19 in the US reported an overall inpatient mortality of 13.2%.[8] Data accepted for presentation at the 2024 CROI conference (March 3rd-6th) indicate 28 day mortality rates of 9.8% (1,196 deaths /12,211 LFO patients receiving standard of care (dexamethasone monotherapy); Use of remdesivir with dexamethasone had a significantly lower mortality risk compared to dexamethasone monotherapy in LFO patients (adjusted HR 0.74 [0.68-0.80]). Importantly, this real-world evidence was generated during the Omicron period (December 2021 to April 2023) and should therefore alleviate some of the committee's uncertainty regarding the clinical efficacy of remdesivir. The RWE data from the US study [8] is aligned with the 14% estimate that has been used previously in the EAG model, which also represents the background mortality estimate against which other COVID treatments that have been recommended by NICE were judged against. Just because the MTA process for remdesivir got delayed due to the appeal of the initial final draft guidance, which documented significant shortcomings in the assessment procedure, it should not impact decision making for remdesivir by adjusting model parameters which have been used to recommend other treatments in the past, especially not when the latest evidence suggests that the input parameter hasn't changed significantly.
8	Page 34 & page 39 – **Even though the committee was aware of the high mortality rate for immunocompromised patients, it failed to recommend remdesivir in this subgroup** The draft guidance references a mortality rate of up to 25% for immunocompromised patients based on a publication by Evans et al., which include data from the Omicron period.[9] The data from Evans et al. leveraged NHS Digital data, and collected a random 25% sample of this dataset, resulting in a patient population of almost 12 million patients, of which roughly 500,000 were immunocompromised.[9] Given the large size and quality of the dataset, the data from Evans is representative for England and therefore is not "highly uncertain" as stated in the draft guidance. Data accepted for presentation at the 2024 CROI conference (March 3rd-6th) demonstrate during the Omicron era, a 28 day mortality rate of 19.2% in >10,000 hospitalised immunocompromised patients. After adjusting for baseline and clinical covariates, those receiving remdesivir showed significantly lower mortality risk compared to non-RDV overall (adjusted hazard ratio [95% CI]: 0.75 [0.68-0.83]) in patients with no supplemental oxygen requirements (0.72 [0.61-0.85]) and in patients with any supplemental oxygen requirement (0.77[0.68-0.87]) at 28 days. Regardless of this high mortality rate for immunocompromised patients, NICE recommends remdesivir only for patients who require LFO and who meet the high risk criteria from McInnes, despite the strong evidence which showcases the mortality benefit for remdesivir in a standalone immunocompromised patient population.[10] In doing so, NICE fails to give access to the broader patient population of all hospitalised patients who are immunocompromised, despite the statement on Page 39 'The committee considered that for immunocompromised people, the mortality rate was likely to be higher than 14%, so remdesivir is a cost-effective use of NHS resources in this group'.
9	Page 39 – **The committee's preferred assumptions do not reflect the available evidence for remdesivir**

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	<u>The committee failed to acknowledge the benefit remdesivir has on clinical improvement:</u> Gilead is concerned that the NICE committee has not appropriately considered the evidence for remdesivir which shows the benefits in clinical improvement. Evidence for the LFO population shows that patients receiving remdesivir are significantly more likely to achieve clinical improvement by day 28, with an adjusted hazard ratio of 1.23 (1.19 – 1.27).[11] Like the study on clinical improvement of remdesivir in a LFO population, the meta-analysis conducted by Beckerman et al. showed improved early and late recovery among LFO patients (RR 1.22, 95%CI 1.09–1.38; RR 1.17, 95%CI 1.09–1.28), thus further validating the benefit remdesivir has in helping patients recover from COVID.[2] <u>The committee choose an inappropriate subset of the Amstutz et al. meta-analysis which is not aligned with the patient population which Gilead is seeking reimbursement for:</u> As outlined in comment 5, the appropriate data subset from Amstutz et al. is the LFO (without SOLIDARITY) dataset.[1] The dataset preferred by the committee is not representative of the LFO patient population <u>Mean results for remdesivir should be considered:</u> In the most recent EAG report (date: 20th October 2023) the EAG introduced a new set of efficacy scenarios. Previously the MTA used the following system to distinguish efficacy levels: high / mean / low. With their latest report, the EAG changed this to: mean, mean-low, low. As stated in the final draft guidance (page 41), tocilizumab was compared against a mean-efficacy scenario.[12] Given the depth of the available evidence for remdesivir in the LFO patient population there is no reason to not apply mean efficacy levels to remdesivir as well.
10	Page 39– **Committee has suggested that an ICER over £20,000 would not be cost-effective, without any explanation for this threshold in the context of section 6 of the Manual** The draft guidance (para 3.35) concludes that for patients where mortality rates are below 14%, the ICERs are above £20,000 per QALY gained "so remdesivir would not be a cost-effective use of NHS resources". No explanation for this conclusion is provided and it conflicts with the requirements of the Manual which do not provide for an automatic conclusion that an ICER over £20,000 per QALY is cost ineffective, but state that the Committee will refer to the matters at paragraphs 6.3.5 and 6.3.6 of the Manual.
11	Page 40 - **The draft guidance acknowledges uncaptured benefits but fails to account for them** Section 3.36 of the draft guidance references uncaptured benefits which have not been reflected within the economic model. As part of a targeted submission Gilead has provided evidence in support of such uncaptured benefits for remdesivir. For example, a publication by Caffrey et al. which covered more than 20,000 patients, showed that patients who had received remdesivir had significantly lower 30-day post discharge readmission compared to the non-remdesivir group.[13]

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	Additionally a study published by Boglione et al. demonstrated that remdesivir reduces the likelihood of long COVID-19 syndrome (LCS).[14] Both reduced readmission rates and reduced likelihood of LCS, which represent uncaptured benefits of remdesivir treatment, have not been properly accounted for in the current draft guidance.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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1. Amstutz, A., et al., *Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials.* The Lancet Respiratory Medicine, 2023.
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11. Garibaldi, B.T., et al., *Real-world effectiveness of remdesivir in adults hospitalized with coronavirus disease 2019 (COVID-19): a retrospective, multicenter comparative effectiveness study.* Clinical Infectious Diseases, 2022. **75**(1): p. e516-e524.
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13. Caffrey, A.R., et al., *Real-World Safety and Effectiveness of Remdesivir and Corticosteroids in Hospitalized Patients with COVID-19.* COVID, 2023. **3**(2): p. 198-217.
14. Boglione, L., et al., *Risk factors and incidence of long-COVID syndrome in hospitalized patients: does remdesivir have a protective effect?* QJM: An International Journal of Medicine, 2021. **114**(12): p. 865-871.

Remdesivir+dexamethasone vs. dexamethasone for the treatment of COVID-19: real-world study in the US

Title—Currently 100 characters (Limit 100 characters incl. spaces)

Authors: Essy Mozaffari, Aastha Chandak, Robert L Gottlieb, Chidinma Chima-Melton, Mark Berry, Thomas Oppelt, Jason Okulicz, Alpesh N Amin, Andre C Kalil, Tobias Welte, Paul Sax

Presenting author: Essy Mozaffari

Target conference: CROI 2024

Character count: 2639 characters (limit-2500 characters including spaces)

Number of figures allowed: 1 figure or 1 table only

Deadline: September 27, 2023

CROI category: (G) Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 or Mpox Virus in Adults: *Studies of antiviral agents and combinations, including virus directed monoclonal antibodies and new antiviral agents (including pre-clinical data, interventional trials, and observational and cohort studies) where the focus is on antiviral therapy and antiviral treatment strategies for HIV or SARS-CoV-2 or mpox virus. Studies of patient and/or provider attitudes about different antiviral treatment options, and studies of adherence should be submitted here.*

Key words: COVID-19 mortality, remdesivir, omicron

Background:

Dual therapy with remdesivir (RDV) and dexamethasone (DEX) among patients with COVID-19 has demonstrated improved clinical outcomes as compared to DEX monotherapy. We evaluated the effectiveness of RDV+DEX vs. DEX monotherapy by applying and comparing two established methods used to balance two inherently different groups due to confounding by indication in observational research.

Methods:

Adults hospitalised during the Omicron period (December 2021 to April 2023) with a primary discharge diagnosis of COVID-19 and also flagged “present-on-admission” who received RDV+DEX or DEX monotherapy initiated in the first 2 days of hospitalisation (baseline period) were identified in the PINC AI Healthcare database. Patients were categorized by baseline supplemental oxygen requirement: no supplemental oxygen charges (NSOc), low-flow oxygen (LFO), high-flow oxygen/non-invasive ventilation (HFO/NIV), or invasive mechanical ventilation/ECMO (IMV/ECMO). Balanced distribution of underlying confounders in the treatment groups was achieved through 1) Propensity score matching (PSM) using 1:1 without replacement approach, which estimates the effectiveness of RDV+DEX by matching patients in the two groups excluding unmatched patients and 2) Inverse probability of treatment weighting (IPTW), which estimates the effectiveness of RDV+DEX in the full study cohort and keeps all eligible patients in the analysis. Cox Proportional Hazards Model was used to assess time to 14- and 28-day mortality for the two methods.

Results:

Among 151,215 hospitalised patients for COVID-19, 61,236 (40%) initiated RDV+DEX and 36,489 (24%) DEX monotherapy in the first 2 days.

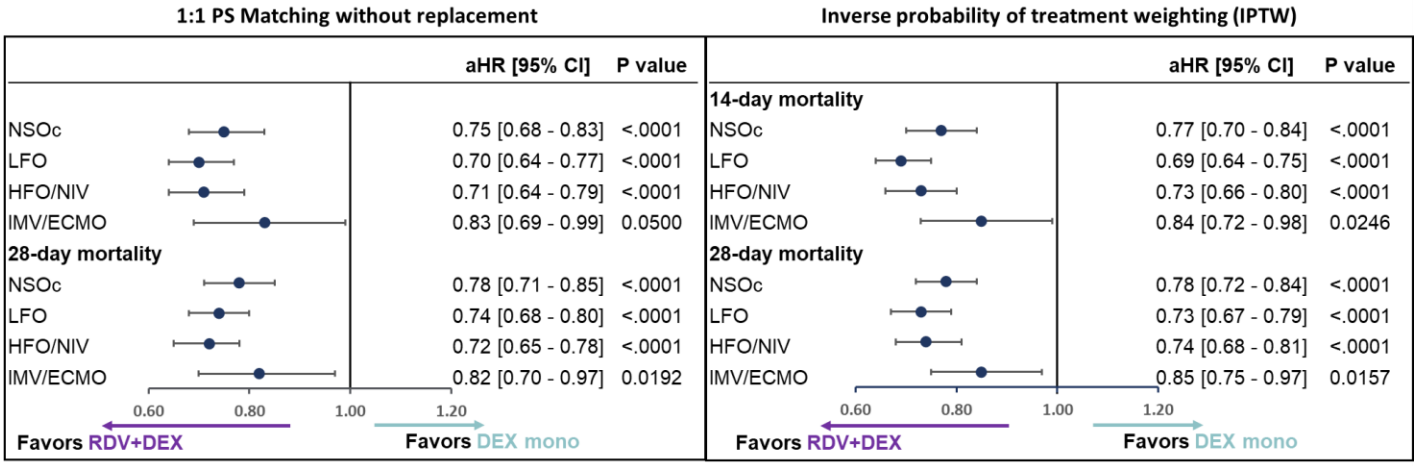
Using PSM, 33,089 RDV+DEX patients were matched 1:1 to 33,089 DEX monotherapy patients. RDV+DEX had a significantly lower mortality risk compared to DEX monotherapy across all supplemental oxygen requirements at 14 days (NSOc: adjusted hazard ratio [95% CI]: 0.75 [0.68-0.83], LFO: 0.70 [0.64-0.77], HFO/NIV: 0.71 [0.64-0.79], IMV/ECMO: 0.83 [0.69-0.99]); 28 days (NSOc: 0.78 [0.71-0.85], LFO: 0.74 [0.68-0.80], HFO/NIV: 0.72 [0.65-0.78], and IMV/ECMO: 0.82 [0.70-0.97]) (Figure).

Using IPTW, consistent results were obtained across all supplemental oxygen levels (Figure).

Conclusions:

The effectiveness of RDV+DEX in reducing mortality compared to DEX monotherapy were confirmed through two well-established methods of addressing confounding by indication bias, thus providing confidence in the observed effectiveness of RDV+DEX therapy as compared to DEX monotherapy. Appropriate methodologies such as the ones applied in this study enables the use of real-world data to complement findings from RCTs.

Figure:



Note: Estimates adjusted for age, admission month, hospital ward upon admission (ICU vs. general ward), and time-varying treatment with other COVID-19 medications (baricitinib, tocilizumab, oral antivirals)
95% CI= 95% confidence interval; aHR= adjusted hazard ratio; DEX=dexamethasone; ECMO=extracorporeal membrane oxygenation; HFO/NIV=high-flow oxygen/non-invasive ventilation; IMV/ECMO=invasive mechanical ventilation/ECMO; LFO=low-flow oxygen; NSOc=no supplemental oxygen charges; RDV=remdesivir

Remdesivir reduces mortality in immunocompromised patients hospitalised for COVID-19 during Omicron

Title—Currently 99 characters (Limit 100 characters incl. spaces)

Authors: Essy Mozaffari, Aastha Chandak, Robert L Gottlieb, Chidinma Chima-Melton, Mark Berry, Alpesh N Amin, Tobias Welte, Paul E Sax, Andre C Kalil
Presenting author: Essy Mozaffari

Target conference: CROI 2024

Character count: 2414 characters (limit-2500 characters including spaces)

Number of figures allowed: 1 figure or 1 table only

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CROI category: (G) Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 or Mpox Virus in Adults: *Studies of antiviral agents and combinations, including virus directed monoclonal antibodies and new antiviral agents (including pre-clinical data, interventional trials, and observational and cohort studies) where the focus is on antiviral therapy and antiviral treatment strategies for HIV or SARS-CoV-2 or mpox virus. Studies of patient and/or provider attitudes about different antiviral treatment options, and studies of adherence should be submitted here.*

Key words: COVID-19 mortality, remdesivir, omicron

Background:

Previous research has established the effectiveness of remdesivir (RDV) in reducing mortality among immunocompromised patients hospitalized for COVID-19. In this study, we present contemporaneous data from the Omicron pre-dominant era (Dec'21-Apr'23) by examining in-hospital all-cause mortality for early RDV initiation vs. not initiating RDV among immunocompromised hospitalized COVID-19 patients.

Methods:

Using the PINC AI Healthcare database, adults with immunocompromised conditions (cancer, transplant, hematologic malignancies, immunosuppressive medications, toxic effects of antineoplastics, primary immunodeficiencies, severe combined immunodeficiencies, asplenia, bone marrow failure/aplastic anaemia, or HIV) hospitalized with a primary discharge diagnosis of COVID-19 flagged as "present-on-admission" between Dec'21 to Apr'23 were identified. Analyses were stratified by no supplemental oxygen charges (NSOc) and any supplemental oxygen requirements upon admission. Patients initiating RDV in the first 2 days of admission vs. those not initiating RDV during the hospitalization were matched using 1:1 preferential within-hospital propensity matching with replacement. Time to 14- and 28-day in-hospital mortality or discharge to hospice was examined using Cox Proportional Hazards Model.

Results:

In the study period, 10,687 RDV-treated patients were matched to 4,989 unique non-RDV patients. Post-matching balance was achieved with 74% being 65+ years, 49% with NSOc, and 51% with any supplemental oxygen charges.

Unadjusted mortality rate for RDV patients vs. non-RDV patients was 10.3% vs. 13.7% at 14 days and 15.0% vs. 19.2% at 28 days, respectively.

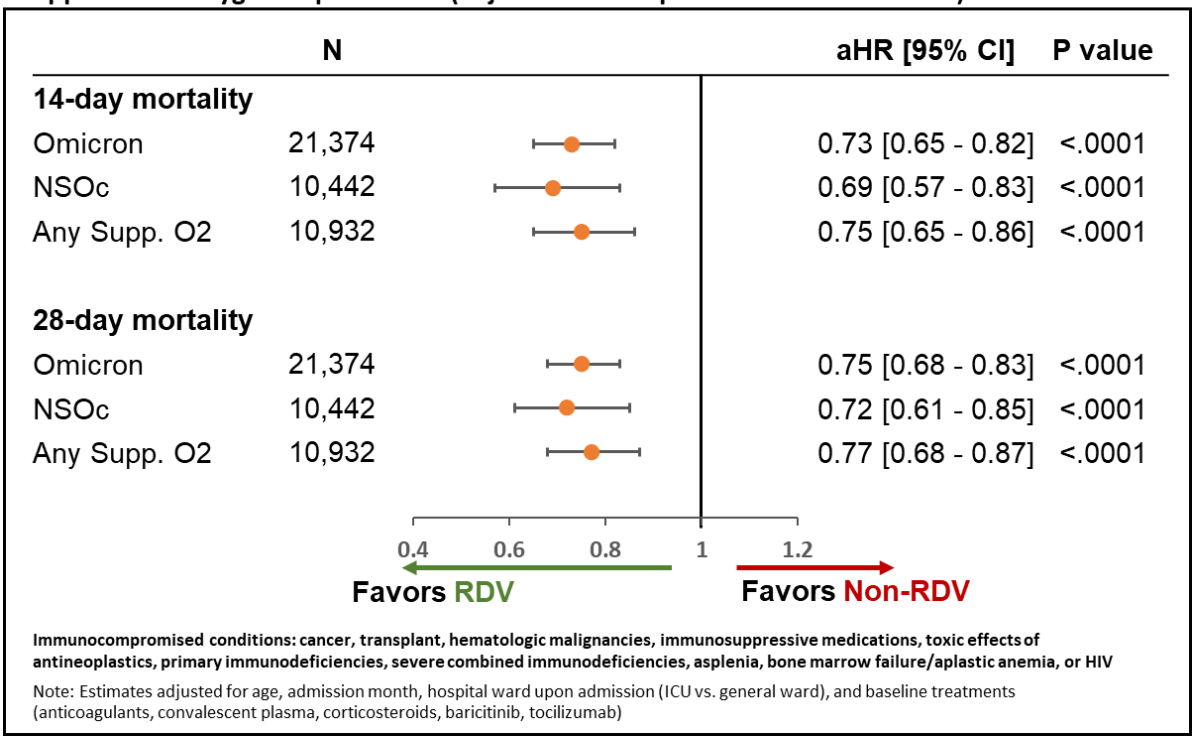
After adjusting for baseline and clinical covariates, RDV showed significantly lower mortality risk compared to non-RDV overall (adjusted hazard ratio [95% CI]: 0.75 [0.68-0.83]) in patients with NSOc (0.72 [0.61-0.85]) and in patients with any supplemental oxygen requirement (0.77[0.68-0.87]) at 28 days. A similar benefit for RDV vs. non-RDV was observed for 14-day mortality overall (0.73 [0.65-0.82]) in patients with NSOc (0.69 [0.57-0.83]) and in patients with any supplemental oxygen requirement (0.75 [0.65-0.86]) (Figure).

Conclusions:

RDV continues demonstrating significant mortality reduction among immunocompromised patients hospitalized with a primary diagnosis of COVID-19 in the more recent Omicron period, irrespective of the supplemental oxygen requirements.

Figure:

Time to 14- and 28-day mortality in immunocompromised hospitalized patients for COVID-19 by supplemental oxygen requirements (adjusted Cox Proportional Hazards model)



Immunocompromised conditions: cancer, transplant, hematologic malignancies, immunosuppressive medications, toxic effects of antineoplastics, primary immunodeficiencies, severe combined immunodeficiencies, asplenia, bone marrow failure/aplastic anemia, or HIV

Note: Estimates adjusted for age, admission month, hospital ward upon admission (ICU vs. general ward), and baseline treatments (anticoagulants, convalescent plasma, corticosteroids, baricitinib, tocilizumab)

Title: Disparities in treatment initiation by race and ethnicity among patients hospitalized for COVID-19

Authors: Essy Mozaffari, Aastha Chandak, Alpesh N Amin, Robert L Gottlieb, Andre C Kalil, Mark Berry, Gina Brown, Jason F Okulicz, Chidinma Chima-Melton

Target conference: CROI 2024

Character count: 2328 characters (limit-2500 characters including spaces)

Number of figures allowed: 1 figure or 1 table only

Deadline: September 27, 2023

CROI category: (G) Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 or Mpox Virus in Adults: *Studies of antiviral agents and combinations, including virus directed monoclonal antibodies and new antiviral agents (including pre-clinical data, interventional trials, and observational and cohort studies) where the focus is on antiviral therapy and antiviral treatment strategies for HIV or SARS-CoV-2 or mpox virus. Studies of patient and/or provider attitudes about different antiviral treatment options, and studies of adherence should be submitted here.*

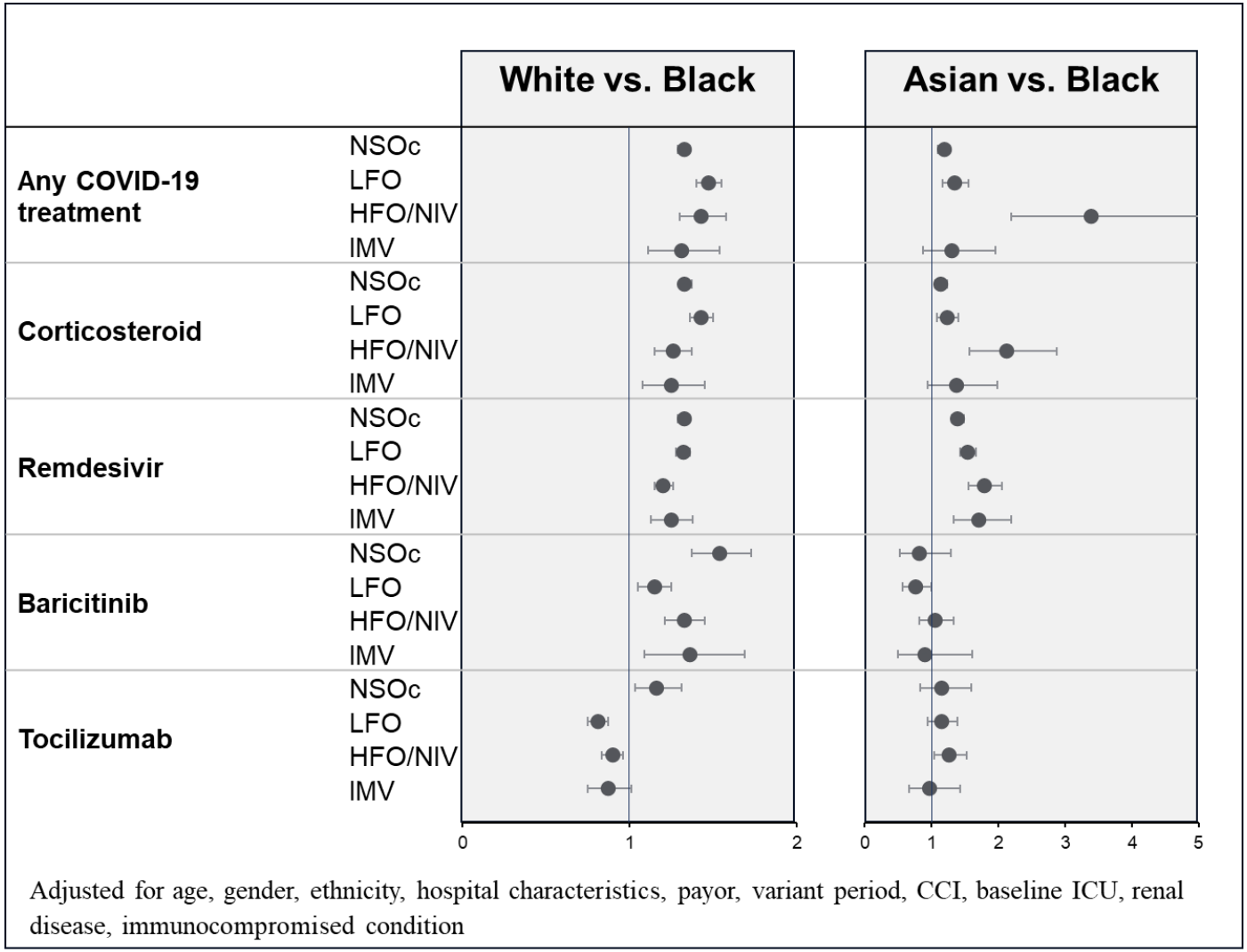
Background: The pandemic has shed light on the heightened risks of morbidity and mortality faced by minority patients hospitalized with COVID-19. However, there is a significant lack of real-world data that explores whether Black inpatients are less likely to receive appropriate pharmaceutical treatment for COVID-19 in the hospital than other racial groups. To address this evidence gap, we evaluated whether the initiation of evidence-based COVID-19 treatments upon hospital admission was related to race and ethnicity.

Methods: Adults hospitalized with a primary diagnosis of COVID-19 between 5/2020- 4/2022 in the PINC AI Healthcare Database were examined. Baseline was defined as the first 2 days of hospitalization. Multivariable logistic regression models adjusting for key demographic, hospital, and clinical characteristics, were used to assess the association between race/ethnicity and initiation of COVID-19 treatments at baseline. Patients with no supplemental oxygen charges (NSOc), low-flow oxygen (LFO), high-flow oxygen/non-invasive ventilation (HFO/NIV) and invasive mechanical ventilation (IMV) at baseline were examined.

Results: Of the 454,761 patients included in the study, 70% were White, 17% Black, 2% Asian, 11% other races, and 16% were Hispanic. Further, 86% patients received any COVID-19 treatment (84% corticosteroids, 52% remdesivir, and 4% received tocilizumab or baricitinib). Across all supplemental oxygen levels, White patients were significantly more likely to receive any COVID-19 treatment as well as corticosteroids, remdesivir, and baricitinib treatment as compared to Black patients (Figure). White patients on NSOc were more likely but those on LFO and HFO/NIV were significantly less likely to receive treatment with tocilizumab than Black patients (Figure). Treatment initiation for Non-Hispanic vs. Hispanic patients varied by baseline supplemental oxygen requirements.

Conclusion: Black patients hospitalized for COVID-19 were significantly less likely to be treated with evidence-based COVID-19 treatments compared to other races across all levels of oxygen supplementation. As we enter the endemic phase, it is crucial that we highlight persistent disparities in patient management and strive towards standardized care for all patients during hospitalization for COVID-19, regardless of racial background or ethnicity.

Figure.



Adjusted for age, gender, ethnicity, hospital characteristics, payor, variant period, CCI, baseline ICU, renal disease, immunocompromised condition

Title: Characteristics and outcomes of kidney transplant patients hospitalized for COVID-19 in the United States

Authors: Essy Mozaffari, Aastha Chandak, Andre C Kalil, Chidinma Chima-Melton, Alpesh N. Amin, Mark Berry, Jason Okulicz, Robert L Gottlieb

Target conference: CROI 2024

Character count: 2355 characters (limit-2500 characters including spaces)

Number of figures allowed: 1 figure or 1 table only

Deadline: September 27, 2023

CROI category: (Q) Epidemiology of HIV, COVID-19, and Mpox: *Studies of the incidence and prevalence of HIV, COVID-19, and mpox. Includes risk factors for acquisition or transmission; biomedical, behavioral and structural determinants; morbidity and mortality; surveillance; transmission including phylogenetics; and molecular epidemiology; studies focused on vulnerable populations.*

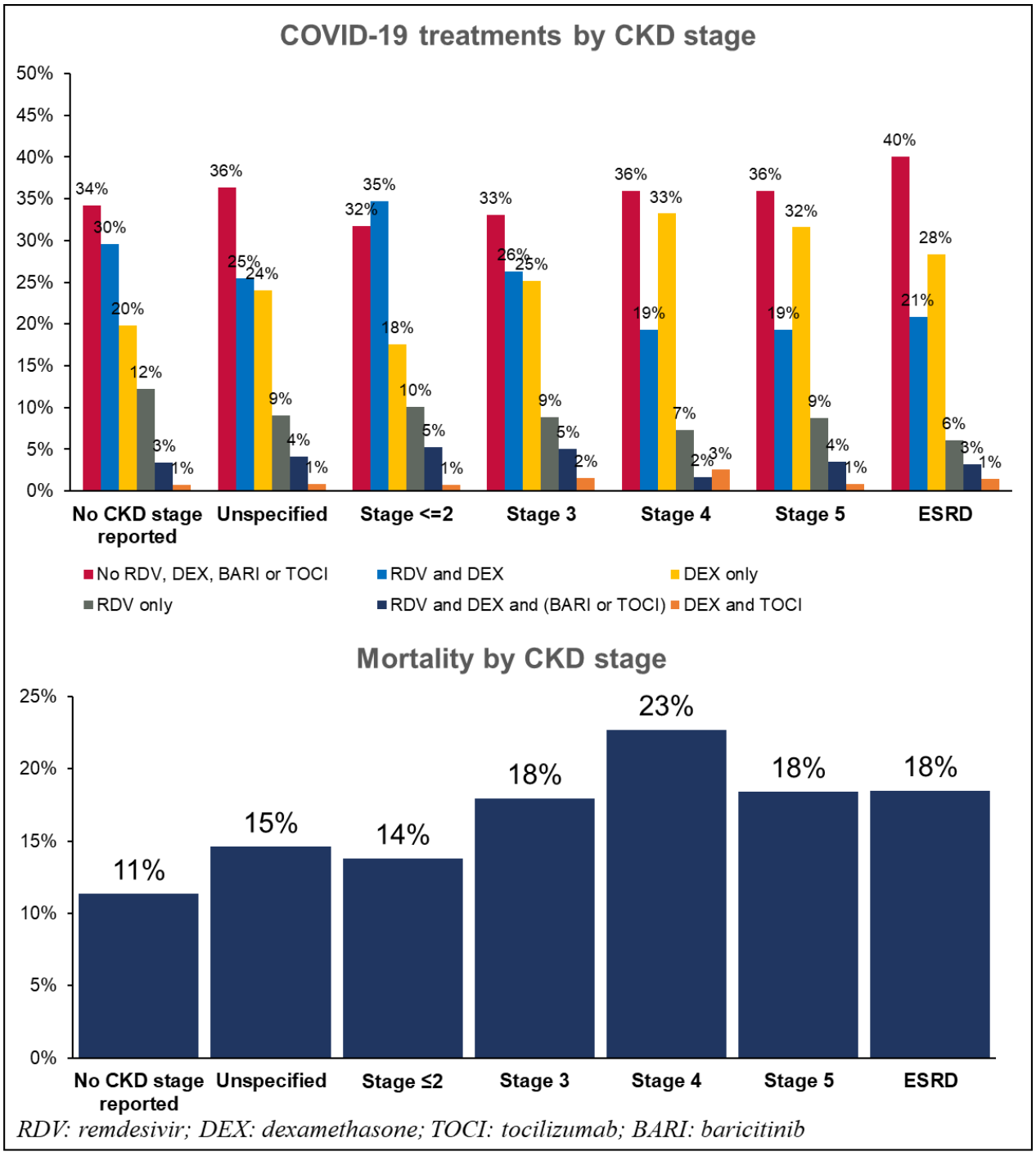
Background: Immunocompromising conditions and advanced renal dysfunction are individually risk factors for adverse outcomes from COVID-19. We explored the intersection of these risk factors by examining variations in treatment patterns and mortality among hospitalized COVID-19 patients with a history of kidney transplant.

Methods: Patients with a history of kidney transplant (ICD-10-CM: Z94.0) hospitalized in the US for COVID-19 (ICD-10-CM: U07.1) between May 2020-Jan 2023 were identified using the Premier Healthcare Database. Baseline was considered as first two days of hospitalization. We characterized patient demographics, treatment patterns and in-hospital all-cause mortality by chronic kidney disease (CKD) stage as a surrogate for renal allograft dysfunction.

Results: Of the 8,785 patients included in this study from 831 hospitals, 55% were White, 27% Black, 40% female with a median age of 62 years [IQR: 52-70]. Key comorbidities included hypertension (90%) and diabetes (60%). Baseline COVID-19 severity included 68% patients with no supplemental oxygen charges, 17% low-flow supplemental oxygen, 10% high-flow/non-invasive ventilation, and 5% invasive mechanical ventilation/ECMO. Patients were hospitalized for a median of 5 days [IQR: 3-10] with 29% admitted to the ICU and 16% mortality rate. Over the variant periods, patient characteristics remained similar except higher supplemental oxygen requirements, ICU stay and mortality rate in the Delta period as compared to Pre-Delta and Omicron. Despite risk of progression, use of COVID-19 treatments was lower with higher CKD stage, and use of triple therapy with remdesivir+dexamethasone with baricitinib/tocilizumab increased with higher supplemental oxygen requirement (Figure). Mortality increased from 14% for CKD Stage ≤2 to 23% for Stage 4 and 18% for Stage 5 (Figure).

Conclusion: In this study of kidney transplant recipients hospitalized with COVID-19, the lack of any COVID-19 treatment was seen more often as renal function diminished despite a notable increase in overall mortality observed in tandem with compromised renal function. This study sheds light on a persistent therapeutic gap that has affected these patients historically, attributed to factors such as potential drug interactions, past uncertainties regarding the renal clearance of therapeutics, and existing gaps in medical education and awareness.

Figure.



RDV: remdesivir; DEX: dexamethasone; TOCI: tocilizumab; BARI: baricitinib

Sent: 01 February 2024 23:02
To:
Cc: > **Subject:** RE: RDV+DEX vs DEX CROI - for NICE MTA

Hi

Great to hear from you, hope you are having a great start in the new year.

Here are the responses to the questions below, hope they are helpful for your response to NICE.

Regards,

- Background mortality rates for the DEX Monotherapy group vs RDV+DEX

	NSOc			LFO			HFO/NIV			IMV/ECMO		
	Dex Mono	**RDV+DEX**		**Dex Mono**	**RDV+DEX**		**Dex Mono**	**RDV+DEX**		**Dex Mono**	**RDV+DEX**	
	n=14774	n=14774		n=12211	n=12211		n=5349	n=5349		n=755	n=755	
14-day mortality rate	910 (6.2%)	796 (5.4%)		947 (7.8%)	750 (6.1%)		837 (15.6%)	699 (13.1%)		205 (27.2%)	189 (25.0%)	
28-day mortality rate	1137 (7.7%)	1036 (7.0%)		1196 (9.8%)	998 (8.2%)		1105 (20.7%)	941 (17.6%)		267 (35.4%)	249 (33.0%)	

- Is this available in recent timeframes – i.e. Omicron period? This study period was the Omicron time period covering Dec 2021 till Apr 2023
- Do we have any details on whether other COVID-19 therapies were used prior to or during admission? The database doesn't provide information on the patient prior to the admission to the hospital. Furthermore, the study criteria excluded those patients that were administered baricitinib or tocilizumab or oral antiviral upon admission (first two days of the hospitalization). If these treatments were started after the first two days, then this was allowed and adjusted using time-varying effect of the treatments dependent on timepoint of initiating these treatments after the first two days.

Congress: 31st Conference on Retroviruses and Opportunistic Infections (CROI)

Congress Date/Location: March 3-6, 2024/Denver, CO, USA

Submission Deadline: January 9, 2024 (17:00 PT, 20:00 ET) Late-breaker abstracts

Abstract Requirements (CROI Guidelines)

Title: 97 characters (limit, 100 characters, including spaces and formatting tags)

Abstract body: 2493 characters (maximum 2500 characters, including spaces and formatting tags; figures/tables do not count towards the character count)

Display items: 1 (limit, 1 figures/tables)

Additional information: 21 words (limit, 50 words, including title, legends, footnotes, abbreviations)

Title: Effect of Remdesivir on Post-COVID Conditions Among Individuals Hospitalized with COVID-19 by Age

Authors

Mark Berry, PhD;[1] Amanda M. Kong, DrPH;[2] Roger Paredes, MD, PhD;[3,4] Rohan Shah, BS;[2] Gina Brown, MD;[1] Rikisha Gupta, MPH;[1] Sohul Shuvo, PhD; [1] Robert L. Gottlieb, MD, PhD;[5,6] Lourdes Mateu, MD, PhD;[4] Mazin Abdelghany, MD;[1] Jason D. Goldman, MD, MPH;[7,8] Anand P. Chokkalingam, PhD[1]

Affiliations

[1]Gilead Sciences, Inc., Foster City, CA, USA; [2]Aetion, Inc., New York, NY, USA; [3]IrsiCaixa AIDS Research Institute, Barcelona, Spain; [4]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [5]Baylor University Medical Center, Dallas, TX, USA [6]Baylor Scott & White Health, Dallas, TX, USA; [7]Providence Swedish Medical Center, Seattle, WA, USA; [8]Division of Allergy and Infectious Diseases, University of Washington, Seattle, WA, USA.

Background

Post-COVID conditions (PCC), or long COVID, are part of a persistent, multisystemic syndrome occurring after COVID-19. The effect of the antiviral remdesivir (RDV) on subsequent outcomes associated with PCC is unknown. Of particular interest are RDV's effects stratified by age, which is a predictor of outcomes in patients hospitalized with COVID-19.

Methods

The HealthVerity database of hospital chargemaster data linked to closed claims for >25 million US patients was queried for individuals aged ≥12 years hospitalized for ≥2 days with COVID-19 between 5/1/2020 and 9/30/2021. The analysis was stratified by age category (<65 vs ≥65 years of age). Cox proportional hazards

models used inverse probability of treatment weighting to calculate hazard ratios (HR) for 16 individual PCC-related symptoms or diagnoses and a composite of any PCC, occurring 90-270 days posthospitalization, in patients hospitalized with COVID-19 receiving RDV versus comparators not receiving RDV. Individuals without ≥90 days of follow-up still contributed person-time up to their day of censoring.

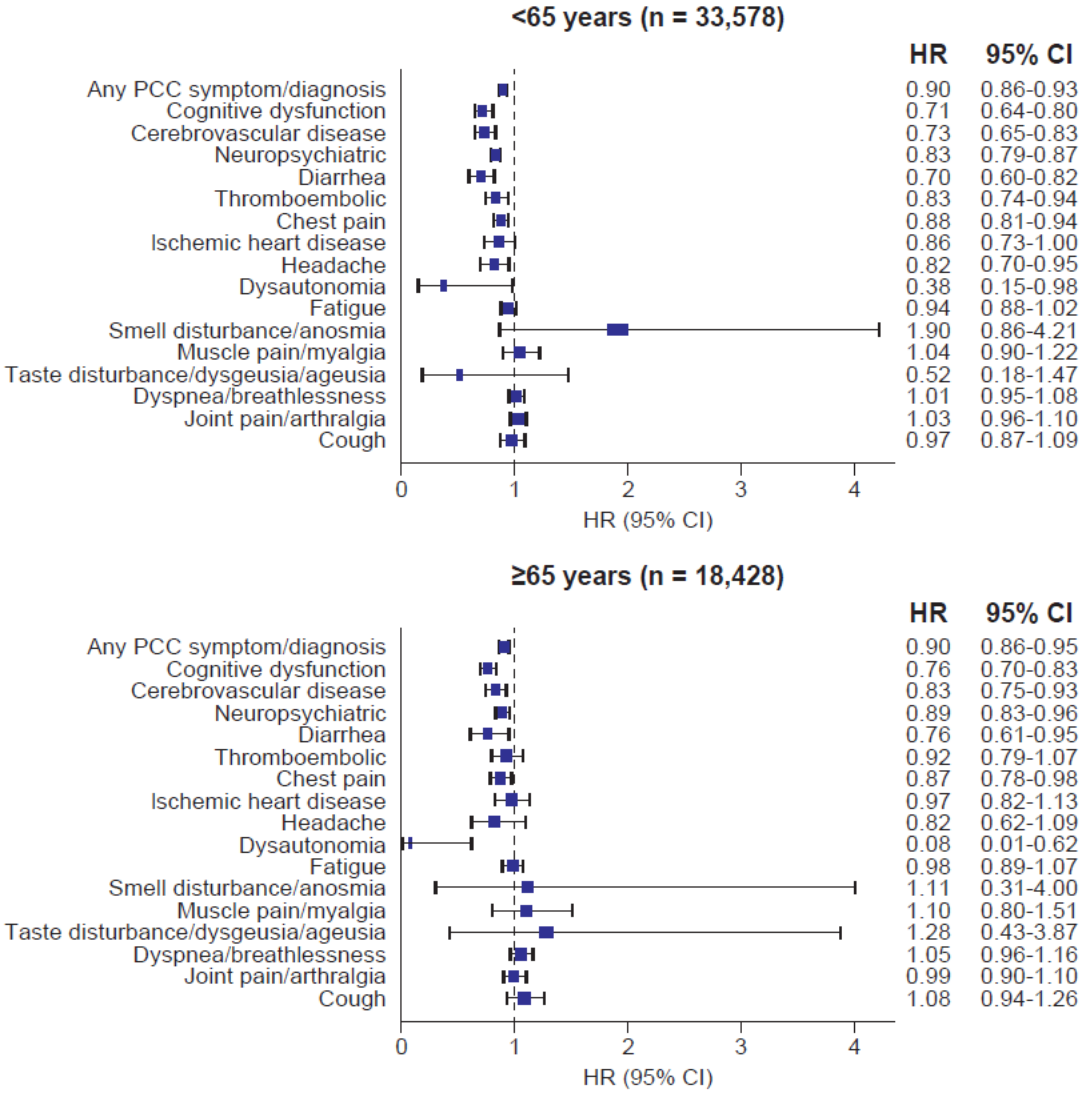
Results

Of 3,661,303 individuals hospitalized for any reason during the study period, 52,006 had acute COVID-19 and met inclusion criteria, of which 33,578 (64.6%) were <65 years of age. In the <65 and ≥65 age groups, respectively, 36.1% and 27.2% received RDV. The most common PCC-related symptom/diagnosis was neuropsychiatric features, with an incident rate per 100 person-years of 58.0 and 52.4 in <65 and ≥65 age groups, respectively. Overall, RDV (vs no RDV) was associated with significantly lower relative hazard of any PCC in both age groups: HR 0.90 (95% confidence interval [CI]: 0.86–0.93) in those <65 years old and HR 0.90 (95% CI: 0.86–0.95) in those ≥65 years old. RDV was associated with lower risk for 6 of 16 individual symptoms/diagnoses in the ≥65 age group (cognitive dysfunction, cerebrovascular disease, neuropsychiatric features, diarrhea, chest pain, and dysautonomia) and for 8 of 16 individual symptoms/diagnoses in the <65 age group (including the same 6 symptoms, as well as thromboembolic disease and headache).

Conclusion

RDV was associated with reduced risk of PCC after COVID-19 hospitalization in patients <65 and ≥65 years of age, though more symptoms were impacted, and the effect size tended to be stronger in the younger age group. The majority of patients did not receive RDV, indicating a missed opportunity for treatment of acute COVID-19 and potential prevention of long-term sequelae of infection.

Figure. Association of Remdesivir with PCC-Related Symptoms or Diagnoses, Stratified by Age
<<21/50 words (title and footnotes)>>



PCC, post-COVID conditions; HR, hazard ratio; CI, confidence interval.

Abstract information

Abstract category/section: (G) Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 or Mpox Virus in Adults

> *Studies of antiviral agents and combinations, including virus-directed monoclonal antibodies and new antiviral agents (including pre-clinical data, interventional trials, and observational and cohort studies) where the focus is on antiviral therapy and antiviral treatment strategies for HIV or SARS-CoV-2 or mpox virus. Studies of patient and provider attitudes about different antiviral treatment options and studies of adherence should be submitted here.*

Search terms (maximum 5): COVID-19; antiviral therapy; Long COVID; Post-COVID Conditions

NICE National Institute for Health and Care Excellence

Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

Draft Guidance comments form

Consultation on the Draft Guidance document – deadline for comments 5pm on Thursday 8 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**British Infection Association**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**NA**]
Name of commentator person completing form:	[redacted]

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Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I would like it to have included severely immunocompromised patients hospitalised but NOT requiring oxygen but recognise that these are few, that if we really want to use it in these rare patients we could on case by case basis, and that the current licence I think does not extend to its use in hospitalised patients not requiring oxygen and so NICE probably can't do anything about that?
2	The 'antiviral' intervention phase should ideally cover from normoxaemia to low flow oxygen state with IV options for hospitalised patients. This should be immunocompromised as well as immunocompetent who fall in the IAP/UKHSA high risk category
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Faculty of Pharmaceutical Medicine
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Faculty of Pharmaceutical Medicine

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Example 1	We are concerned that this recommendation may imply that ……..
1	The committee has had several meetings at which data supporting the use of antiviral therapies for treating COVID- in hospitalised patients and the community were discussed. The current guideline focuses only on remdesivir and the monoclonal antibody combination of tixagevimab and cilgavimab. The contribution of the antiviral effectiveness of these agents to both clinical effect and, thence, cost-effectiveness is not addressed. The monoclonal antibody combination of tixagevimab and cilgavimab failed to neutralise earlier omicron variants effectively. If this remains the situation, it would not be considered clinically effective. Remdesivir remains effective against circulating variants both in vitro and clinically, as shown in the Gilead evidence (Mozaffari et al.). Clinical effectiveness in hospitalised patients in earlier studies was limited to patients treated within ten days of first symptom onset or those in whom immunocompromise was associated with ongoing viral replication. The committee should consider the evidence presented by Gilead in more detail, such as (Beckerman et al.) concerning the timing of the use of relative to ongoing viral replication (which can be diagnosed using PCR with cycle times < 25 indicating replication virus or positive lateral flow test) as remdesivir may not be effective in hospitalised patients in whom viral replication has ceased.
2	The discussion focuses primarily on the cost-effectiveness of remdesivir in hospitalised patients. As noted previously (in response to question 1), the mechanism of remdesivir in treating COVID has not been considered. Additional evidence concerning the timing of use relative to the first onset of symptoms or evidence of ongoing viral replication could be considered. The CE modelling should differentiate vaccinated and non-vaccinated populations (with individuals who have had their last vaccination more than six months ago, classified as non-vaccinated. (1. https://link.springer.com/article/10.1007/s10238-023-01036-x, 2. https://www.sciencedirect.com/science/article/pii/S0163445322002006)
3	The committee has continued to ignore the impact of respiratory virus outbreaks in the community and the need for anti-viral treatments to prevent the repercussions and effects on the functioning of the NHS hospitals. Existing guidance is provided for antiviral treatment of influenza, which permits the community use of antiviral therapy. However, COVID-19 treatment guidance in the community needs to be improved. (https://assets.publishing.service.gov.uk/media/62209cd38fa8f549097b87ec/ukhsa-guidance-antivirals-influenza-11v4.pdf). At this point, COVID has become an endemic disease for which the risk populations overlap with those affected by influenza. While it was reasonable in the early phase of the pandemic, when antiviral therapy was in short supply, to limit the use of such treatments to those at the very highest risk of death from COVID-19, it is no longer reasonable to continue this restriction, instead to consider how best to deploy treatment to reduce

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Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

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	hospitalisations and other covid complications, e.g. myocardial infarction and stroke, the incidence of which is increased in patients that have recovered from covid managed within the community (Knight R et al. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales. Circulation. 2022;146: 892-906). It is also worth considering that parts of the population have been ineligible for COVID-19 vaccination for over two years. Whilst they likely retain some protection from previous vaccination, they may not be adequately protected against current circulating variants, which is likely to contribute to more moderate to severe symptoms, ongoing transmission, and new variant generation. Effective vaccination and treatments for those infected in the community are imperative to prevent this. Clinical experts said hospitalisation and mortality rates are becoming less relevant clinical efficacy measures for COVID-19 treatments. Evidence of the other impacts on QALYs should be considered. The committee should consider the evidence on creating resistant strains and the implications for drug use. It should also look at the volume of distribution data for the drug and ensure that there are no patient types/groups that would be at increased risk of developing a resistant strain. The same is true for the monoclonal antibodies. (1. https://www.cell.com/cell-reports-medicine/pdf/S2666-3791(22)00284-1.pdf, 2. https://pubmed.ncbi.nlm.nih.gov/35482820/, 3. https://academic.oup.com/cid/article/76/2/342/6717535, 4. https://pubmed.ncbi.nlm.nih.gov/35878684/, 5.https://academic.oup.com/jid/article/228/8/1055/7191107, 6. https://www.journalofinfection.com/article/S0163-4453(22)00422-4/fulltext). Vaccines and anti-virals should be available for private purchase outside the current NHS criteria eligibility, considering NHS criteria for eligible vaccinations and anti-virals have been significantly restricted to narrow populations since Autumn 2023. This would further support reducing the impact on the NHS hospitals.
4	There is a broader population who should be eligible for vaccines and anti-viral use in the community beyond the current criteria of at-risk populations of cancer and immunosuppressed patients. Chronic medical conditions, e.g. ischaemic heart disease, chronic respiratory disease, chronic renal and liver disease, diabetes, and healthy elderly, etc, should be included within the at-risk group. These chronic conditions are associated with an altered immune state and, whilst not the same as an immunocompromised patient, are less effective than an individual of a similar age, gender and ethnicity without the condition(s). The absence of these populations from this guidance to the NHS is discriminatory.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

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Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

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Multiple Technology Appraisal

Remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	GamFederation
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes all the relevant evidence been taken into account while considering covid-19 vaccination.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The summaries and cost effectiveness reasonable but expenditure could be less.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Recommendations followed NHS guidelines properly.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Its covered all groups of people, ethnic minority, NRPF (no recourse to public fund), even outreach for illegal immigrants for their vaccination. Unfortunately many didn't receive support and covid-19 vaccination because of their immigration status.

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	University College London Hosplitals NHS Foundation Trust
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

See below comment on section 1.1.
Evidence around efficacy and therefore cost-effectiveness for immunocompromised patients with no oxygen requirement or high flow oxygen requirements does not appear to have been considered.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

See below comment on section 1.1.
Evidence for remdesivir around efficacy and therefore cost-effectiveness for immunocompromised patients with no oxygen requirement or high flow oxygen requirements does not appear to have been considered.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

See below comment on section 1.1.
Evidence for remdesivir around efficacy and therefore cost-effectiveness for immunocompromised patients with no oxygen requirement or high flow oxygen requirements does not appear to have been considered.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

See below comment on section 1.1.
Evidence for remdesivir around efficacy and therefore cost-effectiveness for immunocompromised patients with no oxygen requirement or high flow oxygen requirements does not appear to have been considered.

- Section 1 – Recommendations, point 1.1

"In the previous 'Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised due to COVID-19' (issued November 2022), a similar recommendation was made which included the criteria that remdesivir be offered only to those with 'requiring low-flow supplemental oxygen'. However a caveat was added for immunocompromised patients:
"For significantly immunocompromised patients hospitalised for COVID-19 symptoms: ...The criterion on the need for supplemental oxygen requirement does not apply"

Exclusion of a similar caveat in this NICE TA may exclude/delay access to immunocompromised patients initially presenting without an oxygen requirement or

who present with an immediate high-flow oxygen requirement.

It does not appear from the committee papers or draft NICE TA that these subgroups (immunocompromised + no supplemental oxygen requirement / immunocompromised + high flow supplemental oxygen requirement) has been considered. Instead subgroup analysis appears to have only been considered for supplemental oxygen requirements (irrespective of immune status). This is particularly important given that NICE has concluded that severely immunocompromised patients have worse outcomes and appear to benefit from remdesivir the most.

A notable extract from the Committee papers highlighting an assumption on the oxygen requirement status in immunocompromised patients has been:
"The company did not provide ICERs for children and immunocompromised patients, but the EAG has provided exploratory analyses assuming that only patients receiving LFO are considered"

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	AstraZeneca UK
Location	Not specified
Conflict	No
Notes	

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Thank you for the opportunity to comment on the draft guidance for remdesivir and tixagevimab plus cilgavimab for treating COVID. AstraZeneca note that several of the sections detailed with current draft guidance have not been updated following the third committee meeting. Considering the dynamic and evolving nature of the current COVID-19 landscape in the UK and for the sake of clarity AstraZeneca believe the following sections should be updated:

3.27 Hospitalisation rates:

The sections states that ‘The rate of hospitalisation is a key driver of model outputs’. However, this is relevant only for the mild COVID population. For the third committee meeting hospital rates were not relevant for decision-making and to our knowledge not re-discussed by the committee. The estimates discussed by committee are no longer contemporaneous with the most current recommendation. This section should make clear the committee made its conclusion at the second committee meeting.

AstraZeneca consider consistent sources of evidence should be used where possible and if the committee wanted to update its conclusion consider the most relevant source of evidence for the immunocompromised population to be the INFORM study.

3.19 Generalisability of clinical effectiveness: ‘The committee noted a recent update from the European Medicines Agency’s emergency task force, which cautioned that neutralising monoclonal antibodies currently authorised for COVID-19 are unlikely to be effective against emerging strains of SARS-CoV-2.’

AstraZeneca recognise this paragraph states this was discussed at the second committee meeting. AstraZeneca consider the following amendments would aid in the clarity of the paragraph:

'The committee noted an update from the European Medicines Agency's emergency task force, which cautioned that tixagevimab plus cilgavimab is unlikely to be effective against current strains of SARS-CoV-2.'

3.20 Relative treatment effects for mild COVID-19: It is our understanding the mild COVID-19 setting was not discussed at the third committee meeting. Whilst AstraZeneca does not consider there is relevant new evidence that would impact the overall decision, for clarity this section should state these conclusions are from the second committee meeting.

3.34 Cost-effectiveness estimates; Treatments for mild COVID-19: For clarity this section should state where conclusions are from the second or third committee meeting.

3.36 Uncaptured benefits: NICE has provided a list of potential uncaptured benefits. However, it has stated that committee considered some of the listed benefits fall outside of the NICE reference case. NICE should specifically refer to the benefits it considers should not be captured in future COVID-19 evaluations.

- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Thank you for the opportunity to comment. Whilst mortality rates have been decreasing due to improvements in the management of care these improvements are not realised equally across population subgroups and the immunocompromised population at still at subsequent risk of infection and adverse outcomes following admission. AstraZeneca agree with the Assessment Group (AG) that the INFORM study is the best evidence to inform mortality estimates in the immunocompromised population. However, approximately half of COVID-19 deaths occur in individuals without prior hospitalisation. Therefore, the AG's approach that uses the total COVID-19 deaths reported in the publication leads to a substantial overestimation in the mortality rate for those who are hospitalised and need low flow oxygen.

Unpublished data on file for the INFORM study includes the number of COVID-19 deaths in the subset of individuals who have been hospitalized at least once for COVID-19. AstraZeneca consider the best estimate of mortality rate for those in the low flow oxygen group to be 10.39%. This assumes patients whose greatest level of care is admission to the general ward (that is, excluding those admitted to the ICU or on mechanical ventilation) best represents this group. The table below includes a correct calculation of mortality rate for the population being considered:

AG approach (Evans et al 2023); Broadly defined immunocompromised (IC) population

All hospitalised episode(s): 4585

Total number of Covid-19 deaths (including those not hospitalised): 1145

Covid-19 morality rate: 24.98%

AstraZeneca data on file; Broad IC hospitalised patients, general ward only

All hospitalised episode(s): 4525

Total number of Covid-19 deaths: 470

Covid-19 morality rate: 10.39%

Whilst both these data are from 1st January 2022 – 31st December 2022 due to the nature of using NHS-linked national datasets marginally more hospitalised and mortality events were captured compared to that reported in Evans et al 2023. Whilst 2023 data is not yet available, based on expert clinical opinion we could expect the mortality rate to be similar or have improved compared to the 2022 data.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

AstraZeneca welcome recommendations that refer directly to the populations defined by the independent advisory group commissioned by the Department of Health and Social Care (McInnes report) and the recognition that these definitions may be revised over time.

NICE refer throughout the draft guidance to the high levels of uncertainty within the analyses and potential uncaptured benefits. NICE have also recognised in the draft guidance and in its recent process statement on surveillance and rapid update the potential need to update its recommendations in the rapidly evolving Covid-19 landscape. Within this guidance NICE has the opportunity to also provide clear recommendations to the wider system on what evidence could be generated or its preference on how benefits could be captured within the model ahead of any future review.

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No comments

Molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]: EAG critique of the response from Gilead to NICE's Draft Guidance

Produced by	Sheffield Centre of Health and Related Research (SCHARR), The University of Sheffield
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Declared competing interests of the authors

No author declares a conflict of interest.

1 INTRODUCTION

This document should be read in conjunction with the initial EAG report,[1] erratum,[2] and a subsequent EAG report,[3] discussing additional analysis undertaken after NICE issued its Appraisal Consultation Document, the EAG's critique of evidence submitted after appeal,[4] NICE's draft guidance[5] and the subsequent response to this by Gilead.[6] These provide more details on the work which has originally undertaken for treatments assessed in-hospital for severe COVID-19, which was NICE ID4038.

This report takes the following structure: Section 1 is an introduction; Section 2 summarises the company's response to draft guidance and provides the EAG's critique of this response; Section 3 details the amendments made to the EAG's model and provides the additional analyses undertaken; Section 4 provides the results from the new analyses; Section 5 provides a discussion of these results; whilst Section 6 contains the references cited in the report. Appendix 1 details the methodology used by the EAG to estimate one efficacy value for remdesivir.

2 A SUMMARY OF THE COMPANY'S RESPONSE TO DRAFT GUIDANCE

The company's response took the form of 11 points. These points will be summarised and critiqued independently by the EAG in Sections 2.1 to 2.11.

2.1 Restrictive patient population

This point was divided into two parts. The first was that patients who were receiving low flow oxygen (LFO) but who did not meet the criteria set by the Department of Health and Social Care (referred to by NICE (and henceforth) as the McInnes report[7]) could not receive remdesivir treatment despite evidence showing a mortality benefit; the second was that patients who were at high-risk but who were not receiving LFO could not receive remdesivir treatment.

The first part appears to be a judgement made by the Appraisal Committee having reviewed the cost-effectiveness estimates of people who were deemed to be immunocompromised, and those that were not, that were reported in the EAG's report of October 2023.[4] The EAG has not commented on this point as it was an Appraisal Committee decision.

Regarding the second part, in its guidance document, NICE recommended the use of remdesivir in higher-risk patients (defined as those listed in the McInnes report[7]) who also required LFO. In its response document it became clear that the company was attempting to position remdesivir as an option for patients at high-risk who did not require LFO – the EAG had not understood this, and the company had not corrected the EAG in its previous work[4] or clarified this at the Appraisal Committee. A response from the British Infection Association confirmed that there are patients that would not require oxygen but who are severely immunocompromised,[8] although this occurrence is rare.

In order to inform the Appraisal Committee, the EAG has run analyses for adult immunocompromised patients not requiring LFO.

2.2 The NICE recommendation does not align with the cost-effectiveness results shown during the third Appraisal Committee meeting

The company states that in all of the 27 scenarios presented by the EAG the ICER was below £30,000 per quality-adjusted life year (QALY) gained and that scenarios using high efficacy were not presented. The EAG comments that the Appraisal Committee preferred a different estimate of mortality to that used by the EAG in its analyses and that this would have increased the ICERs. As this is an Appraisal Committee decision the EAG has not commented further.

2.3 The Appraisal Committee has misrepresented the company's positioning of remdesivir

This point is linked to the second part of Section 2.1. The company states that the wording in the draft guidance of "*Gilead positioned remdesivir only for adults with pneumonia needing low-flow oxygen, for adults with pneumonia needing low-flow oxygen who are immunocompromised and for children*" is incorrect. The company provides further information to state that "*Gilead stated that remdesivir should be recommended for use in adults who are immunocompromised irrespective of whether they require low-flow oxygen*." Whilst the wording is a matter for NICE, the EAG has provided analyses for immunocompromised patients not requiring LFO.

2.4 The Appraisal Committee fails to acknowledge the mortality risk in patients requiring LFO

The company states that the Appraisal Committee has failed to acknowledge that patients requiring LFO have a high rate of mortality if they do not get treatment with an intervention recommended previously. As this is an Appraisal Committee decision the EAG has not commented further.

2.5 The Appraisal Committee has made a misleading statement related to the difference in relative benefit between the no oxygen and LFO groups in Amstutz *et al*.[9]

The company states that the publication by Amstutz *et al*.[9] states that there was a "*similar relative benefit*" between patients who were receiving no oxygen and patients receiving LFO and that there was no mention of statistical significance. Further, the company states that the results between LFO with SOLIDARITY (0.79, 0.68 – 0.92) and LFO without SOLIDARITY (0.59, 0.43 – 0.82) "*are very different*." The company therefore claims that "*the LFO (without SOLIDARITY) dataset should be used for decision making*."

The EAG notes that none of the relevant comparisons in the Amstutz *et al.*[9] paper are statistically significantly different as one of the 95% confidence intervals contains the point estimate from the other group in all comparisons.[10] The EAG has estimated the p-values between the comparisons using Monte Carlo simulation with the results reported in Table 1. It is seen that there appears to be no statistically significant differences between groups irrespective of i) whether SOLIDARITY is included or not, or ii) whether it is a patient group that requires LFO or that requires no supplemental oxygen.

To inform the Appraisal Committee, the EAG has run analyses with and without SOLIDARITY data but maintains its preference for including SOLIDARITY data as these were used in the NICE rapid guideline, there are no statistically significant differences, and the larger data set reduces the 95% confidence intervals; however the EAG acknowledges that this may be unfavourable to remdesivir due to the inclusion of some patients receiving high-flow oxygen (HFO) (see Section 2.6).

Table 1: The *p*-values estimated by the EAG for comparisons between different oxygen requirements and whether SOLIDARITY data are included

	No supplemental oxygen including SOLIDARITY (0.86, 0.53-1.39)	No supplemental oxygen excluding SOLIDARITY (0.77, 0.34-1.74)	Low-flow oxygen including SOLIDARITY (0.79, 0.68-0.92)	Low flow oxygen excluding SOLIDARITY (0.59, 0.43-0.82)
No supplemental oxygen including SOLIDARITY (0.86, 0.53-1.39)		*p*-value = 0.82	*p*-value = 0.74	*p*-value = 0.20
No supplemental oxygen excluding SOLIDARITY (0.77, 0.34-1.74)			*p*-value = 0.95	*p*-value = 0.55
Low-flow oxygen including SOLIDARITY (0.79, 0.68-0.92)				*p*-value = 0.11

2.6 Decisions from earlier Appraisal Committee meetings could be seriously misleading as the scope of the evaluation has changed

The company "*is concerned that the reasons why Gilead was initially arguing for the inclusion of SOLIDARITY and – following the appeal – is now arguing for why SOLIDARITY should be excluded for the assessment of the LFO population are not fully understood by the committee and thus might have a negative impact on decision making.*" The company states that it highlighted the SOLIDARITY study as in the initial appraisal NICE had not differentiated between people requiring LFO or HFO. Once the modelling differentiated between LFO and HFO, the company states that data from SOLIDARITY should not be used as it did not "*distinguish between level of oxygenation*."

The EAG comments that if remdesivir works less well in people requiring HFO then the inclusion of SOLIDARITY data may underestimate the efficacy of remdesivir as a proportion of patients required HFO. However, the NICE rapid guideline included SOLIDARITY data and there appears to be no

statistically significant difference between the groups (Table *1*). As this point is questioning the understanding of the Appraisal Committee, the EAG has not commented further.

2.7 The mortality rate applied by the Appraisal Committee is inappropriate and different values have been used between appraisals

The company states that the draft guidance provides a range for the mortality rate of 2% to 12% which was informed by two clinical experts. The company states that it was informed that the Appraisal Committee considered a mortality rate of 7%. The company comments that this value does not appear in the draft guidance, lacks transparency, has no robust rationale or origin and is the average of the two values cited by the clinical experts.

The company provides additional sources of information for the mortality rate. Office for National Statistics data suggest approximately 9%[11] in the UK between the period 1st of January to the 19th of December 2023 which the company states will likely underestimate mortality as the data does not distinguish between oxygenation status or treatment received. The company also cites the blinded mortality rate for the sotrovimab arm of the RECOVERY study[12] to be [redacted] which it states is likely to be an upper estimate.

The company therefore believes that a more plausible range is 9% to [redacted] and states that *'Most published real-world evidence (RWE) of studies focused on the LFO population falls into this range*.' While the company did not provide a comprehensive citation list of all evidence sources, it did provide real-world evidence examples from the USA that supports this range with Mozaffari *et al*.[13] reporting a mortality rate in the comparator arm of 12.3% in patients requiring LFO and an overall inpatient mortality of 13.2%. Moreover, the company did not provide a full critique of the strengths and limitations of these evidence sources, and the EAG notes that real-world data may be confounded, and not be generalisable to the current conditions in the UK.

In the study by Mozaffari *et al*.[13] the authors relied on a retrospective comparative effectiveness analysis of in-hospital mortality data from a US Healthcare Database (representing approximately 25% of all hospitalisations) using propensity score methods among patients aged ≥18 years who required supplemental oxygen during the first 2 days of COVID-19 hospitalisation between December 2020 and April 2022. The authors highlighted that *'the primary limitation of this and other comparative effectiveness studies is the potential for residual confounding and subsequent indication bias…, study period was until April 2002 and data on vaccinations were not available.*' Similarly, Isath *et al*.,[14] who analysed the overall inpatient mortality in the US Nationwide Inpatient Sample data set (n= >1.6M

patients) during the peak of the pandemic in the year of 2020, also noted the potential for residual confounding and misclassification of COVID-19 diagnosis, and data on vaccinations were not available.

The company also present data embargoed until early March 2024 that indicates mortality rates in patients requiring LFO and receiving dexamethasone of 9.8% (1196 deaths from 12,211 patients). These data were collected during December 2021 to April 2023 when Omicron was prevalent. Remdesivir was shown to have a beneficial impact on mortality compared to dexamethasone alone in LFO patients (adjusted HR 0.74, 0.68 to 0.80). The EAG notes that it currently has scant details on the dataset apart from that presented above and cannot rule out that there are confounding factors when generalising these data to the UK.

The company states that the values provided are aligned with the 14% estimate used previously in the EAG model and that this value was used when other COVID-19 interventions were appraised. The company states that "*Just because the MTA process for remdesivir got delayed due to the appeal of the initial final draft guidance, which documented significant shortcomings in the assessment procedure, it should not impact decision making for remdesivir by adjusting model parameters which have been used to recommend other treatments in the past, especially not when the latest evidence suggests that the input parameter hasn't changed significantly*." The issue of consistency between appraisals of COVID-19 intervention is for NICE and as such, the EAG has not commented further on this aspect.

2.8 The Appraisal Committee did not recommend remdesivir for all immunocompromised patients despite high mortality rates

This point has overlap with Section 2.1 as it is for the immunocompromised patients who are not receiving LFO where remdesivir has not been recommended. The company cites a mortality rate of up to 25% reported by Evans *et al*.[15] in a dataset including approximately 500,000 immunocompromised patients. Data that is embargoed until early March 2024 indicates a mortality rate of 19.2% in over 10,000 hospitalised immunocompromised patients. Remdesivir was shown to have a statistically significant mortality benefits at 28 days with adjusted hazard ratios (HRs) of 0.75, 0.68-0.83, for the full population and comparable results for patients not requiring supplemental oxygen (0.72, 0.61-0.83) and for patients requiring LFO (0.77, 0.68-0.87). In addition, in response to the draft guidance Astra Zeneca[16] has provided unpublished evidence (data on file) on the mortality rate in immunocompromised patients from the INFORM study. In a subgroup of hospitalised immunocompromised patients who were admitted to the general ward, there were 470 COVID-19 deaths from 4525 hospitalisation episodes (equivalent to a mortality rate of 10.39%).

The company notes that the draft guidance states that "*the committee considered that for immunocompromised people, the mortality rate was likely to be higher than 14%, so remdesivir is a cost-effective use of NHS resources in this group*" but did not recommend remdesivir in the full immunocompromised patient group. The EAG believes this is due to the ambiguity of where remdesivir was positioned (see Section 2.1 and 2.3). In order to inform the Appraisal Committee, the EAG has run analyses for immunocompromised patients not requiring LFO.

2.9 The Appraisal Committee preferred assumptions do not reflect the available evidence

The company subdivides this point into three parts. The first is that the Appraisal Committee did not consider evidence for remdesivir which shows benefits in clinical improvement. The second is that the Appraisal Committee used SOLIDARITY data in estimating the efficacy of remdesivir in patients receiving LFO (see Section 2.5). The third is that the mean efficacy value for remdesivir should be used.

The EAG comments that the Appraisal Committee were presented with a scenario that represented the company's preferred assumptions should the Appraisal Committee wish to select this as most plausible. As the committee's preferred assumptions are an Appraisal Committee decision the EAG has not commented further.

2.10 The threshold for cost-effectiveness was suggested to be £20,000 per QALY without an explanation.

The company highlights that in the draft guidance that there is text implying that a threshold of £20,000 per QALY gained was used in the appraisal of remdesivir. The company states that no explanation for this threshold was provided and that "*it conflicts with the requirements of the Manual which do not provide for an automatic conclusion that an ICER over £20,000 per QALY is cost ineffective, but state that the Committee will refer to the matters at paragraphs 6.3.5 and 6.3.6 of the Manual.*"

The choice of the threshold is an Appraisal Committee decision and as such, the EAG has not commented further.

2.11 The draft guidance acknowledges uncaptured benefits but fails to account for them

The company highlights that Section 3.36 of the draft guidance references uncaptured benefits that are not reflected in the economic model. The company cites a paper by Boglione *et al*. demonstrating that remdesivir reduces the likelihood of long COVID-19 syndrome[17] and also a paper by Caffrey *et al*. which appears not to have been previously cited where there was a significantly lower readmission rate

30 days after discharge.[18] The company states that neither aspect has been properly accounted for in the draft guidance.

The EAG notes that how uncaptured benefits are incorporated into the Appraisal Committee's decision is a matter for NICE and the committee and as such, has not commented further on this matter.

3 AMENDMENTS TO THE EAG'S MODEL AND DESCRIPTION OF THE SCENARIOS RUN

The EAG has made amendments to the mortality percentages without remdesivir; the assumed efficacy of remdesivir; and the starting ordinal scale of patients who do not need supplemental oxygen.

The EAG did not intend to run analyses for subgroups where NICE provided positive recommendations in the draft guidance which were children requiring LFO and immunocompromised adults requiring LFO. However, NICE requested that Scenarios 2 and 3 for immunocompromised adults requiring LFO that had been in the previous EAG report[4] be run using a mortality percentage of 10.39%, which was a value provided by a stakeholder and these results have been provided. This value was chosen as it was lower than the value of 14% that the Appraisal Committee may have used in its decision making (see Section 3.29 of the draft guidance[5])

The EAG were not aware of mortality data for immunocompromised children who do not require supplemental oxygen and so no results were presented for this subgroup.

The company's agreed patient access scheme was incorporated into all the analyses.

3.1 Changes to the mortality percentages without remdesivir

In response to the new evidence on mortality provided by the company the EAG has run additional analyses using alternative sources for the mortality percentage.

For adult patients who are not at high-risk as defined in the McInnes report[7] but who require LFO the EAG has used: 7% (which is the value the company states was preferred by the Appraisal Committee); 9.8% which is the value provided by the company which is currently embargoed; and 14% which was the value used by the EAG in its previous report taken from Amstutz et al.[9]

For adult patients who are immunocompromised but not requiring LFO the EAG has used: 10.39% (the unpublished estimate for immunocompromised patients admitted in the general ward from the INFORM study – see Section 2.8); 14% (which the draft guidance suggested could be a lower value based on the evidence presented at the last committee meeting[5]); and 19.2% (data provided by the company which is currently embargoed).

3.2 Changes to the assumed efficacy of remdesivir in preventing mortality

As previously undertaken, the EAG has reported results using three efficacy levels (mean, mean-low and low). The EAG acknowledges that every high efficacy scenario was estimated to give ICERs below £20,000.

The EAG has used three broad sources of evidence to assess the efficacy of remdesivir. These are: data from Amstutz et al including SOLIDARITY data; [9] data from Amstutz et al excluding SOLIDARITY data; [9] and data provided by the company which is currently embargoed.

With the company positioning remdesivir also in immunocompromised patients with no requirement for supplemental oxygen the EAG had to decide whether to use the efficacy from the specific subgroup (that is, patients requiring LFO for adults requiring LFO, and patients not requiring supplemental oxygen for the immunocompromised group without the need for supplemental oxygen) or from the pooled patients requiring supplemental oxygen and patients requiring LFO groups. Data from Amstutz het al.[9] does not show any statistical significant difference between these groups. Additionally, recent data presented in Section 2.8 shows similar impact of remdesivir in patients requiring LFO and patients who do not need supplementary oxygen. This would suggest that the pooled data would provide a more precise estimate of efficacy. However, the pooled data differs from values used previously in patients requiring LFO. To be comprehensive, the EAG has run analyses using the pooled data, and the group specific data allowing the Appraisal Committee to choose its preferred source.

The EAG calculated the mean value for the distribution of efficacy from each source, used the lower 95% confidence interval for the low-efficacy estimate, and averaged these two values for the mean-low estimate. Odds ratios and relative risks were then transformed into HRs. For the methods used to estimate the pooled efficacy results excluding SOLIDARITY see Appendix 1.

Table 2 provides the HRs calculated by the EAG for each source and efficacy scenario where data are pooled between patients requiring LFO and patients not requiring supplemental oxygen. The company did not provide the data to allow this pooling for patients who are not immunocompromised.

Table 2: EAG calculated HRs for time to death using pooled data from patients requiring LFO and patients not requiring supplemental oxygen.

Source for mortality data relating to remdesivir	Mean Efficacy	Low efficacy	Mean-Low efficacy
Amstutz *et al.*[9] including SOLIDARITY[19]	0.814	0.935	0.875
Amstutz *et al.*[9] excluding SOLIDARITY[19]	0.636	0.850	0.744
Company's embargoed data for patients receiving LFO	N/A	N/A	N/A
Company's embargoed data for immunocompromised patients	0.751	0.830	0.790

Table 3 provides the HRs calculated by the EAG for each source and efficacy scenario using only data from patients who require LFO. Table 4 provides the HRs calculated by the EAG for each source and efficacy scenario using only data from patients who did not require supplemental oxygen.

Table 3: EAG calculated HRs for time to death for patients who require LFO using only data from patients requiring LFO

Source for mortality data relating to remdesivir	Mean Efficacy	Low efficacy	Mean-Low efficacy
Amstutz *et al.*[9] including SOLIDARITY[19]	0.817	0.930	0.865
Amstutz *et al.*[9] excluding SOLIDARITY[19]	0.635	0.839	0.723
Company's embargoed data for patients receiving LFO	0.741	0.800	0.770

Table 4: EAG calculated HRs for time to death for immunocompromised adult patients who require no supplemental oxygen using only data from patients not requiring supplemental oxygen

Source for mortality data relating to remdesivir	Mean Efficacy	Low efficacy	Mean-Low efficacy
Amstutz *et al.*[9] including SOLIDARITY[19]	0.894	Capped at 1	Capped at 1
Amstutz *et al.*[9] excluding SOLIDARITY[19]	0.850	Capped at 1	Capped at 1
Company's embargoed data for immunocompromised patients	0.723	0.850	0.786

3.3 Changes to the starting ordinal stage for adult patients who are immunocompromised but who do not require supplemental oxygen

The model built by the EAG allocates patients to ordinal stages on entry to hospital based on care and supplemental oxygen requirements, with patients requiring LFO starting in ordinal stage 5. Immunocompromised patients with no supplementary oxygen requirements now start in ordinal stage 4.

3.4 The scenarios run by the EAG

The EAG scenarios for adults on LFO, and immunocompromised patients in no need of oxygen are provided in Table 5 and Table 6 respectively. The scenarios represent combinations of the data source used for the HR for overall survival, the assumed efficacy (mean, low and mean-low) and whether any impact on clinical improvement and time to discharge are considered. details the scenarios run for patients requiring LFO.

Table 5: Scenarios and parameter values used in the EAG's analyses for patients requiring LFO

Scenario	Study used for remdesivir efficacy	Pooled data††	Efficacy scenario	Efficacy parameters*
Scenarios 1-15 assume an impact on overall survival only				
1	Amstutz *et al.*[9†]	Yes	Mean	0.814, unity, unity
2	Amstutz *et al.*[9†]	Yes	Low	0.935, unity, unity
3	Amstutz *et al.*[9†]	Yes	Mean-Low	0.875, unity, unity
4	Amstutz *et al.*[9†]	No	Mean	0.817, unity, unity
5	Amstutz *et al.*[9†]	No	Low	0.930, unity, unity
6	Amstutz *et al.*[9†]	No	Mean-Low	0.865, unity, unity
7	Amstutz *et al.*[9]	Yes	Mean	0.636, unity, unity
8	Amstutz *et al.*[9]	Yes	Low	0.850, unity, unity
9	Amstutz *et al.*[9]	Yes	Mean-Low	0.744, unity, unity
10	Amstutz *et al.*[9]	No	Mean	0.635, unity, unity
11	Amstutz *et al.*[9]	No	Low	0.839, unity, unity
12	Amstutz *et al.*[9]	No	Mean-Low	0.723, unity, unity
13	Company's embargoed data	No	Mean	0.741, unity, unity
14	Company's embargoed data	No	Low	0.800, unity, unity
15	Company's embargoed data	No	Mean-Low	0.770, unity, unity
Scenarios 16-30 assume an impact on overall survival and on clinical improvement				
16	Amstutz *et al.*[9†]	Yes	Mean	0.814, 1.040, unity
17	Amstutz *et al.*[9†]	Yes	Low	0.935, 0.990, unity
18	Amstutz *et al.*[9†]	Yes	Mean-Low	0.875, 1.015, unity
19	Amstutz *et al.*[9†]	No	Mean	0.817, 1.040, unity
20	Amstutz *et al.*[9†]	No	Low	0.930, 0.990, unity

21	Amstutz *et al.*[9†]	No	Mean-Low	0.865, 1.015, unity
22	Amstutz *et al.*[9]	Yes	Mean	0.636, 1.040, unity
23	Amstutz *et al.*[9]	Yes	Low	0.850, 0.990, unity
24	Amstutz *et al.*[9]	Yes	Mean-Low	0.744, 1.015, unity
25	Amstutz *et al.*[9]	No	Mean	0.635, 1.040, unity
26	Amstutz *et al.*[9]	No	Low	0.839, 0.990, unity
27	Amstutz *et al.*[9]	No	Mean-Low	0.723, 1.015, unity
28	Company's embargoed data	No	Mean	0.741, 1.040, unity
29	Company's embargoed data	No	Low	0.800, 0.990, unity
30	Company's embargoed data	No	Mean-Low	0.770, 1.015, unity
Scenarios 31-45 assume an impact on overall survival and on time to discharge				
31	Amstutz *et al.*[9†]	Yes	Mean	0.814, unity, 1.270
32	Amstutz *et al.*[9†]	Yes	Low	0.935, unity, 1.100
33	Amstutz *et al.*[9†]	Yes	Mean-Low	0.875, unity, 1.187
34	Amstutz *et al.*[9†]	No	Mean	0.817, unity, 1.270
35	Amstutz *et al.*[9†]	No	Low	0.930, unity, 1.100
36	Amstutz *et al.*[9†]	No	Mean-Low	0.865, unity, 1.187
37	Amstutz *et al.*[9]	Yes	Mean	0.636, unity, 1.270
38	Amstutz *et al.*[9]	Yes	Low	0.850, unity, 1.100
39	Amstutz *et al.*[9]	Yes	Mean-Low	0.744, unity, 1.187
40	Amstutz *et al.*[9]	No	Mean	0.635, unity, 1.270
41	Amstutz *et al.*[9]	No	Low	0.839, unity, 1.100
42	Amstutz *et al.*[9]	No	Mean-Low	0.723, unity, 1.187
43	Company's embargoed data	No	Mean	0.741, unity, 1.270
44	Company's embargoed data	No	Low	0.800, unity, 1.100
45	Company's embargoed data	No	Mean-Low	0.770, unity, 1.187

† Including data from SOLIDARITY[19]

†† whether data for patients not requiring supplemental oxygen has been pooled with data for patients requiring LFO

*Parameter values are: hazard ratio for time to death; relative risk for clinical improvement; hazard ratio for time to discharge

Table 6 details the scenarios run for adult patients who are immunocompromised who do not need supplemental oxygen. As it was not possible to have a 2-point improvement in ordinal scale for patients in hospital starting at ordinal scale 4, clinical improvement was not incorporated.

Table 6: Scenarios and parameter values used in the EAG's analyses for immunocompromised patients not requiring supplemental oxygen

Scenario	Study used for remdesivir efficacy	Pooled data††	Efficacy scenario	Efficacy parameters*
Scenarios 1-18 assume an impact on overall survival only				
1	Amstutz *et al.*[9†]	Yes	Mean	0.814, unity, unity
2	Amstutz *et al.*[9†]	Yes	Low	0.935, unity, unity
3	Amstutz *et al.*[9†]	Yes	Mean-Low	0.875, unity, unity
4	Amstutz *et al.*[9†]	No	Mean	0.894, unity, unity
5	Amstutz *et al.*[9†]	No	Low	unity, unity, unity
6	Amstutz *et al.*[9†]	No	Mean-Low	unity, unity, unity
7	Amstutz *et al.*[9]	Yes	Mean	0.636, unity, unity
8	Amstutz *et al.*[9]	Yes	Low	0.850, unity, unity
9	Amstutz *et al.*[9]	Yes	Mean-Low	0.744, unity, unity
10	Amstutz *et al.*[9]	No	Mean	0.850, unity, unity
11	Amstutz *et al.*[9]	No	Low	unity, unity, unity
12	Amstutz *et al.*[9]	No	Mean-Low	unity, unity, unity
13	Company's embargoed data	Yes	Mean	0.751, unity, unity
14	Company's embargoed data	Yes	Low	0.830, unity, unity
15	Company's embargoed data	Yes	Mean-Low	0.790, unity, unity
16	Company's embargoed data	No	Mean	0.723, unity, unity
17	Company's embargoed data	No	Low	0.850, unity, unity
18	Company's embargoed data	No	Mean-Low	0.786, unity, unity
Scenarios 19-36 assume an impact on overall survival and on time to discharge				
19	Amstutz *et al.*[9†]	Yes	Mean	0.814, unity, 1.270
20	Amstutz *et al.*[9†]	Yes	Low	0.935, unity, 1.100
21	Amstutz *et al.*[9†]	Yes	Mean-Low	0.875, unity, 1.187
22	Amstutz *et al.*[9†]	No	Mean	0.894, unity, 1.270
23	Amstutz *et al.*[9†]	No	Low	unity, unity, 1.100
24	Amstutz *et al.*[9†]	No	Mean-Low	unity, unity, 1.187
25	Amstutz *et al.*[9]	Yes	Mean	0.636, unity, 1.270
26	Amstutz *et al.*[9]	Yes	Low	0.850, unity, 1.100
27	Amstutz *et al.*[9]	Yes	Mean-Low	0.744, unity, 1.187
28	Amstutz *et al.*[9]	No	Mean	0.850, unity, 1.270

29	Amstutz *et al.*[9]	No	Low	unity, unity, 1.100
30	Amstutz *et al.*[9]	No	Mean-Low	unity, unity, 1.187
31	Company's embargoed data	Yes	Mean	0.751, unity, 1.270
32	Company's embargoed data	Yes	Low	0.830, unity, 1.100
33	Company's embargoed data	Yes	Mean-Low	0.790, unity, 1.187
34	Company's embargoed data	No	Mean	0.723, unity, 1.270
35	Company's embargoed data	No	Low	0.850, unity, 1.100
36	Company's embargoed data	No	Mean-Low	0.786, unity, 1.187

† Including data from SOLIDARITY[19]
†† whether data for patients requiring LFO has been pooled with data for patients requiring no supplemental oxygen
*Parameter values are: hazard ratio for time to death; relative risk for clinical improvement; hazard ratio for time to discharge

Table 7 details the scenarios run for adult patients who are immunocompromised who require LFO

Table 7: Scenarios and parameter values used in the EAG's analyses for patients requiring LFO

Scenario	Study used for remdesivir efficacy	Efficacy scenario	Efficacy parameters*
2	Amstutz *et al.*[9†]	Low	0.930, unity, unity
3	Amstutz *et al.*[9†]	Mean-Low	0.865, unity, unity

† Including data from SOLIDARITY[19]
*Parameter values are: hazard ratio for time to death; relative risk for clinical improvement; hazard ratio for time to discharge

4 RESULTS FROM THE EAG'S MODEL

Results are presented for two patient subgroups: adults requiring LFO who do not meet the criteria in the McInnes report; and immunocompromised patients not requiring LFO. The results reported use the patients access scheme discount for remdesivir and as list price ICERs have been previously reported, the ICERs are highlighted commercial-in-confidence to stop back-calculation of the discount.

4.1 ICERs estimated by the EAG for remdesivir when treating adult patients requiring LFO

Table 8 provides the ICERs for remdesivir when compared with SoC for treating adults requiring LFO. The EAG highlights that clinical improvement is not a key driver of results and, as such, there are only slight differences between the results obtained in Scenarios 1 to 15 and those obtained in Scenarios 16 to 30. In contrast, when remdesivir was assumed to have a beneficial effect on time to discharge the ICERs were markedly more favourable. The ICERs are also noticeably influenced by the assumed mortality rate, with lower ICERs at 14% than at 7%.

The source for the efficacy data (Amstutz *et al.*[9] with SOLIDARITY data, Amstutz *et al.*[9] without SOLIDARITY data and the company's embargoed data) had a large impact on the ICER, although whether data were pooled between patients requiring LFO and patients who did not need supplemental oxygen only had a slight impact on the ICER.

Table 8: The ICERs generated by the EAG analyses for adult patients requiring LFO

Scenario number	Mortality rate of 7.0%	Mortality rate of 9.8%	Mortality rate of 14.0%
Scenarios 1-15 assume an impact on overall survival only			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]

15	[redacted]	[redacted]	[redacted]
Scenarios 16-30 assume an impact on overall survival and on clinical improvement			
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
Scenarios 31-45 assume an impact on overall survival and on time to discharge			
31	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
37	[redacted]	[redacted]	[redacted]
38	[redacted]	[redacted]	[redacted]
39	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]
41	[redacted]	[redacted]	[redacted]
42	[redacted]	[redacted]	[redacted]
43	[redacted]	[redacted]	[redacted]
44	[redacted]	[redacted]	[redacted]
45	[redacted]	[redacted]	[redacted]

4.2 ICERs estimated by the EAG for remdesivir when treating adult patients who are immunocompromised but do not require supplemental oxygen

Table 9 provides the ICERs for remdesivir when compared with SoC for treating adults patients who are immunocompromised but who do not require supplemental oxygen. When remdesivir was assumed to have a beneficial effect on time to discharge the ICERs were markedly more favourable. The ICERs are noticeably influenced by the assumed mortality rate and are higher using 10.39% than when using 19.2%. In contrast to the results in Section 4.1, whether or not the efficacy is estimated by pooling patients that require LFO and patients that do not require supplemental oxygen has a large impact on the ICER when data from Amstutz *et al.*[9] is used. This is because the efficacy estimates for remdesivir reported in Amstutz *et al.*[9] for patients not requiring supplemental oxygen have wide confidence intervals that cross unity implying that remdesivir may be harmful to patients.

Table 9: The ICERs generated by the EAG analyses for immunocompromised patients not requiring supplemental oxygen

Scenario number	Mortality rate of 10.39%	Mortality rate of 14%	Mortality rate of 19.2%
Scenarios 1-18 assume an impact on overall survival only			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
Scenarios 19-36 assume an impact on overall survival and on time to discharge			
19	[redacted]	[redacted]	[redacted]

20	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
31	[redacted]	[redacted]	[redacted]
32	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]
34	[redacted]	[redacted]	[redacted]
35	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]

4.2 ICERs estimated by the EAG for remdesivir when treating adult patients who are immunocompromised and that require LFO

The ICERs for the two scenarios requested by NICE, which used a mortality rate of 10.39% for adult patients who are immunocompromised but requiring LFO were [redacted] for Scenario 2 and [redacted] for Scenario 3 of Table 7.

5 DISCUSSION

The EAG has produced comprehensive results for two distinct populations: adult patients who require LFO and adult patients who are immunocompromised but do not need supplemental oxygen. For both groups, there is a wide range of ICERs which are dependent on the assumed underlying mortality at 28 days, the source of efficacy data for remdesivir, and whether remdesivir is assumed to have a beneficial impact on discharge. Additionally, for the adult patients who are immunocompromised but do not need supplemental oxygen, when the efficacy data comes from Amstutz *et al.*,[9] whether data are pooled between patients requiring LFO and patients who do not require supplemental oxygen, or just taken from the no supplemental oxygen group has a large impact on the results.

The EAG also provided results from scenarios requested by NICE for immunocompromised adults requiring LFO using a lower mortality rate of 10.39% at 28 days. These results are commercial-in-confidence and with only two results generated, no comments can be made on patterns, although, previous analyses (see Table 4 of the previous EAG report[4]) have shown that these ICERs are amongst the least favourable to remdesivir.

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7 APPENDIX 1: CALCULATION OF ADJUSTED ODDS RATIO FOR MORTALITY AT DAY 28 WITHOUT ADDITIONAL SOLIDARITY DATA FOR PATIENTS WHO RECEIVED NO OXYGEN OR LOW-FLOW OXYGEN

Amstutz et al.[1] reported results for mortality at day 28 without SOLIDARITY for patients who received no supplemental oxygen and for patients who received low-flow oxygen (Appendix Figure S8). However, Amstutz et al.[1] did not report the results without SOLIDARITY when data for patients who received no oxygen or low-flow oxygen were pooled.

Without SOLIDARITY, for patients who received no supplemental oxygen, 14 of 525 patients (2.7%) assigned to remdesivir died compared with 12 of 332 patients (3.6%) assigned to no remdesivir (adjusted odds ratio [aOR] 0.77, 95% confidence interval [CI] 0.34-1.74). Without SOLIDARITY, for patients who received low-flow oxygen, 75 of 1094 patients (6.9%) assigned to remdesivir died compared with 114 of 1012 patients (11.3%) assigned to no remdesivir (aOR 0.59, 95% CI 0.42-0.82).

Given that only aggregate results from the subgroups were available a weighted average approach was used to obtain the estimate for patients who received no supplemental oxygen or low-flow oxygen. An inverse variance weighting approach was applied to derive the appropriate weight for the no supplemental oxygen subgroup and low-flow oxygen subgroup using the meta package in R.[2] The estimated weight was 0.131 and 0.869 for the no supplemental oxygen and low-flow oxygen group, respectively. The reported aORs for the two groups (0.77 for the no oxygen group and 0.59 for the low-flow oxygen group) were used to calculate the weighted average aOR. The standard error for the weighted average was calculated based on the effective sample size as suggested by Bevington,[3] that is the square root of the variance for the weighted average divided by the effective sample size.

The pooled aOR (remdesivir vs. no remdesivir) for mortality at day 28 without SOLIDARITY data for patients who received no oxygen or low-flow oxygen was 0.61 95% CI 0.44-0.84.

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COVID-19 statistics from OpenSAFELY-TPP database

Study population: all people hospitalised with COVID-19 as a diagnosis in any position between 1st January 2023 and 31st December 2023. Inpatient hospital records come from the Secondary Uses Service. For further detail on data sources and methods please see previously published work.

We present the 28-day mortality for all people and stratified by intensive care admission, early and late 2023 and whether COVID-19 was coded as the primary reason for admission. Due to the change in delivery of COVID therapeutics away from Community Medicines Delivery units we no longer receive meaningful data from NHS England and so the numbers identified to be treated prior to admission were too small to release.

Study period: 1st January 2023 to 31st December 2023

Population	**N**	**Events**	**28-day mortality rate**
All	60,460	1,095	1.81%
Hospitalised (no ICU admission)	57,930	990	1.71%
Hospitalised (ICU admission)	2,530	105	4.15%
Admitted January-June 2023	37,760	750	1.99%
Admitted July-December 2023	22,700	345	1.52%
COVID-19 primary reason for admission	17,395	230	1.32%
COVID-19 not primary reason for admission	43,065	865	2.01%