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. **Post-appeal targeted submission from Gilead**
   a. Targeted submission
   b. Addendum

2. **External Assessment Group response to targeted submission** prepared by the School of Health and Related Research (ScHARR)

3. **External Assessment Group response – factual accuracy check**

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

Gilead targeted submission following the decision of the appeal hearing for the multiple technology assessment for COVID-19 treatments [ID6261]

Evidence submission to support the resolution of the upheld appeal points

Drug	Remdesivir (Veklury)
Therapeutic indication	Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in: • adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment). • adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
Appraisal number	ID6261
Company representative	Mirko von Hein Associate Director, Market Access UK & Ireland Mirko.vonhein@gilead.com
2nd company representative	Gordon Lundie Executive Director, Market Access UK & Ireland Gordon.lundie@gilead.com
Date of submission	Friday, 01 September 2023

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Table of Contents

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

List of tables

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

List of figures

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

List of abbreviations

Abbreviation	Definition
ACM	Appraisal committee meeting
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CEP	Cost-effectiveness plane
CI	Confidence interval
CROI	Conference on retroviruses and opportunistic infections
EAG	Evidence assessment group
FDG	Final draft guidance
HFO	High flow oxygen
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
LCS	Long COVID syndrome
LFO	Low flow oxygen
LOS	Length of stay
MTA	Multiple technology assessment
NICE	National institute for health and care excellence
NIH	National Institute of Health
NMA	Network meta-analysis
ONS	Office of national statistics
OR	Odds ratio
PSA	Probabilistic sensitivity analysis
PSM	Propensity score matching
QALY	Quality adjusted life year
RCT	Randomized controlled trial
RR	Rate ratio
RWE	Real world evidence
SLR	Systematic literature search
SOC	Standard of care
STA	Single technology appraisal
TTD	Time to discharge
VOC	Variant of concern
WTP	Willingness to pay

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

1 Executive summary

Gilead appreciates the opportunity to submit new evidence on remdesivir for the treatment of COVID-19 in preparation for a third committee meeting for the COVID-19 multiple technology appraisal [ID6261]. Following the successful appeal of the MTA final draft guidance (FDG), it is in the interest of patients to make treatment with remdesivir available as quickly as possible. For this reason, Gilead has chosen to work with NICE to progress the assessment of remdesivir in a third committee meeting within the current appraisal process, instead of pursuing the alternative option presented by NICE of a separate, single technology appraisal process, (A summary of the procedural history is provided in section 2.1)

In upholding Gilead's appeal, the Appeal Panel found that the original MTA process was unfair. As part of resolving this unfairness, NICE has agreed that four aspects must be addressed, namely (1) the opportunity for Gilead to make a targeted evidence submission, (2) an opportunity for engagement with the evidence assessment group (EAG) on economic modelling for remdesivir, (3) the ability for Gilead to comment on the EAG report following model adaptation and (4) an agenda for the third appraisal committee meeting (ACM) which allows appropriate room for discussion of the relevant evidence for remdesivir.

Even though COVID-19 surveillance efforts in England are decreasing, patients are still admitted to hospital in need of treatment – even though not at same rates which were observed during the height of the pandemic. These patients deserve access to a broad variety of treatment alternatives in the hospital setting, in which remdesivir plays a vital role as a key antiviral.

Gilead is convinced of the value which remdesivir provides for patients covered in the entire label population (viz. section 3). However, this evidence submission focuses on the patient populations in which remdesivir is most effective, which include patients requiring low-flow oxygen (LFO), children as well as immunocompromised patients.

To generate the evidence synthesis presented in this targeted submission, Gilead conducted both clinical and economic systematic literature reviews (SLR) for the in-hospital use of remdesivir (viz. section 4.1). These systematic searches were supplemented by targeted searches for the patient populations which are covered by the scope of this submission (viz. section 4.2).

As demonstrated by the evidence referenced in this submission, remdesivir provides significant clinical benefit to patients on LFO (viz. section 5.1.1). Multiple independent SLRs and meta-analyses of randomized controlled trials (RCT) have shown a significant mortality benefit of remdesivir compared to standard of care (SOC), which is further validated by the results from real-world-evidence (RWE) studies. Similarly, remdesivir patients on LFO show clinical improvement, better recovery and slower progression to invasive mechanical ventilation (IMV) or death compared to SOC.

Remdesivir has also been proven to be safe and well tolerated among children, making it the only viable treatment option for this vulnerable patient population in patients aged <12 years (viz. section 5.2).

Furthermore, remdesivir shows promising data in other vulnerable patient populations – such as immunocompromised patients (viz. section 5.3) – as demonstrated by statistically significant 14- and 28-day mortality benefit across multiple variant areas.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

In addition to the evidence provided in this targeted submission, Gilead has provided an alternative cost-effectiveness model (CEM) to supplement the economic modelling done by the EAG. The Gilead CEM shows that remdesivir is not only clinically effective, but also highly cost-effective for treating LFO patients, with an incremental-cost-effectiveness ration (ICER) of £2,331 (viz. section 6.1.2).

Lastly, Gilead has provided suggestions on how to structurally amend the EAG CEM to incorporate a LFO patient population (viz. section 6.2.1), which would allow the generation of independent cost-effectiveness estimates, alongside recommendations for the most appropriate data input sources to be used for LFO patients (viz. section 6.2.2).

This targeted evidence submission demonstrates the significant clinical benefit and cost-effectiveness for remdesivir in LFO, paediatric and immunocompromised patients. Gilead is eager to collaborate with NICE and the EAG to ensure that patients benefiting the most from treatment with remdesivir get access to the antiviral drug.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

2 Background

2.1 Procedural history

Starting in early 2022, the NICE COVID-19 multiple technology appraisal (MTA) went through two appraisal committee meetings after which NICE published final draft guidance (FDG) in which remdesivir was not recommended as a treatment option for COVID-19. Gilead has successfully appealed this FDG, on grounds summarised in section 2.2 below, including in respect of unfairness of the MTA process.[1]

After the appeal panel decision, NICE proposed two options to Gilead to address the upheld appeal points. These two options included:

- Going back to committee meeting (option 1)
- Starting a new single technology assessment procedure for remdesivir (option 2)

Given that it is in Gilead's interest to resolve the upheld appeal points as quickly as possible so that patients can benefit again from having remdesivir available to them as a treatment option for COVID-19, Gilead agreed with NICE to pursue option 1, on condition that this option would include the following, to help redress the unfairness in the earlier stages of the MTA process:

- The opportunity for Gilead to make a targeted evidence submission
- The opportunity for Gilead to engage with the EAG on the adaptation of the EAG CEM
- The opportunity for Gilead to comment on the EAG report
- The guarantee from NICE that the agenda for the 3rd committee meeting will be structured to ensure adequate discussion of the evidence for remdesivir

(See Appendix 1 for detail). NICE has accepted these conditions.

2.2 Upheld appeal points

In its decision, the appeal panel has upheld Gilead's appeal on 4 grounds.[1] A summary of the Gilead appeal points which were upheld and dismissed is provided in Table 1. In addition to the 4 upheld appeal points, the NICE committee has been invited by the appeal panel to provide further clarification in the final draft guidance in relation to Gilead appeal points 1(a)3 and 2.1.[1] For the appeal points which were upheld, the appeal panel has provided direction on how to resolve these appeal points. A summary of these directional statements from the appeal panel is provided in Table 2.

Table 1: Gilead appeal points summary

Appeal ground	Appeal point	Outcome
1(a)1	NICE acted unfairly because the lack of time and resource allocated to this MTA meant companies were not given the opportunity to make a full evidence submission and NICE refused Gilead's request to submit an economic model, resulting in important evidence not being considered by the Committee	Upheld
1(a)2	NICE acted unfairly because the lack of time meant that the EAG relied on pre-existing living systematic reviews and network meta-analyses which were not originally designed to address the decision problem and were not sufficiently validated, resulting in significant flaws in the information considered by the Committee	Upheld
1(a)3	NICE acted unfairly because cost-effectiveness estimates were not informed by a probabilistic sensitivity analysis without adequate justification, and so the Committee failed to sufficiently explore parameter uncertainty	Dismissed*
1(a)6	NICE acted unfairly because the Committee has not given adequate reasons for why the population requiring "low-flow oxygen" was not considered as a potential subgroup	Upheld
1(a)8	NICE acted unfairly because it treated Gilead unfairly compared to another stakeholder company by refusing to consider new data that could potentially change the Committee's final conclusions	Dismissed
1(a)10	NICE acted unfairly because the Committee's exclusion of treatment effects for hospital time to discharge data for remdesivir is unfair because these treatment effects were reflected in the base-case ICER results for tocilizumab	Dismissed
1(b)1	NICE exceeded its powers as the Committee did not conduct a thorough assessment of treatments for children with severe COVID-19 and the resulting failure to recommend any treatment for children with severe COVID-19 is unfair and discriminatory	Upheld
2.1	The Committee's conclusion that significant uncertainty remains in terms of generalisability of the trial evidence for remdesivir in severe COVID-19 is unreasonable because it ignores clinical practice and in-vitro data that has not been countered	Dismissed*
* NICE has been incentivized by the appeal panel to provide further clarification in the final draft guidance		

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Table 2: Appeal panel direction for the upheld Gilead appeal points

Appeal ground	Outcome	Appeal Panel direction
1(a)1	Upheld	The appraisal committee must address the unfairness resulting from the deviation from NICE's processes for MTA defined in the Manual, specifically the challenges to stakeholder engagement resulting from the re-sequencing of the appraisal process and the abbreviation of the usual timeframe.
1(a)2	Upheld	
1(a)6	Upheld	The appraisal committee should provide a clear explanation of why the cohort of patients with severe COVID-19 who require low-flow oxygen was not considered suitable for sub-group analysis and should reconsider whether an analysis of this subgroup would be informative.
1(b)1	Upheld	The appraisal committee should reconsider whether their decision not to recommend any therapy for children with severe COVID-19 is a proportionate means to achieve NICE's legitimate aims.

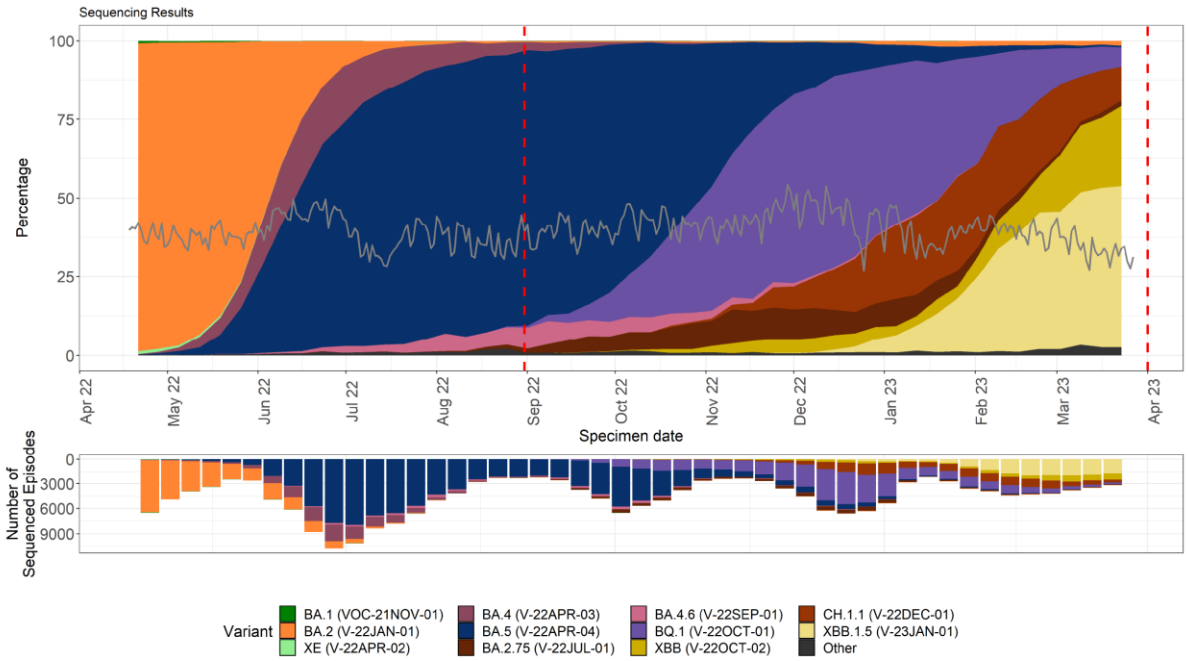
Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

2.3 Development of the COVID-19 landscape

Even though current COVID-19 surveillance has decreased, and the latest available epidemiological data from UKHSA suggests a stabilisation in incidence estimates as well as a slow decline in hospitalisations, patients who are being admitted to hospital still require adequate treatment alternatives for COVID-19 to prevent long hospitalisation, high morbidity and mortality.

As shown in Figure 1, the UKHSA technical briefing 52 shows a high prevalence of the XBB (Omicron) variants as per their latest data assessment point in April 2023. Even though ONS monitoring for COVID-19 in England has been paused, patients are still getting admitted to hospital for COVID-19 – even though at a lower rate compared to late 2020 and 2021 – (viz. Figure 2) requiring treatment for Omicron and other variants of concern (VOC).

Figure 1: Variant prevalence (UKHSA designated variant definitions only) of available sequenced cases for England from 18 April 2022 to 2 April 2023, based on UKHSA technical briefing 52 [2]



The grey line indicates proportion of cases sequenced. The first red dashed line denotes the start of England's 'Living with COVID' plan at the start of April 2022 and the second indicates the pause of asymptomatic testing for high-risk settings at the end of August 2022. The dashed red vertical line denotes changes in PCR testing in April 2023. The data used in this graph can be found in the accompanying spreadsheet.

Figure 2: Hospital admission rates due to COVID-19 in England, based on data from the office of national statistics (ONS) [3]

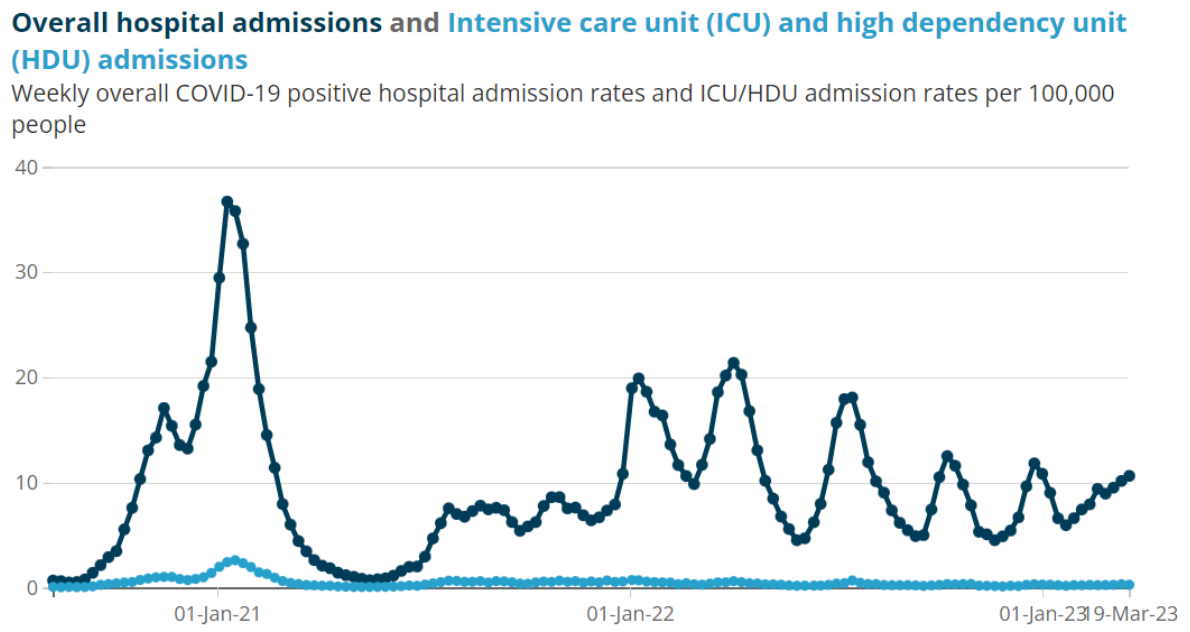
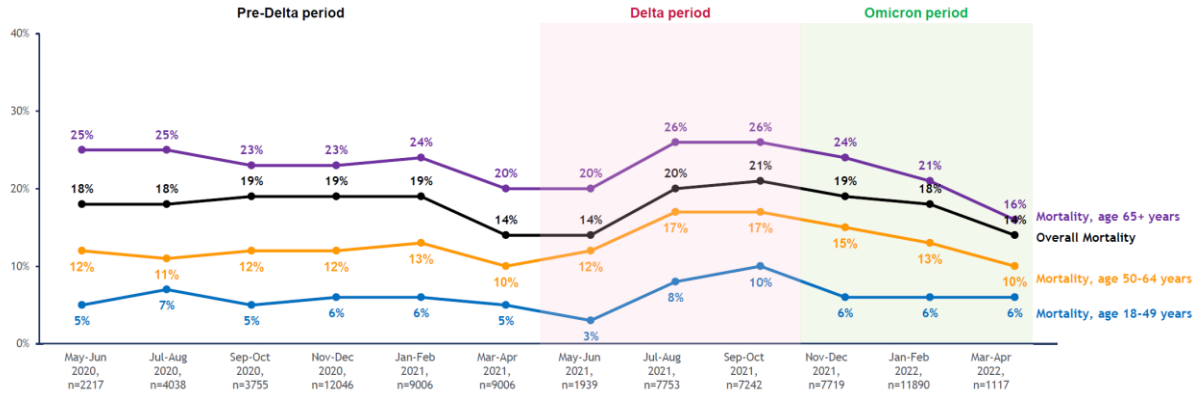


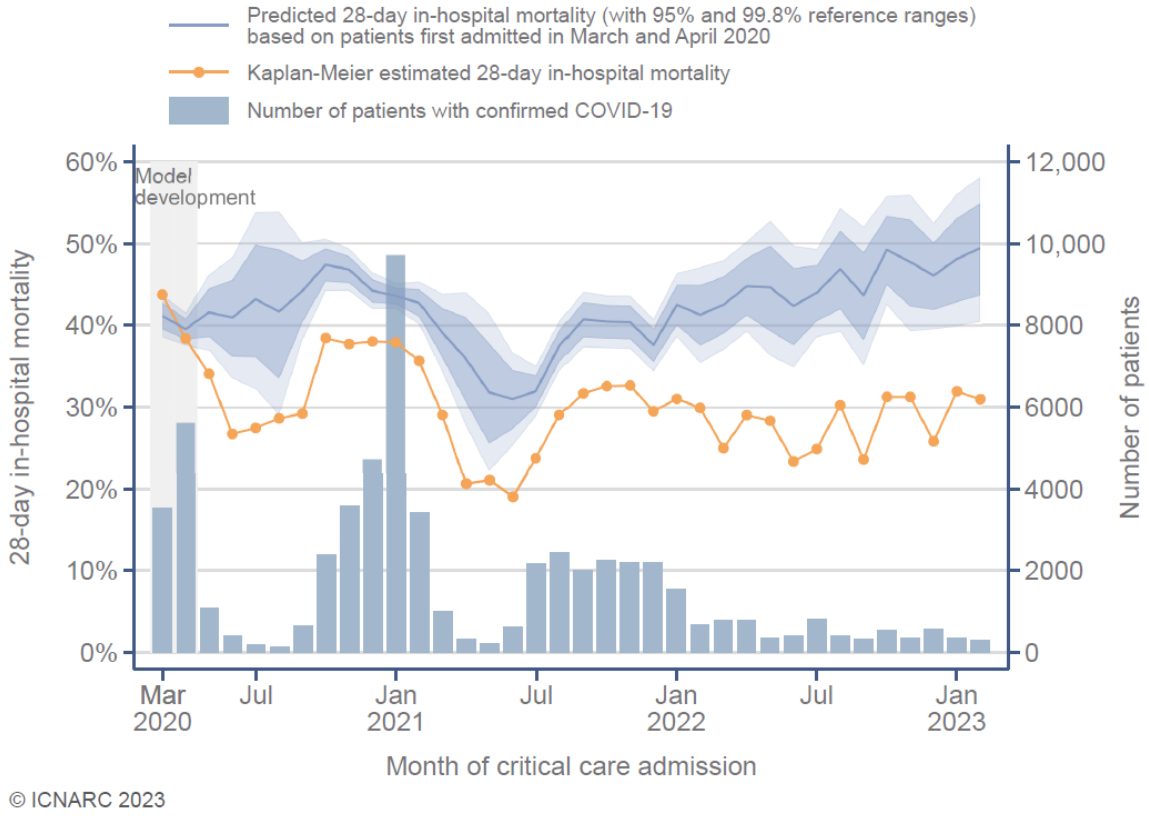
Figure 3: Mortality by age group among immunocompromised COVID-19 patients, based on data presented at ECCMID [4]



Similarly, even though mortality for COVID-19 patients has decreased, patients are still dying from the virus, as shown in the mortality trend for immunocompromised COVID-19 patients in Figure 3. As can be seen from Figure 3, mortality for immunocompromised patients has declined from its peak during the delta variant period, ranging from 10% (age 18-49) to 26% (age 65+) depending on age group, to 6% to 16% respectively.[4]

Further data published in the ICNARC report from June 2023 paints a similar picture. As shown in Table 4, observed 28-day hospital mortality (orange dotted line) hasn't changed significantly over the last 24 months, reporting observed mortality rates in July 2021 similar if not lower than mortality observed in January 2023.[5]

Figure 4: Risk-adjusted 28-day in-hospital mortality, based on the ICNARC report (June 2023) [5]



3 Scope of the targeted submission

Remdesivir (Veklury) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.[6]

Even though Gilead is convinced of the value which remdesivir provides for the patients in the entire label population as defined above, Gilead appreciates the opportunity to provide NICE with a summary of the evidence for the patient populations in which remdesivir is most effective. These patient populations include patients requiring low-flow oxygen (LFO), children as well as immunocompromised patients. A definition of each of these patient populations is provided in Table 3 below.

Table 3: Definition of relevant patient populations for remdesivir

Patient population	Definition
Low-flow oxygen (LFO)	Patients requiring oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min as per the NICE COVID-19 rapid guidelines [7]
Children	The paediatric patient population includes • paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) • paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 as outlined in the summary of product characteristics (SmPC) for remdesivir [6]
Immunocompromised patients	Patients who have a weakened immune system due to a particular health condition or patients who are on medication or treatment that suppresses their immune system

The scope of this targeted submission is to provide NICE with clinical evidence on the patient populations (see Table 3) in which remdesivir is most effective (viz. section 5), present cost-effectiveness results using the Gilead cost-effectiveness model (CEM) (viz. section 6.1) and elaborate on suggestions on how to adapt the CEM developed by the evidence assessment group (EAG) (viz. section 6.2).

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

4 Methods

4.1 Systematic literature search

Gilead has conducted both clinical and economic systematic literature reviews (SLR) for the in-hospital use of remdesivir which are provided to NICE as part of this targeted submission. The clinical and economic inpatient SLR were originally conducted in January 2022 and last updated in December 2022. These SLRs were initially designed to cover a broader use case of remdesivir in the inpatient sector, without a focus on subgroups. Aligned with the scope of this targeted submission (viz. section 3), these SLRs were screened for studies that match with the scope of this targeted submission, i.e., LFO, children and immunocompromised patients. To not further delay the appraisal process for remdesivir, no distinct systematic searches were carried out for the subgroups which are in scope of this targeted submission.

4.2 Targeted literature search

To complement the review of the systematic searches presented in 4.1, an additional targeted search was conducted up until August 2023, which focused on patients receiving LFO, paediatric patients as well as patients who are immunocompromised. The resulting evidence capture both using systematic and targeted searches is presented in section 5.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

5 Clinical evidence

5.1 Low-flow oxygen

5.1.1 Mortality

Remdesivir has a significant mortality benefit in patients receiving LFO, as proven by several studies, including network-meta-analyses (NMA) of randomized controlled trials as well as real-world evidence (RWE) spanning across multiple COVID variants of concern.

As demonstrated in Table 4, LFO patients receiving remdesivir had significantly improved 28-day mortality compared to patients receiving SOC. The strongest 28-day mortality effect measured by risk ratio (RR) comparing remdesivir against SOC was reported by Beckerman et al. 2022, who report a RR of 0.24 [0.11, 0.48].[8] Even the most conservative estimates for the 28-day mortality benefit of remdesivir showcase and adjusted hazard ratio (aHR) of 0.85 [0.77, 0.92], as reported by Garibaldi et al. 2022.[9]

Additionally, none of the upper confidence intervals (CI) reported in the studies assessing 28-day mortality cross 1, indicating a high certainty of a mortality benefit associated with remdesivir.

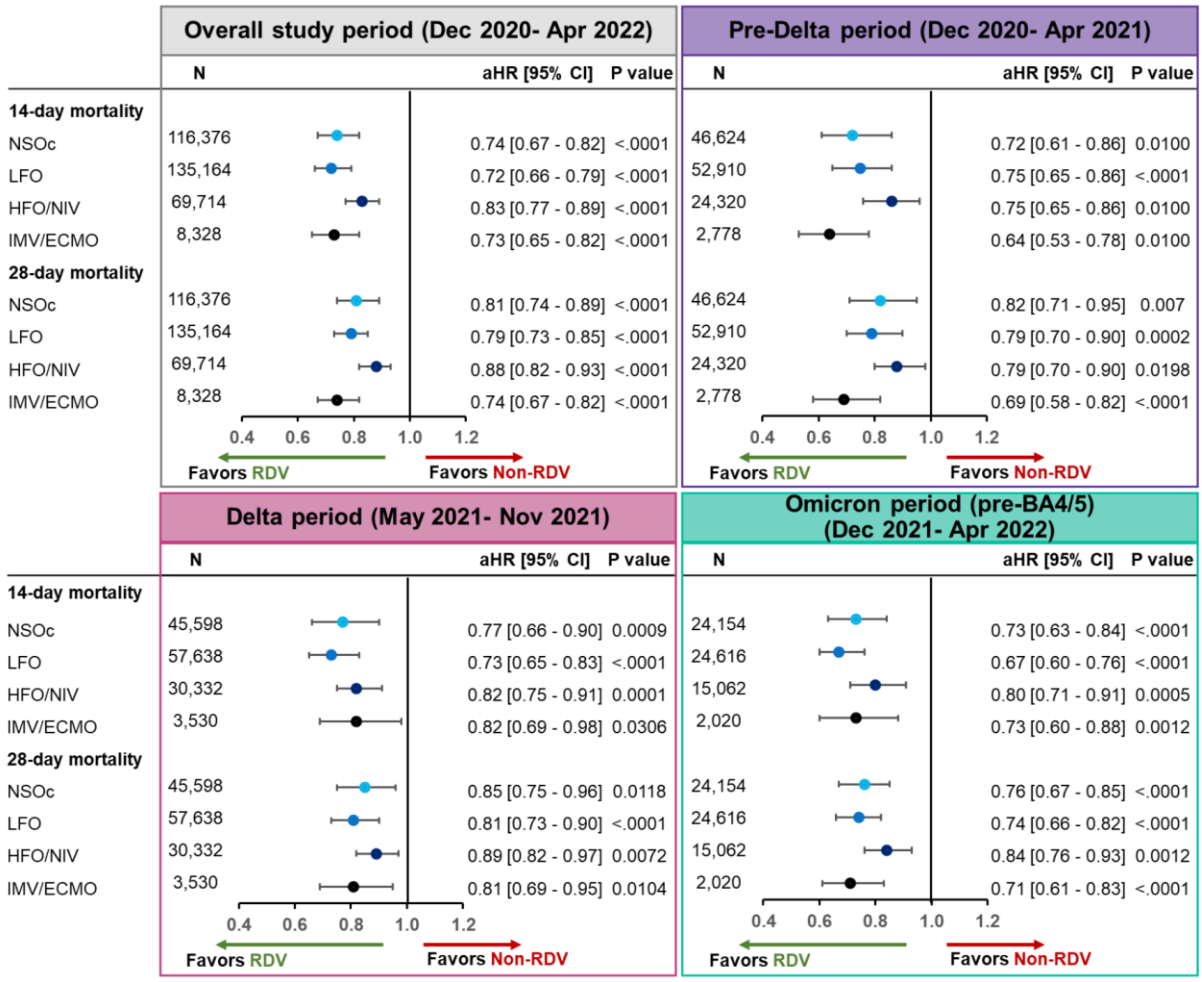
Table 4: Evidence overview by evidence type for RDV 28-day mortality in low-flow patients compared to SOC

Study	Evidence type	Outcome [95% CI]
Huang et al. 2023 [10]	SLR / NMA (RCT)	RR 0.59 [0.43, 0.80]
Beckerman et al. 2022 [8]	SLR / NMA (RCT)	RR 0.24 [0.11, 0.48]
Amstutz et al. 2023 [11]*	SLR / NMA (RCT)	aOR 0.80 [0.70, 0.93]
Beigel et al. 2020 (ACTT-1) [12]	RCT	HR 0.30 [0.14, 0.64]
Mozaffari et al. 2023 (CROI) [13]	RWE	aHR 0.79 [0.73, 0.85]
Jeyapalina et al. 2022 [14]	RWE	HR 0.58 [0.42, 0.80]
Chokkalingam et al. 2022 [15]	RWE	HR 0.81 [0.73, 0.90]
Garibaldi et al. 2022 [9]	RWE	aHR 0.85 [0.77, 0.92]
Mozaffari et al. 2022 [16]	RWE	HR 0.77 [0.68, 0.86]
Olender et al. 2021 [17]	RWE	OR 0.29 [0.14, 0.58]
aHR: adjusted hazard ratio; aOR: adjusted odds ration; OR: odds ratio; CI: Confidence interval; CROI: Conference on Retroviruses and Opportunistic Infections; HR: hazard ratio; NMA: network meta-analysis; RCT: Randomized controlled trial; RR: risk ratio; RWE: Real-world-evidence; SLR: systematic literature review * Amstutz et al. analyse patients with no or low-flow oxygen requirements as a single patient population		

The evidence supporting the mortality benefit of remdesivir in LFO patients is further validated by results from recent RWE studies such as the one conducted by Mozaffari et al. 2022.[13, 16] As shown in Figure 5, mortality results for the LFO patient population covering the entire study duration show a significant mortality benefit for remdesivir, as expressed by an aHR of 0.79 [0.73, 0.85]. The study also reported results for the most recent Omicron VOC, in which mortality results were consistent with the results for the overall study duration (aHR 0.74 [0.66, 0.82]).

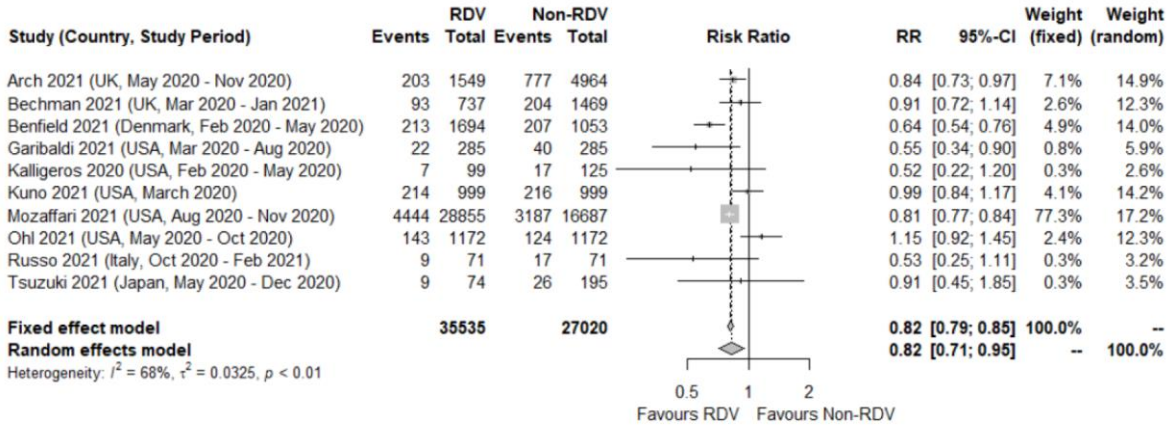
On top of that recent evidence suggests that giving remdesivir early – i.e. within 2 days of hospital admission – reduces hospital mortality compared to no early remdesivir and no remdesivir, thus highlighting the need for rapid treatment with remdesivir once patients are hospitalised.[18]

Figure 5: Mortality results presented by Mozaffari et al. at CROI [13]



The positive impact remdesivir has in a real-world setting is further proven by a NMA which assessed and summarized late-stage mortality results for all hospitalised patients. In their study Barnieh et al. report a RR of 0.82 [0.71, 0.95] using a random effects model as well as a RR of 0.82 [0.79, 0.85] using a fixed effects model (viz. Figure 6).[19]

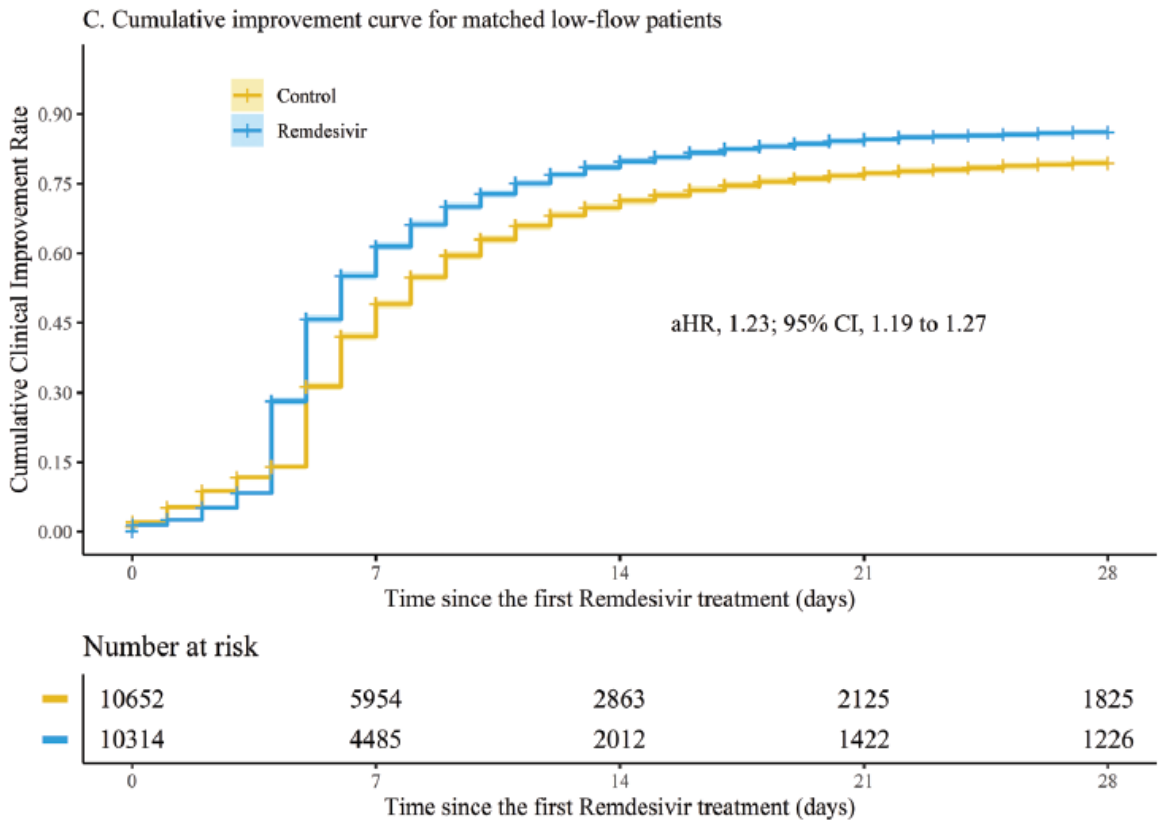
Figure 6: Forest plot for later mortality assessment for all hospitalized patients from Barnieh et al. 2022 [19]



5.1.2 Clinical improvement

Patients on remdesivir have superior outcomes for clinical improvement, as demonstrated in a retrospective, multicentre comparative effectiveness study conducted by Garibaldi et al. from 2022.[9] As shown in the curves presented in Figure 7, remdesivir shows an aHR of 1.23 [1.19, 1.27] for patients on LFO. This means that LFO patients on remdesivir took a median of 6 days compared to a median of 7 days (controls) to achieve clinical improvement.

Figure 7: Clinical improvement for LFO patients, based on Garibaldi et al. [9]



This benefit of remdesivir to demonstrate clinical improvement compared to SOC beyond the LFO patient population has also been shown in various other meta-analysis, which evaluated clinical improvement in a broader patient population, such as the studies from Gholamhoseini et al. and Singh et al., alongside with results on clinical improvement from the COVID NMA initiative.[20-22]

5.1.3 Time to discharge

Data on time to discharge (TTD) from hospital for remdesivir patients compared to SOC is sparse. As already flagged in the Gilead response to the NICE draft guidance, the ACTT-1 found a significant reduction in TTD or to a National Early Warning Score (NEWS) of ≤2 compared to SOC. As outlined in Figure 8, the hazard ratio for TTD reported in ACTT-1 is 1.27 [1.10-1.46], showing clear separation in Kaplan-Meier curves, indicating a TTD benefit for remdesivir.[23]

In contrast to the results from ACTT-1, Spinner et al. 2020 report the cumulative percentage of patients discharged from hospital in patients receiving both 5 and 10-day remdesivir as well as SOC.[24] As depicted in Figure 9, 5-day remdesivir, 10-day remdesivir as well as SOC show overlapping discharge curves over time.

It should be noted that neither the ACTT-1 nor the results from Spinner et al. for the TTD outcome were analysed for a patient population receiving low-flow oxygen, which is the patient population in which remdesivir is most effective.

Figure 8: Kaplan-Meier Curves of Time to Discharge or to a National Early Warning Score (NEWS) of ≤2 by Treatment Group (ITT Population) [23]

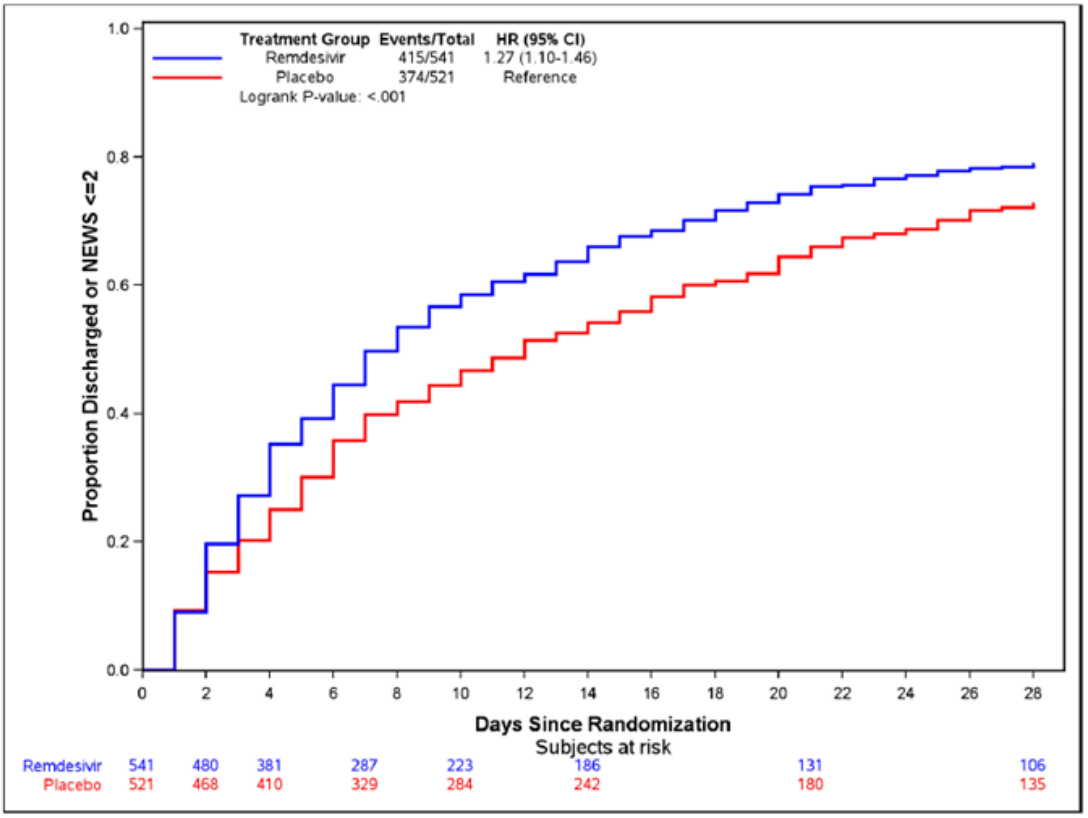
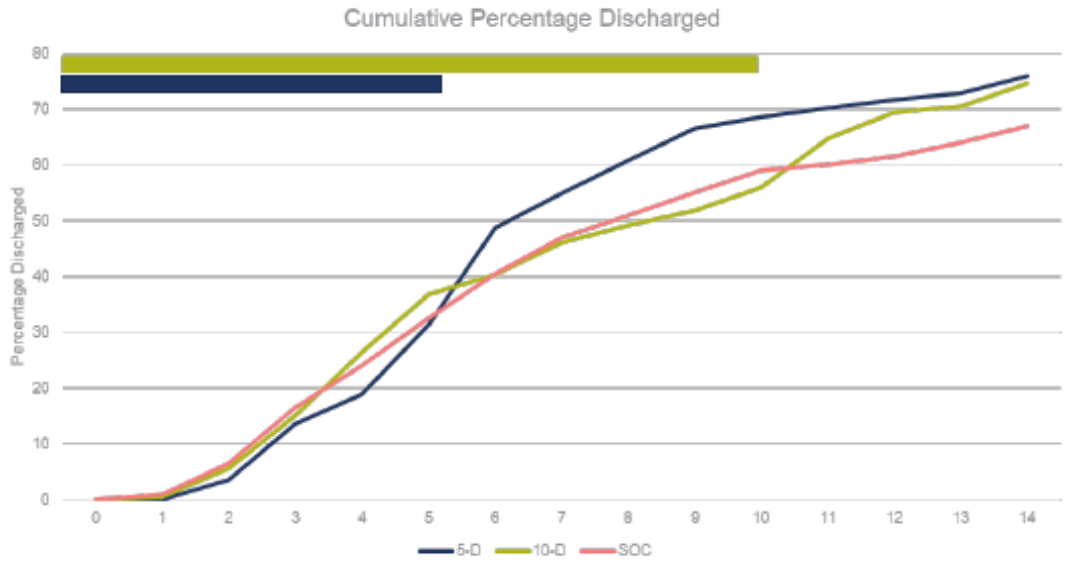


Figure 9: Cumulative percentage of patients discharged from hospital on 5-day remdesivir, 10-day remdesivir and SOC, based on supplementary materials from Spinner et al. 2020 [24]

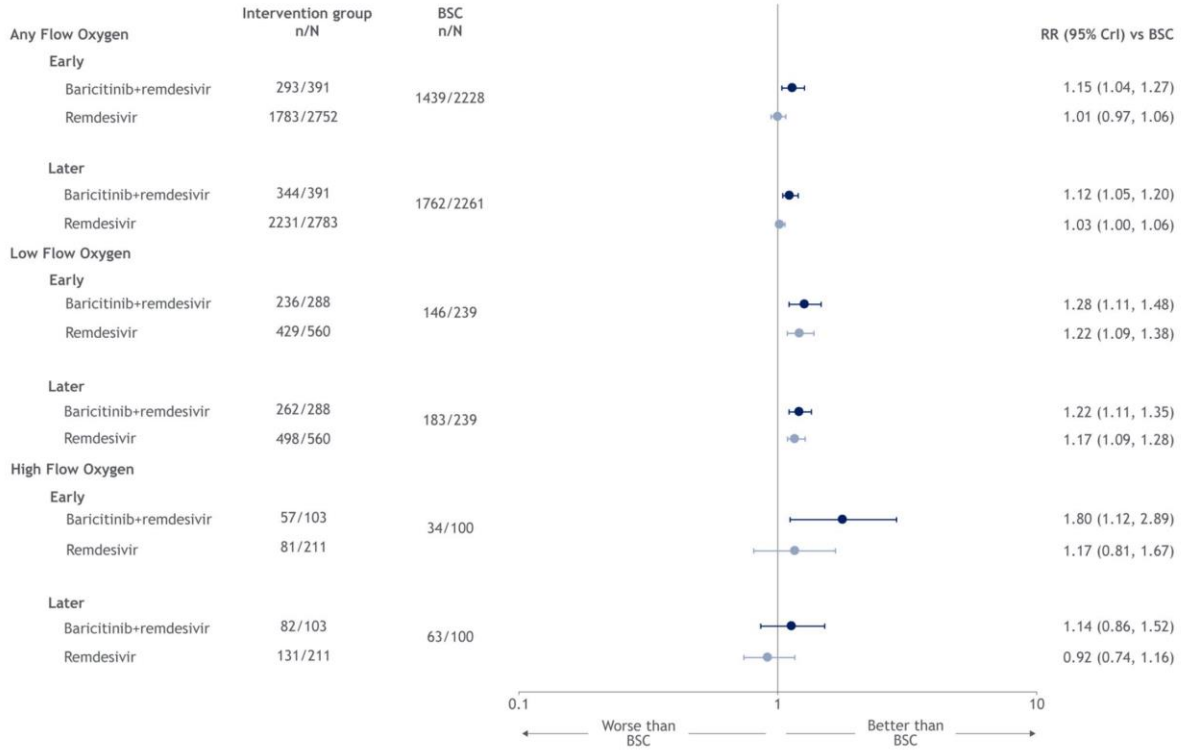


Results for remdesivir's effect on TTD are also reported in the meta-analyses conducted by Amstutz et al., which report that patients on average spent 2.25 days less in hospital if they had gotten remdesivir compared to patients in the non-remdesivir group.[11] The sensitivity analyses conducted by Amstutz et al. reported an aHR 1.29 [1.12–1.48] when only low risk of bias studies were included. In the primary analysis Amstutz et al. did not find an effect on TTD.

5.1.4 Recovery

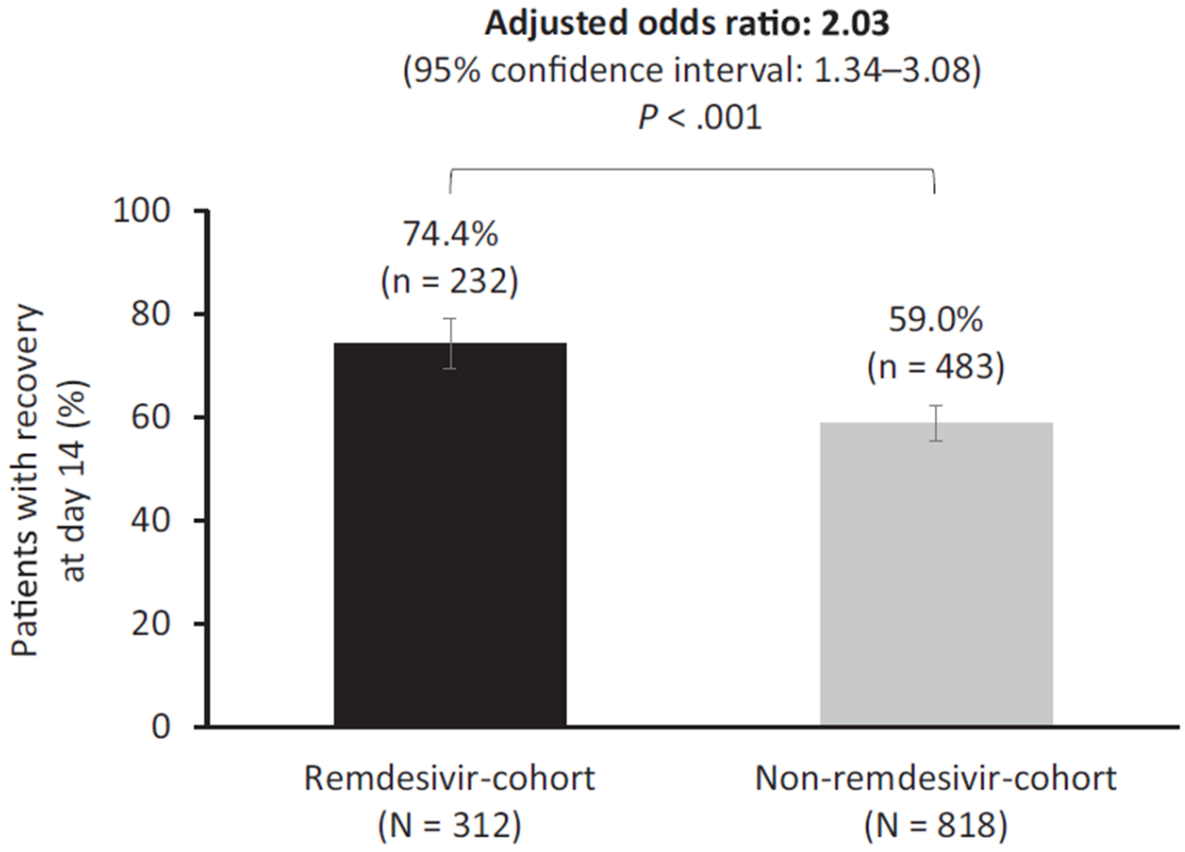
In the study by Beckerman et al. recovery was defined as either recovery from COVID-19 or discharge from hospital.[8] As can be seen from Figure 10 below, treatment with remdesivir was superior in improving recovery among those patients on low-flow oxygen at both the early (RR: 1.22 [1.09, 1.38]) and later (RR: 1.17 [1.09, 1.28]) assessment in the NMA conducted by Beckerman and colleagues.[8]

Figure 10: Forest plot for recovery endpoint, by type of non-invasive oxygen support, results from Beckerman et al. 2022 [8]



Olender et al. also assessed the recovery endpoint, which they defined as proportion of patients with recovery on day 14, dichotomized from a 7-point clinical status ordinal scale.[25] Olender et al. compared remdesivir versus SOC treatment in adults with severe COVID-19, reporting that at day 14, 74.4% of patients in the remdesivir-cohort had recovered versus 59.0% in the non-remdesivir-cohort (adjusted odds ratio [aOR] 2.03: 95% confidence interval [CI]: 1.34–3.08, P < .001) (viz. Figure 11). Olender et al. also report that greater 14-day recovery was associated with less need for high-flow or invasive oxygen use.

Figure 11: Recovery of patients with severe COVID-19 receiving remdesivir compared to SOC, as reported by Olender et al.[25]



5.1.5 Hospital readmission

There is published evidence which reports an association between remdesivir use and reduced hospital readmission rates. In a multi-centre cohort study by Finn et al., who included patients discharged from hospital between April and December 2020, found that patients treated with remdesivir were less likely to be readmitted to hospital within 30 days, with the strongest effect observed in mild COVID-19 patients (RR: 0.31; 95% CI: 0.13, 0.75).[26]

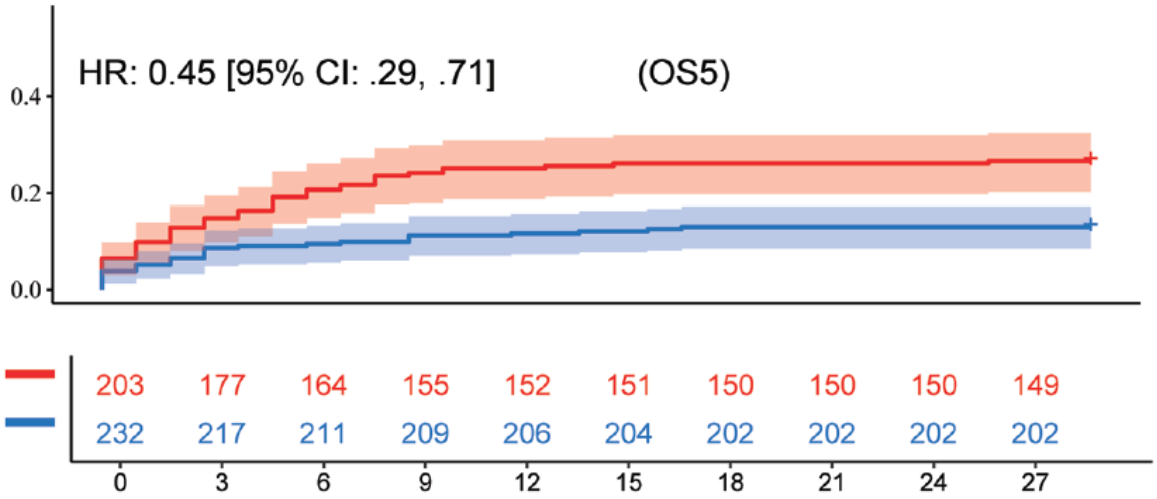
Similar results are reported by Wiley et al., who analysed 30-day readmission rates following discharge from eight hospitals in Atlanta, between March and December 2020. As reported by Wiley et al., patients receiving remdesivir had lower odds of hospital readmission (OR 0.5 (95% CI: 0.4 to 0.8).[27]

This effect is also observed in LFO patients specifically, as demonstrated by the results of Mozaffari et al., which report an aOR of 0.73 [0.70, 0.76] for 30-day all-cause readmission, analysing a data set of over 115,000 remdesivir patients and almost 70,000 non-remdesivir patients.[28]

5.1.6 Progression to IMV or death

Remdesivir for the treatment of patients in LFO has been shown to reduce the risk of progression to invasive mechanical ventilation (IMV) or death compared to SOC. Analysing data from the ACTT-1 trial, Paules et al. found that treatment with RDV was associated with fewer progressions to IMV or death across the entire cohort (hazard ratio [HR] 0.67; [0.52, 0.87] P = 0.0023), as well as in OS5 (HR 0.45; [0.29, 0.71] P = 0.0003).[29]

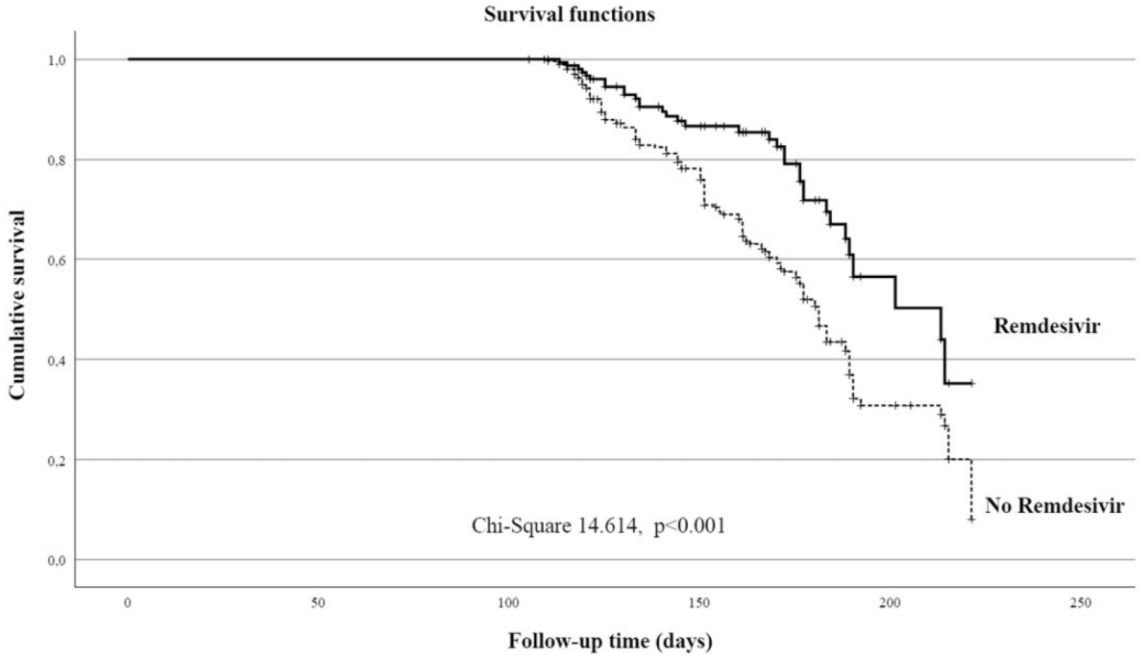
Figure 12: Progression of patients to IMV or death, results reported by ordinal score 5 (OS5 / low-flow oxygen), blue line reflects remdesivir results (x-axis: days relative to baseline; y-axis: probability of progression to IMV or death), extracted from Paules et al. [29]



5.1.7 Long COVID syndrome

Long COVID syndrome (LCS) has been shown to be a significant burden for patients who have been infected with COVID-19, causing them to suffer from the long-term consequences of the disease. In a study conducted by Boglione et al., remdesivir was found to have a positive effect on LCS, leading to a 35.9% reduction in the LCS rate in follow-up compared to no remdesivir treatment.[30] This is demonstrated in Figure 13, which shows clear separation in the cumulative LCS survival curves for patients on remdesivir compared to no remdesivir treatment.

Figure 13: Survival analysis for LCS presence in a cohort of patients with previous COVID-19 according to remdesivir treatment, based on Boglione et al. 2021 [30]

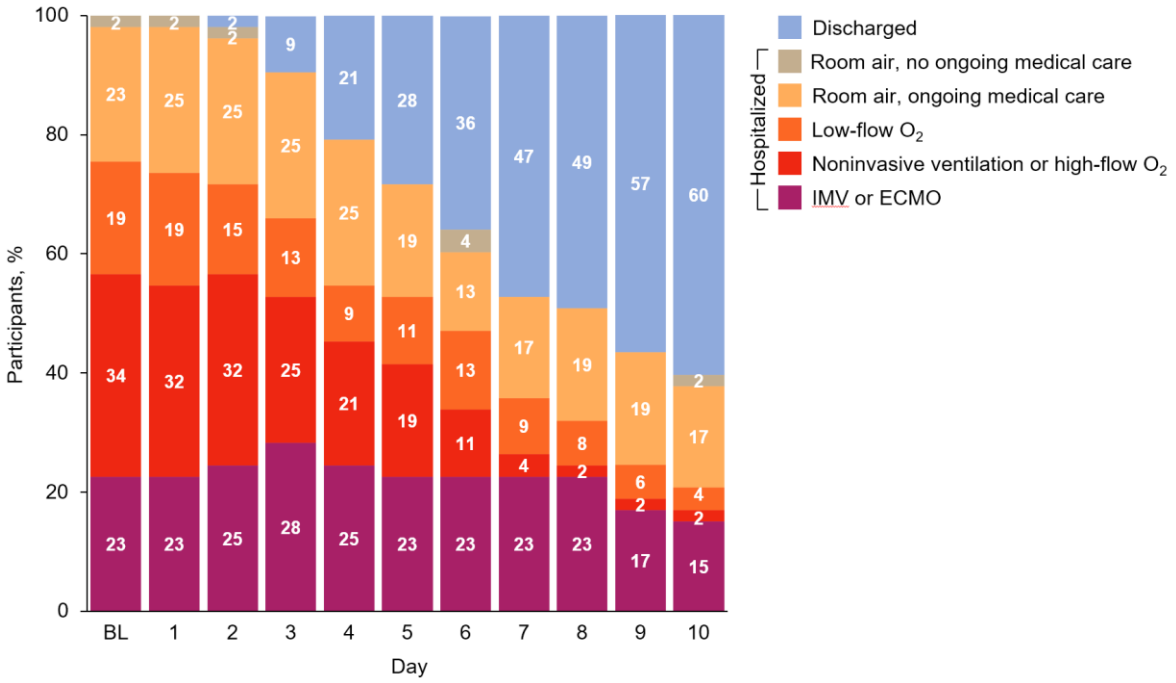


5.2 Children

The key trial assessing the safety and tolerability for paediatric patients treated with remdesivir is the CARAVAN study (NCT04431453).[31] The authors found that remdesivir was safe and well tolerated among children aged 28 days – <18 years treated for COVID-19.

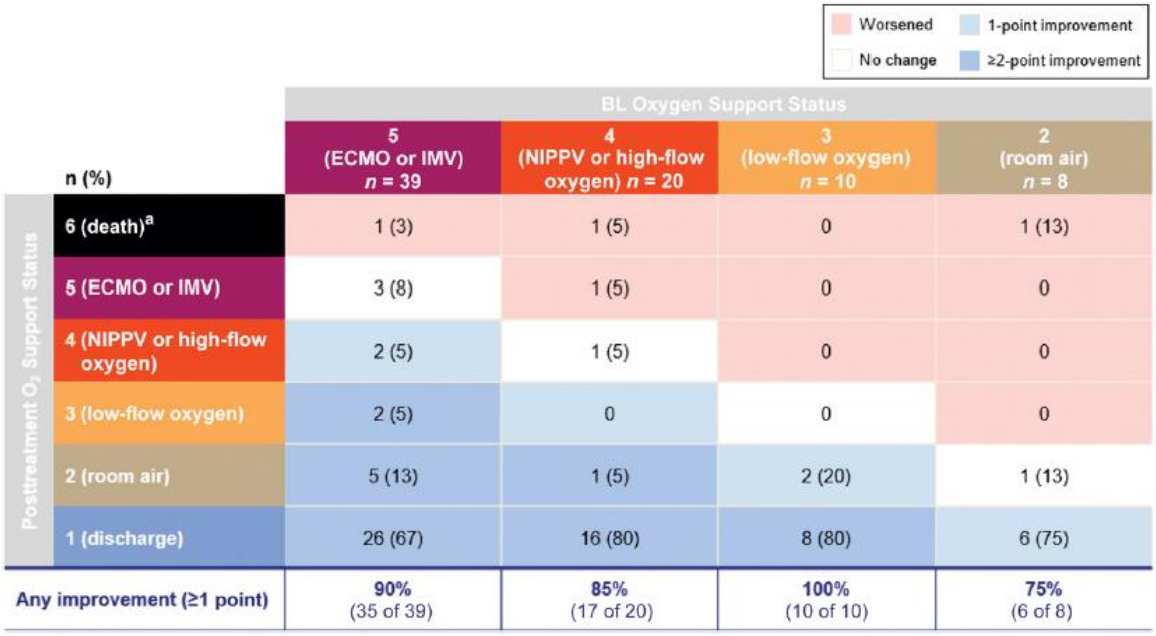
Overall, 75% and 85% showed clinical improvement (≥2 point increase on the ordinal scale) at Day 10 and last assessment, respectively. Additionally, patients were discharged from hospital early, with 60% and 83% of patients discharged by day 10 and day 30, respectively.[31]

Figure 14: Percentages of Participants at Each Ordinal, results from the CARAVAN study [31]



More evidence which suggests that remdesivir is effective in helping children recover from COVID-19 is provided in an analysis of 77 hospitalised patients <18 years old who received remdesivir treatment via a compassionate use program between March 21 and April 22.[32] The authors found that among 77 children treated with remdesivir for severe COVID-19, most recovered and the rate of serious adverse events was low. As can be seen from Figure 15, all children with a baseline oxygen support status in category 3 (LFO) had an improvement of ≥1 point. Similarly, children with a different baseline oxygen support status had equally promising results, showing clinical improvement between 90% (category 5), 85% (category 4) and 75% (category 2).[32]

Figure 15: Clinical outcomes in children treated with remdesivir at day 28 – results from the compassionate use program [32]



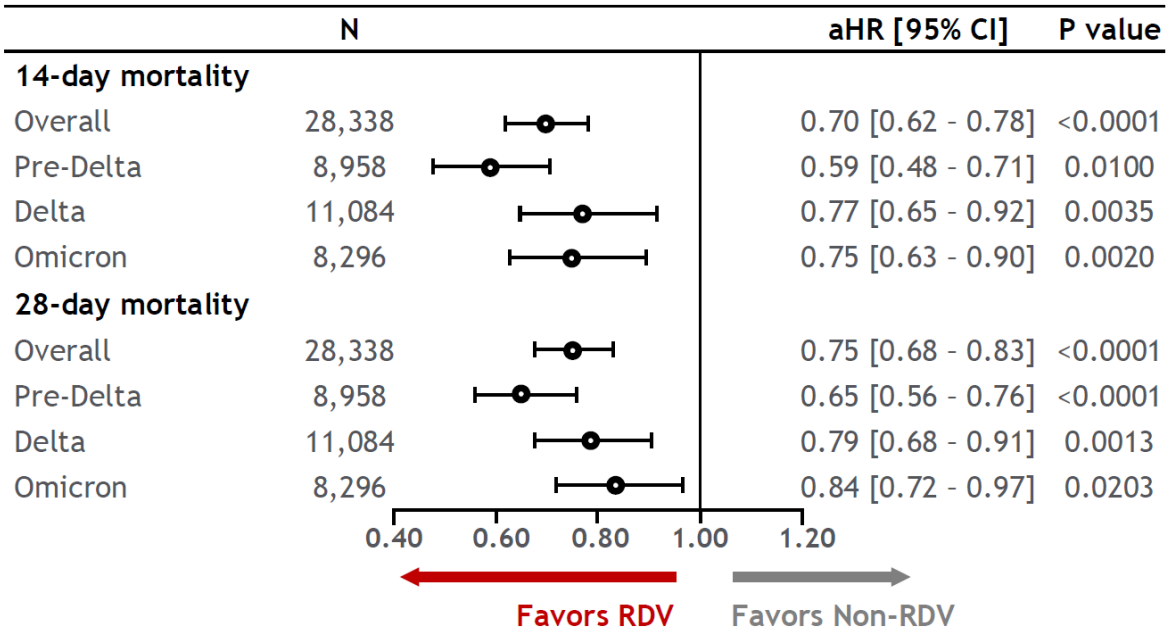
Another study conducted in children receiving remdesivir treatment for COVID-19 analysed data from 48 patients admitted to a paediatric academic medical centre in the United States.[33] In line with the findings from Ahmed et al. and Goldman et al., the authors of this retrospective study found that remdesivir was a safe medication in the patient population with no significant adverse effects.[33]

Besides the results from the larger studies assessing the use of remdesivir in children, including the CARAVAN study, the compassionate use program as well as the study conducted by Samuel et al., several case studies have been published reporting on physicians' experience of treating children with remdesivir. A good summary of the published case studies for remdesivir use in children is provided by Chera & Tanca, who concluded that many studies and case reports show good results in favour of using remdesivir for the treatment in children.[34]

5.3 Immunocompromised patients

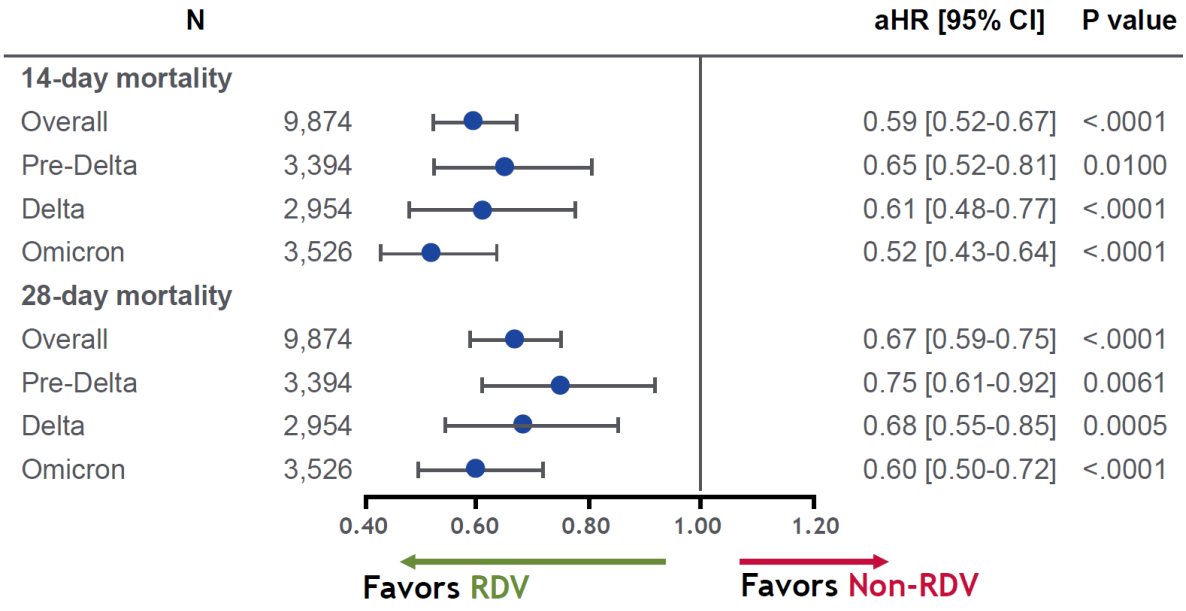
Recently remdesivir has been found to be highly effective in patients who are immunocompromised. In an RWE study conducted by Mozaffari et., which analysed data of 19,184 remdesivir patients that were matched to 11,213 non-remdesivir patients, leveraging data from a US claims database, the authors assessed 28-day mortality for immunocompromised COVID-19 patients.[4, 35] As shown in Figure 16, patients on remdesivir showed a significant mortality benefit across all VOC areas, including the Omicron variant. Mozaffari et al. report an adjusted hazard ratio (aHR) of 0.75 [0.68, 0.83] over the entire study duration, with an aHR of 0.84 [0.72, 0.97] during the Omicron period.

Figure 16: 14-and 28-day mortality across variant periods for immunocompromised patients [4, 35]



The 28-day mortality benefit of immunocompromised patients receiving remdesivir is particularly strong in patients with cancer, with an aHR of 0.67 [0.59, 0.75] for the overall population and 0.60 [0.50, 0.72] during the Omicron period. Results for 14- and 28-day mortality in COVID-19 patients with cancer is presented in Figure 17.

Figure 17: Mortality in Cancer Patients Across COVID-19 Variant Periods [4, 35]



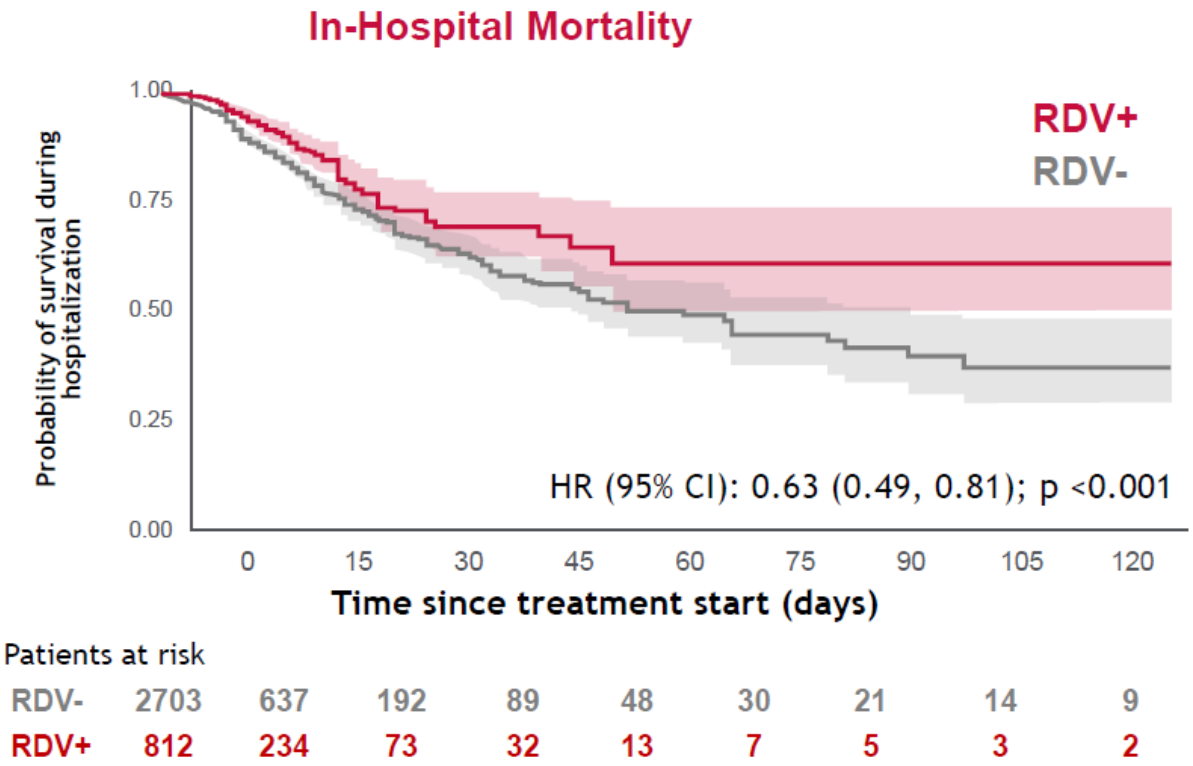
Matched cohort: 1.7% IMV/ECMO; 15.8% HFO/NIV; 39.5% LFO;43.0% NSOc

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

Additionally, data from an analyses of three hospitals in Spain, which evaluated data from close to 5,000 patients, showed a significant mortality benefit for patients with pneumonia.[4] As shown by

the Kaplan-Meier curves presented in Figure 18, remdesivir patients had a significant mortality benefit, resulting in a HR of 0.63 [0.49, 0.81].[4, 36]

Figure 18: In-hospital mortality in patients with moderate/severe COVID-19 pneumonia treated with RDV vs. non-RDV between January 2021 and March 2022 from three Spanish hospitals using natural language processing [4, 36]



A comprehensive overview of further RWE studies which have assess the use of remdesivir in vulnerable populations such as immunocompromised patients, patients with impaired renal function, pregnant women or other populations is provided by Akinosoglou et al. in their 2023 publication.[37] Summarizing the results of 200 research articles, the authors concluded "remdesivir increases the chance of recovery, reduces progression to severe disease, lowers mortality rates, and exhibits beneficial post-hospitalization outcomes, especially when used early in the course of the disease", with the evidence also suggesting "the expansion of remdesivir use in special populations (e.g., pregnancy, immunosuppression, renal impairment, transplantation, elderly and co-medicated patients).[37]

5.4 Generalisability of the clinical evidence

The generalisability of some of the evidence for remdesivir has previously been questioned by both the EAG and the NICE committee, especially related to results produced by the SOLIDARITY trial, which showed a mortality benefit for patients receiving oxygen (RR 0.87 [0.76, 0.99]).[38] Gilead would like to reemphasize that we disagree with this statement and that we believe that evidence for remdesivir is generalisable to an endemic setting.

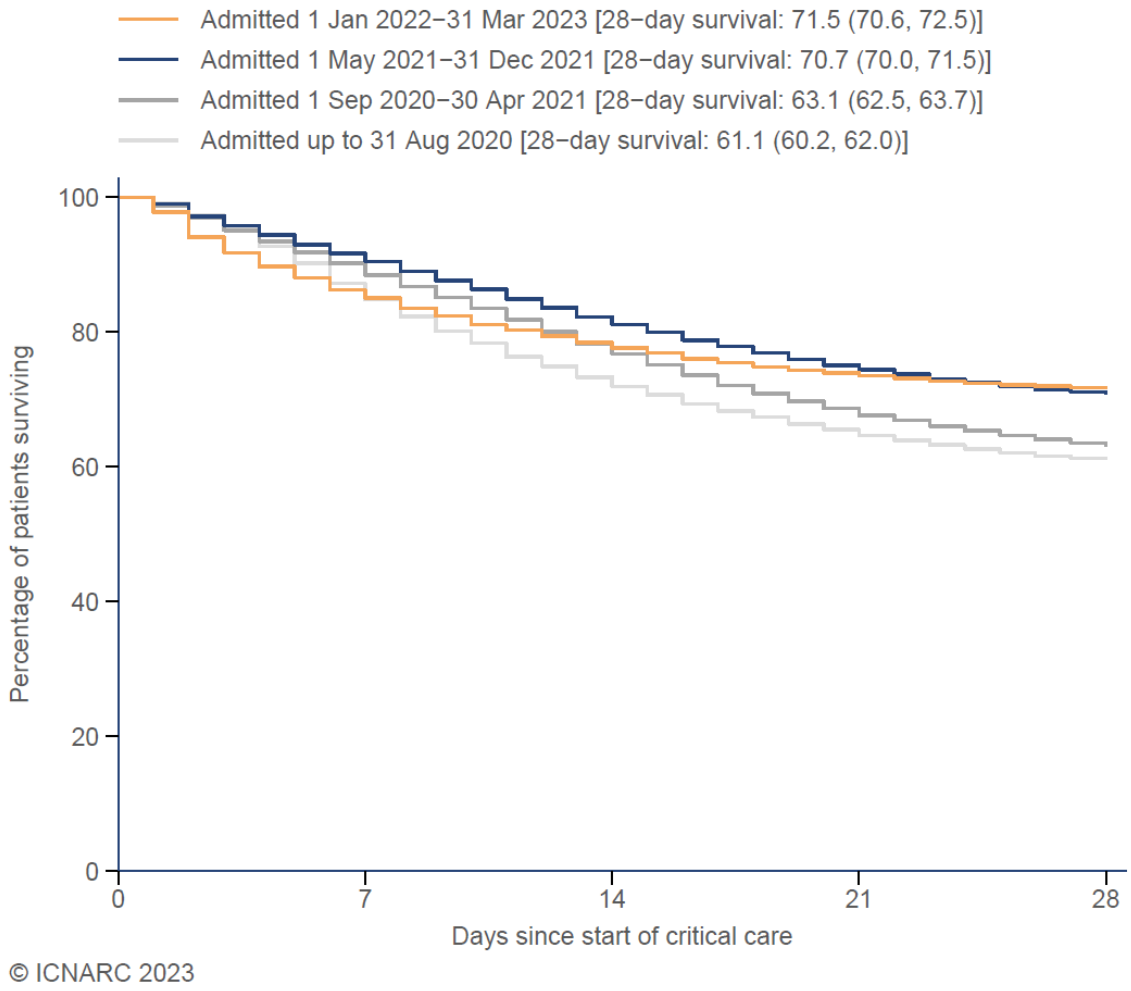
The generalisability concerns which discussed as part of the appeal process as well as in the oral appeal hearing included the following:

I. Changes in population immunity through natural immunity and vaccination
II. Changes in pathogenicity of the virus
III. Changes in best supportive care
IV. Other changes

Even though appeal point 2.1, which focused on the generalisability concerns, was not upheld in the final judgement of the appeal panel, the panel concluded that the appraisal committee should provide further clarification of its decision. As outlined below, Gilead is of the opinion that these four generalisability concerns were never fully justified and substantiated by any data.

I. While vaccination rates are much higher compared to the days in which many of the RCTs for COVID drugs were conducted, this doesn't change the fact that patients who arrive at the hospital still require urgent treatment for COVID, given that immunocompromised patients for example, have only slightly lower mortality rates compared to the hight of the pandemic.[4] Similarly, data from the latest ICNARC report suggests that 28-day mortality isn't significantly different comparing the latest dataset (Jan 2022 to Mar 2023) versus older datasets (e.g. May 2021 to Dec 2021), as outlined in Figure 19.[5] Furthermore, while higher vaccination rates have likely resulted in reduced hospital admission rates, those patients who end up in hospital are more likely to be unvaccinated, thus negating the argument of the impact of vaccination changes for hospitalised patients.[39]
II. No evidence has been provided by either the EAG or the NICE committee which supports the assertion that changes in the pathogenicity of the virus affected the efficacy of remdesivir treatment.
III. No data has been produced by either the EAG or the NICE committee which demonstrates that changes in best supportive care over the time of the pandemic affect the generalisability of the clinical data for remdesivir. In contrast, recent RWE studies from Mozaffari et al. showcase that remdesivir provides significant benefit to patients with COVID, even during the Omicron variant area.[13]
IV. "Other changes" specific to the context of a pandemic setting were never specified and no quantitative evidence was provided to how this would impact the generalisability of the evidence for remdesivir

Figure 19: In-hospital survival to 28 days following admission to critical care, based on the ICNARC report (June 2023)



Gilead is concerned that similarly unsubstantiated statements such as the ones outlined above, which have previously been used to disregard results from the SOLIDARITY trial, could potentially be used to discredit the available evidence for remdesivir in the subpopulations presented in this targeted evidence submission. Even though there are limitations to the evidence presented in this submission, which are presented in section 7, remdesivir has proven to be both clinically and cost-effective across many meta-analyses, RCTs and RWE studies.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

6 Cost-effectiveness evidence

6.1 Gilead model

6.1.1 Model overview

The Gilead costs-effectiveness model (CEM) is comprised of an early decision-tree like module (viz. Figure 20), in which 90-day outcomes are estimated, to which long-term pay-offs are assigned based on whether patients survive, either having endured a stay in intensive care, or less severe in-hospital outcome. Comparator arms are best supportive/usual care, dexamethasone, and remdesivir (with dexamethasone).

The Gilead CEM is currently being reviewed and updated to incorporate the latest available evidence for remdesivir. An updated version of the Gilead CEM is expected to be available by early October 2023. It should be noted that the results presented in this reported may deviate from the updated Gilead CEM. Once the updated Gilead CEM is available, Gilead will share its model with the EAG and NICE. These interim results should be seen as supplementary evidence to the adapted EAG CEM.

6.1.1.1 Early model structure

The population enters the model with a baseline ordinal score of 4-7. By default, the population is then weighted according to the numbers in ACTT-1 with each score selected for inclusion by the user. Alternatively, the user may specify their own ordinal score distribution on the <<Entry>> sheet, or a single ordinal score (on the <<Results>> sheet).

Basic patient characteristics of age and sex are also entered in the <<Entry>> sheet, along with time horizon and discount rate for health outcomes. As no costs are modelled beyond 90 days discounting for costs is not considered.

The primary data source to support the modelling of in-hospital outcomes is the ACTT-1 study. Given that hospital outcomes change over the course of the pandemic, both due to advances in standard of care and the advent of vaccination, outcomes modelled on ACTT-1 cab be modified to reflect assumptions as to relevant outcomes in comparison to those seen in ACTT-1. These adjustment s can be entered as odds ratios (with standard errors on the log scale). The proportion of the model population vaccinated is also to be entered here. Vaccinated patients may then also face lower risks of adverse outcomes, with odds ratios to be entered as for general adjustments for change in standard of care.

In-hospital outcomes are as shown in Figure 1. These are modelled as the most severe outcome suffered during admission. Data from ACTT-1 on outcome at 15 days is employed, with a pseudo-dataset constructed based on summary data reported in Beigel et al employed in fitting an ordered logistic regression for these.[12] Data at this level covering ultimate hospital discharge were not available. 29-day outcomes are based on day 15 (though outcomes among all day-15 survivors are accounted for, these do not condition on 15-day status), modified for day 15-29 mortality. Note this mortality is stratified by ordinal score at baseline, rather than being conditional on day 15 outcome.

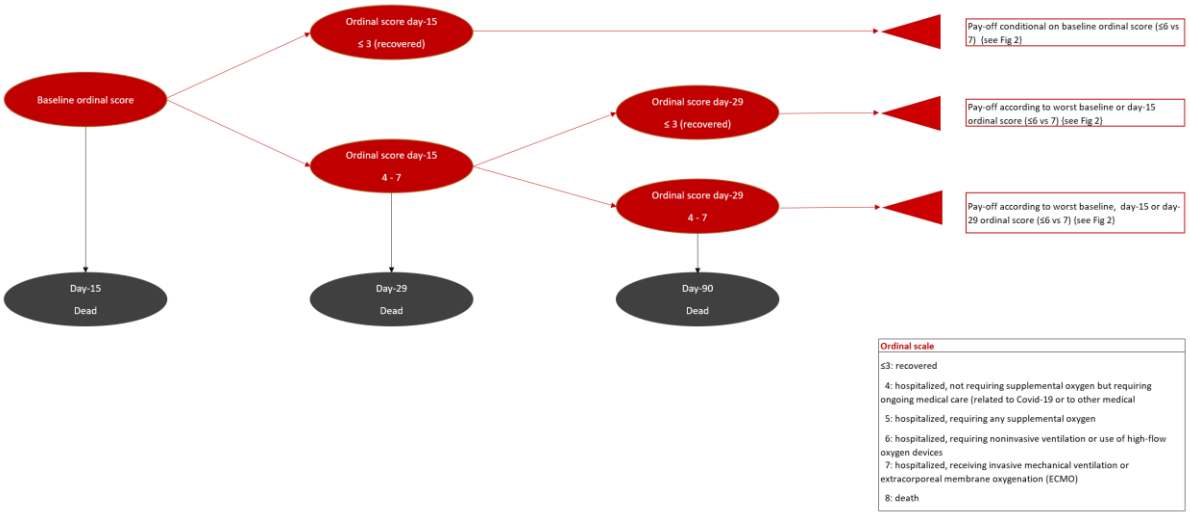
For dexamethasone a single odds ratio (vs usual care) based on the Recovery study is applied to the modelled usual care outcomes. The effects of remdesivir and dexamethasone are assumed to be additive, therefore, this effect can be added to that modelled for remdesivir in the remdesivir arm.

As it is possible for a proportion of patients to remain in hospital at 29 days the model contains parameters to assign 90 days mortality to such patients (stratified by baseline ordinal score).

Background quality of life is modelled based on UK population norms using the method of Ara and Brazier (2010).[40] Data used in the US ICER model and in Sheinson et al are available as multiplicative utility decrements to reflect the modelled outcomes.[41] Users may select which of these to employ, and whether to apply further adjustments in the period up to five years after discharge.

Length of stay (<<LOS>> sheet) in each of general ward, high dependency unit (HDU), and intensive care (ICU), is dependent upon whether the worst in-hospital outcome was hospital/low-flow oxygen, high-flow/non-invasive ventilation, or mechanical ventilation. The model is supplied with basic assumptions based on a UK publication and the December 2021 ICNARC report.[42] Dosing of remdesivir and dexamethasone is controlled on the <<Dosing>> sheet.

Figure 20: Early model structure - 90-day outcomes

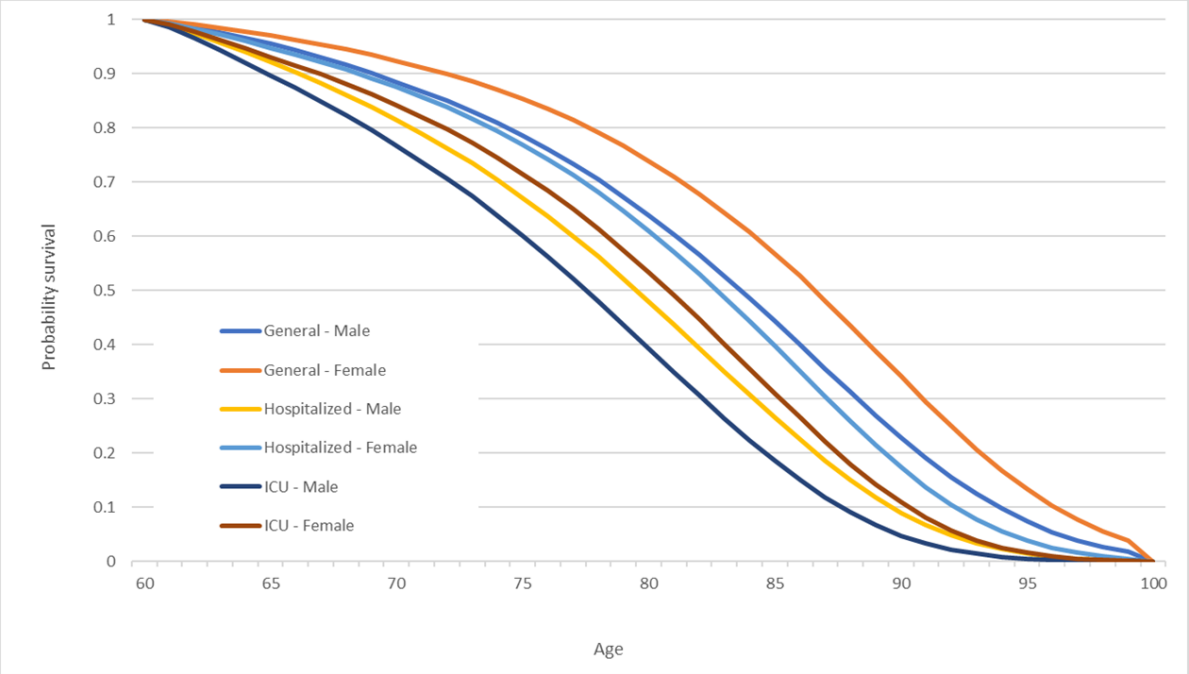


6.1.1.2 Long-term model structure

Independently of the early module quality adjusted life expectancy for each 90-day survivor is estimated. Mortality rates for the general population are drawn from Office for National Statistics UK lifetables.[43] The user may elect to apply excess mortality due to hospital ward and ICU stay (worst ordinal score 7), ICU stay alone, or to model life expectancy based solely on the life tables. Excess mortality is estimated from Lone et al.[44] ICU survivors were estimated to have a hazard ratio of 1.33 compared to patients discharged without ICU admission (note this study is of ICU admitted patients and not of COVID-19 patients). Patients discharged without ICU admission also had an excess mortality. However, as this study is not in Covid patients there is uncertainty as to how excess mortality should be interpreted, therefore, the option exists to specify ICU excess mortality alone, without assigning any other excess. Where excess mortality is applied, this is for five years, with tapering beyond this for a specified period. Mortality rates by age and sex for hospitalised and ICU discharged patients are then applied in calculating expected survival (Figure 21).

After ten years all surviving patients are modelled to have the quality of life of the general population. Prior to this, utility decrements as controlled on the <<HrQoL>> sheet are applied, up to the year specified for this quality-of-life decrement. Expected life years and quality adjusted life expectancy are then assigned to 90 days survivors of the early module, conditional on ICU admission.

Figure 21: Modelled survival in 90-day survivors



Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

6.1.2 Model results

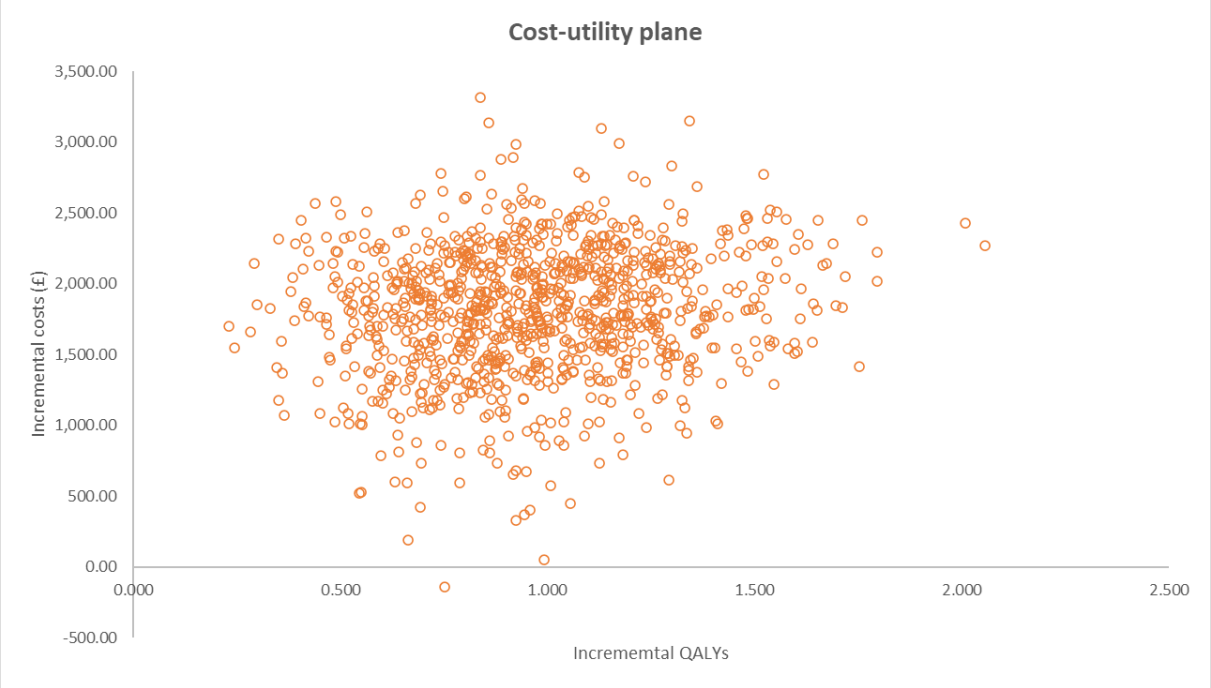
As demonstrated by the deterministic base case results using the Gilead CEM, remdesivir is highly cost-effective for the treatment of LFO patients. As shown in Table 5 below, remdesivir has an ICER of £2,331 compared to dexamethasone use alone.

Table 5: Deterministic cost-effectiveness results for ordinal scale 5 patients, based on the Gilead CEM

Intervention	Cost	QALYs	Inc. costs	Inc. QALYs	ICER
Remdesivir (+ dexamethasone)	8,516	10.116	2,300	0.987	£2,331
Dexamethasone	6,216	9.129	-482	0.496	Dom. BSC
Best supportive care (BSC)	6,699	8.633			
BSC: Best supportive care; Dom: dominates; ICER: Incremental cost effectiveness ratio; QALY: Quality adjusted life year					

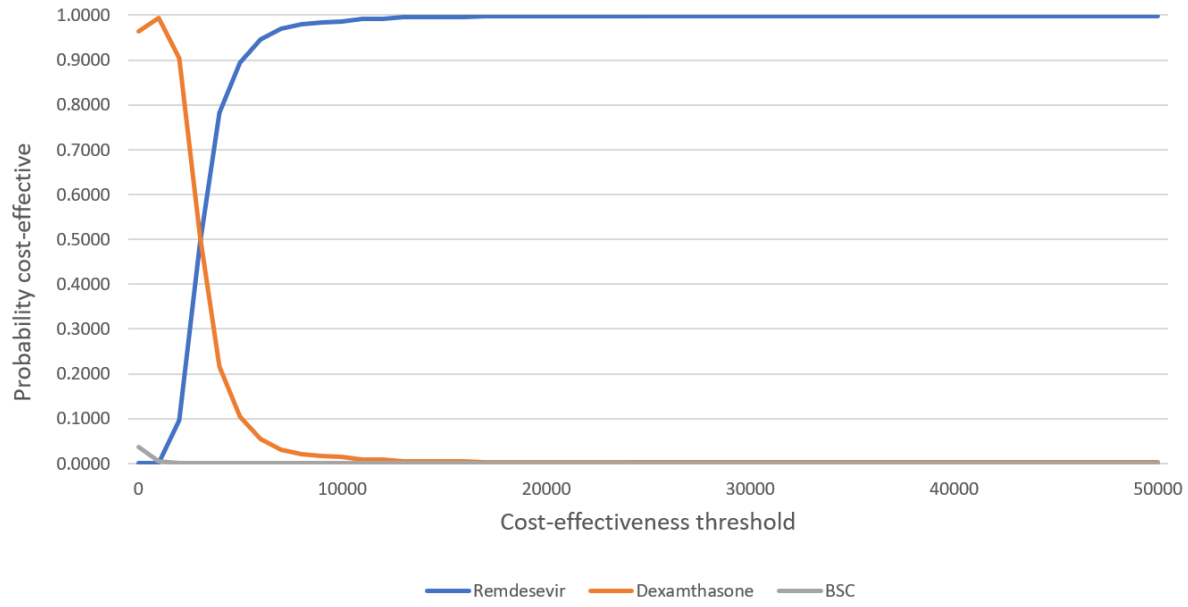
Furthermore, there is high certainty of cost-effectiveness for remdesivir as demonstrated by the results of the probabilistic sensitivity analysis (PSA) presented in Figure 22. As can be seen from Figure 22, almost all iterations generated by the PSA fall into the north-east quadrant of the cost-effectiveness plane (CEP), indicating higher incremental quality-adjusted life years (QALYs) at a higher incremental cost relative to its comparator.

Figure 22: Cost-effectiveness plane, based on the Gilead CEM



Furthermore, remdesivir is cost-effective for the treatment of LFO patients at a very low willingness to pay (WTP) threshold. As presented in Figure 23, which shows the cost-effectiveness acceptability curves (CEAC) for remdesivir, the probability of remdesivir being cost-effective approaches 100% around the £10,000 WTP.

Figure 23: Cost-effectiveness acceptability curve (CEAC), based on the Gilead CEM



Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

6.2 EAG model

6.2.1 Structural adaptations

The EAG cost-effectiveness model (CEM) needs to be adapted to estimate cost-effectiveness results for a LFO patient population. Currently the EAG CEM does allow the distinction of two patient populations in the hospital setting – either for patients without oxygen or patients with oxygen. Conveniently the EAG CEM already leverages an 8-category ordinal scale which was also used in the ACTT-1 trial, which is depicted in Table 6 below.

Table 6: 8-category ordinal scale used in the EAG CEM, based on ACTT-1

Ordinal scale	Definition of clinical status
1	not hospitalised and no limitations of activities
2	not hospitalised, with limitation of activities, home oxygen requirement, or both
3	hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection-control or other nonmedical reasons)
4	hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions)
5	hospitalised, requiring any supplemental oxygen such as low-flow oxygen (LFO)
6	hospitalised, requiring non-invasive ventilation (NIV) or use of high-flow oxygen (HFO) devices
7	hospitalised, receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO)
8	Death

As outlined in the EAG report on page 36, “during their hospital stay, patients are distributed according to their hospital/oxygen requirement derived from the placebo arm of the ACTT-1 study”. For the no oxygen population currently in the EAG model this means that at week 0 the health state occupancy of ordinal scale 4 is set to 100%, i.e., all patients are hospitalised not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions). Similarly, for the patient population with oxygen, patients are distributed across ordinal scale 5, 6 and 7 at week 0 (baseline).

To incorporate a LFO patient population into the EAG CEM, new traces need to be added which set week 0 health state occupancy to 100% at ordinal scale 5, i.e., reflecting that all patients require LFO at baseline. Furthermore, health state transitions needed to be adjusted in the “clinical status” sheet in the EAG CEM to reflect the ordinal scale shift behaviour of those patients who are ordinal scale 5 in the ACTT-1 placebo group (viz. Table 7).

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Table 7: Ordinal score shift tables, based on ACTT-1 [12]

	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=541)	Placebo (N=521)	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
Recovery										
No. of recoveries	399	352	73	58	206	156	57	61	63	77
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)	5 (4–6)	6 (4–7)	7 (6–8)	9 (7–10)	15 (10– 27)	20 (14– 26)	29 (24–NE)	28 (24–NE)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])		1.29 (0.91–1.83)		1.45 (1.18–1.79)		1.09 (0.76–1.57)		0.98 (0.70–1.36)	
Mortality through day 14‡										
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)		0.42 (0.04–4.67)		0.28 (0.12–0.66)		0.82 (0.40–1.69)		0.76 (0.39–1.50)	
No. of deaths by day 15	35	61	1	2	7	21	13	17	14	21
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)	1.3 (0.2–9.1)	3.2 (0.8–12.1)	3.1 (1.5–6.4)	10.5 (7.0–15.7)	14.2 (8.5–23.2)	17.3 (11.2–26.4)	10.9 (6.6–17.6)	13.8 (9.2–20.4)
Mortality over entire study period‡										
Hazard ratio (95% CI)	0.73 (0.52–1.03)		0.82 (0.17–4.07)		0.30 (0.14–0.64)		1.02 (0.54–1.91)		1.13 (0.67–1.89)	
No. of deaths by day 29	59	77	3	3	9	25	19	20	28	29
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)	4.1 (1.3– 12.1)	4.8 (1.6–14.3)	4.0 (2.1–7.5)	12.7 (8.8–18.3)	21.2 (14.0–31.2)	20.4 (13.7–29.8)	21.9 (15.7–30.1)	19.3 (13.8–26.5)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	157 (29.0)	115 (22.1)	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
2	117 (21.6)	102 (19.6)	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
3	14 (2.6)	8 (1.5)	8 (10.7)	4 (6.3)	6 (2.6)	4 (2.0)	0	0	0	0
4	38 (7.0)	33 (6.3)	3 (4.0)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
5	58 (10.7)	60 (11.5)	3 (4.0)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)
6	28 (5.2)	24 (4.6)	1 (1.3)	0	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
7	95 (17.6)	121 (23.2)	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
8	34 (6.3)	58 (11.1)	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.5 (1.2–1.9)		1.5 (0.8–2.7)		1.6 (1.2–2.3)		1.4 (0.9–2.3)		1.2 (0.8–1.9)	

Lastly, key input parameters used in the EAG CEM such as 28-day mortality, 28-day clinical improvement and time to hospital discharge need to be updated to reflect the LFO population. The suggested input parameters to be used for this are outlined in section 6.2.2.

6.2.2 Data inputs for patients on low-flow oxygen

Gilead suggests using the data inputs outlined in Table 8 in the adapted EAG model to derive cost-effectiveness estimates for the LFO patient population.

Table 8: Data inputs for the low-flow oxygen patient population to be used in the EAG economic model

Input parameter	Effect estimate	95% confidence interval	Reference
28-day mortality	RR 0.59	0.43, 0.80	Huang et al. [10]
28-day clinical improvement	aHR 1.23	1.19, 1.27	Garibaldi et al. [9]
Time to hospital discharge	HR 1.27	1.10, 1.46	ACTT-1 [23]

For the 28-day mortality endpoint, results from the meta-analysis conducted by Beckerman et al. 2022 should also be considered, since it provides another summary of RCTs focused on LFO patients.[8]

Furthermore, results from Amstutz et al. for the 28-day mortality endpoint should be considered as sensitivity analysis, given the large patient numbers included in the analysis set of the study.[11] Given that the results from Amstutz et al. include a broader patient population (i.e. patient on no oxygen or low flow oxygen) this study should only be considered as supplementary evidence.

6.2.3 Economic modelling for children

As outlined in section 5.2, the evidence for the paediatric patient population receiving remdesivir does consist of non-comparative, single arm trials. Given this lack of comparative data, deriving incremental cost-effectiveness estimates against a SOC comparator are not feasible.

One option to tackle this problem would be to assume similar benefits of remdesivir in children as observed in other adult patient populations, for example patients receiving LFO. Taking this assumption, the same suggested input parameters presented in section 6.2.2 could be used for modelling the cost-effectiveness of using remdesivir to treat children with COVID-19.

A second option would be to consider a naïve comparison in a comparable paediatric patient population who did not receive remdesivir treatment. However, given the lack of treatment options for children, such a naïve comparison seems challenging, on top of other concerns of high risk of bias related to such naïve comparisons.

The lack of treatment options for paediatric patients which are recommended by NICE is most significant in children <12 years of age. While the NICE FDG recommends Sotrovimab as an option for treating COVID-19 in people aged 12 years and over and weighing at least 40 kg, this recommendation only applies if those patients do not need supplemental oxygen. As per the latest National Institute of Health (NIH) COVID guidelines, hospitalised children who require conventional oxygen should be treated with remdesivir.[45] Similarly, recommendations in the NIH guideline for paediatric patients requiring high-flow-oxygen (HFO), involve remdesivir in combination with dexamethasone.[45]

For non-hospitalised paediatric patients there is a similar gap for those children aged <12, where remdesivir is the only licensed treatment option. Additionally, remdesivir is recommended alongside Paxlovid for children aged 12-17 in a non-hospitalised setting.[45]

Furthermore, recommending remdesivir as a further treatment option in children is important due to the rare nature of COVID-19 in children, which consequently would cause minimal burden on the overall NHS resource utilisation. As reported in a recent cohort study by Wilde et al, which analysed data from electronic health care records in England, the authors found that out of all children and adolescents who had a recorded SARS-CoV-2 invention between July 2020 and February 2022, less than 1% of those patients were admitted to hospital, with younger children (<5 years) more likely to be admitted to hospital.[46] Out of those 1%, less than 6% of patients required paediatric critical care, which demonstrates the need for a treatment option for this small, but very vulnerable patient population.[46]

Faced with the challenge of determining the economic value of remdesivir treatment in children, Gilead encourages NICE to focus on the clinical evidence for remdesivir in the paediatric patient population, given the good tolerability and safety profile of the drug, making it the only available treatment option for children.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

7 Limitations

7.1 Clinical evidence

The clinical evidence for remdesivir presented in this targeted submission is mainly limited by three aspects, including the (1) timeframe during which the studies were conducted, (2) the use statistical methods such as propensity score matching (PSM) to generate matched controls in RWE studies and (3) the lack of a subgroup specific SLR.

As shown in the overview presented in Appendix 2, many of the included studies in this submission collected their data in 2020 and 2021, with only a few studies covering data collection during 2022. Even though some of these studies were collecting data during earlier phases of the pandemic, it should be assumed that the outcomes generated by these studies still hold in an endemic context, given the absence of opposing evidence and the confirmatory findings of recent RWE studies.

Due to a lack of head-to-head comparative RCTs conducted more recently, the latest evidence for remdesivir comes from RWE studies, which leverage methods such as PSM to generate matched cohorts to derive comparative results. While these types of studies come with certain limitations, they are still a valid tool to derive comparative results in the absence of direct comparative trials.[47] Furthermore, the remdesivir studies which used PSM all validated the results produced by earlier RCTs such as ACTT-1.[9, 12, 14-16]

Additionally, the clinical evidence for the subgroups presented in this evidence submission is limited by the lack of a subgroup specific SLR. As outlined in section 4, two SLRs were conducted focused on the use of remdesivir in the hospital sector, but no systematic searches were conducted for FLO, children or immunocompromised patients specifically. This approach was taken to provide the most comprehensive overview of the available evidence for remdesivir in a reasonable timeframe and to facilitate rapid guidance for remdesivir.

Lastly, other limitations might include concerns around changes in population immunity through natural immunity and vaccination, changes in pathogenicity of the virus, changes in best supportive care alongside “other changes” in the context of the COVID landscape. As outlined in section 5.4 on generalisability, Gilead has not seen credible evidence associated with these claims.

7.2 Cost-effectiveness evidence

As outlined in section 6.1, the Gilead cost-effectiveness model is currently being updated and reviewed to ensure the quality of the cost-effectiveness outcomes produced by this model. Therefore, the cost-effectiveness estimates presented in this targeted submission should be seen as supplementary evidence. This decision has been taken to facilitate rapid decision making and to avoid further delays as part of the COVID-19 MTA. Once an updated and reviewed Gilead CEM is available, this model will be shared with the EAG and NICE. Gilead expects this updated model to be available by October 2023.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

8 Conclusion

Remdesivir is a highly effective treatment option for patients requiring LFO, showcasing a significant 28-day mortality benefit over SOC, which has been observed in various meta-analysis, RCTs and which is further validated by RWE studies which cover recent COVID-19 variants, including Omicron. LFO patients receiving remdesivir experience faster clinical improvement compared to SOC, and benefit from several other improved outcomes, such as improved recovery, slower progression to IMV or death and reduced TTD from hospital.

Similarly, remdesivir is a safe and well tolerated treatment for children, providing the only viable treatment option for severe paediatric patients aged <12 years.

Furthermore, remdesivir shows significant clinical benefits in other vulnerable patient populations – such as immunocompromised patients – as demonstrated by statistically significant 14- and 28-day mortality benefits across multiple variant areas.

Not only is remdesivir a clinically effective treatment for LFO, paediatric and immunocompromised patients, but it is also cost-effective. As shown by the results generated using the Gilead CEM, LFO patients on remdesivir have an ICER of £2,331, with most PSA iterations falling into the north-east quadrant of the CEP. Gilead is confident that similar cost-effectiveness estimates for remdesivir can be recreated in the EAG CEM, when structural adaptations are made to the EAG model as suggested.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

9 References

1. NICE, *Molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261] - final judgement by the appeal panel*. 2023.
2. UKHSA. *SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 52*. 2023 [cited 2023; Available from: hiips://www.gov.uk/government/publications/investigation -of-sars-cov-2-variants-technical-briefings.
3. ONS. *Hospital admissions with COVID-19*. 2023 [cited 2023; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/hospitals.
4. ECCMID, *Pre-congress presentation - data on file.* 2023.
5. ICNARC, *ICNARC report on COVID-19 in cri?cal care: England, Wales and Northern Ireland 23 June 2023*. 2023.
6. EMC. *Veklury 100 mg powder for concentrate for solution for infusion*. 2023; Available from: hiips://www.medicines.org.uk/ emc/product/11597/smpc#gref.
7. NICE, *COVID-19 rapid guideline: Managing COVID-19*. 2023.
8. Beckerman, R., et al., *Remdesivir for the treatment of patients hospitalized with COVID-19 receiving supplemental oxygen: a targeted literature review and meta-analysis.* Scientific Reports, 2022. **12**(1): p. 9622.
9. 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.
10. Huang, C., T.-L. Lu, and L. Lin, *Remdesivir Treatment Lacks the Effect on Mortality Reduction in Hospitalized Adult COVID-19 Patients Who Required High-Flow Supplemental Oxygen or Invasive Mechanical Ventilation.* Medicina, 2023. **59**(6): p. 1027.
11. 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.
12. Beigel, J.H., et al., *Remdesivir for the Treatment of Covid-19 — Final Report.* New England Journal of Medicine, 2020. **383**(19): p. 1813-1826.
13. CROI. *REMDESIVIR REDUCES MORTALITY IN HOSPITALIZED COVID-19 PATIENTS ACROSS VARIANT ERAS*. 2023 [cited 2023; Available from: hiips://www.croiconference.org/abstract/remdesivir -reduces-mortality-in-hospitalized-covid-19-patients-across-variant-eras/.
14. Jeyapalina, S., et al. *1127. Effectiveness of Remdesivir as Treatment for COVID-19 Positive US Veterans*. in *Open Forum Infectious Diseases*. 2022. Oxford University Press US.
15. Chokkalingam, A.P., et al., *Association of remdesivir treatment with mortality among hospitalized adults with COVID-19 in the United States.* JAMA Network Open, 2022. **5**(12): p. e2244505-e2244505.
16. Mozaffari, E., et al., *Remdesivir treatment in hospitalized patients with coronavirus disease 2019 (COVID-19): a comparative analysis of in-hospital all-cause mortality in a large multicenter observational cohort.* Clinical Infectious Diseases, 2022. **75**(1): p. e450-e458.
17. Olender, S.A., et al. *Remdesivir versus standard-of-care for severe coronavirus disease 2019 infection: an analysis of 28-day mortality*. in *Open forum infectious diseases*. 2021. Oxford University Press US.
18. Breskin, A., et al., *Effectiveness of remdesivir treatment protocols among patients hospitalized with COVID-19: a target trial emulation.* Epidemiology, 2023. **34**(3): p. 365-375.
19. Barnieh, L., et al., *Real-world effectiveness of remdesivir for hospitalized patients with COVID-19: systematic review and meta-analysis.* European Respiratory Journal, 2022. **60**(suppl 66): p. 4498.

20. Singh, S., et al., *Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis.* BMJ open, 2021. **11**(6): p. e048416.
21. Gholamhoseini, M.T., et al., *Safety and efficacy of remdesivir for the treatment of COVID-19: a systematic review and meta-analysis.* Journal of Pharmacy & Pharmaceutical Sciences, 2021. **24**: p. 237-245.
22. COVID NMA Initiative. *Living COVID-19 NMA*. 2023 [cited 2023; Available from: hiips://covid - nma.com/metacovid/.
23. Gilead Sciences, *ACTT-1 clinical study report - data on file*. 2020.
24. Spinner, C.D., et al., *Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial.* Jama, 2020. **324**(11): p. 1048-1057.
25. Olender, S.A., et al., *Remdesivir for severe coronavirus disease 2019 (COVID-19) versus a cohort receiving standard of care.* Clinical Infectious Diseases, 2021. **73**(11): p. e4166-e4174.
26. Finn, A., et al., *Association of Treatment with Remdesivir and 30-day Hospital Readmissions in Patients Hospitalized with COVID-19.* The American journal of the medical sciences, 2022. **363**(5): p. 403-410.
27. Wiley, Z., et al., *Clinical characteristics and social determinants of health associated with 30-day hospital readmissions of patients with COVID-19.* Journal of Investigative Medicine, 2022. **70**(6): p. 1406-1415.
28. CROI, *REMDESIVIR IS ASSOCIATED WITH REDUCED READMISSION AFTER COVID 19 HOSPITALIZATION*. 2023.
29. Paules, C.I., et al., *Remdesivir for the prevention of invasive mechanical ventilation or death in coronavirus disease 2019 (COVID-19): a post hoc analysis of the Adaptive COVID-19 Treatment Trial-1 cohort data.* Clinical Infectious Diseases, 2022. **74**(7): p. 1260-1264.
30. 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.
31. Ahmed, A., et al., *P168 Remdesivir in the treatment of children 28 days to < 18 years of age hospitalised with COVID-19 in the CARAVAN study.* Thorax, 2022. **77**(Suppl 1): p. A172-A173.
32. Goldman, D.L., et al., *Compassionate use of remdesivir in children with severe COVID-19.* Pediatrics, 2021. **147**(5).
33. Samuel, A.M., et al., *Remdesivir use in pediatric patients for SARS-CoV-2 treatment: single academic center study.* The Pediatric Infectious Disease Journal, 2023. **42**(4): p. 310.
34. Chera, A. and A. Tanca, *Remdesivir: the first FDA-approved anti-COVID-19 Treatment for Young Children.* Discoveries, 2022. **10**(2).
35. Mozaffari, E., et al., *Remdesivir reduced mortality in immunocompromised patients hospitalized for COVID-19 across variant waves: Findings from routine clinical practice.* Clin Infect Dis, 2023.
36. ECCMID. *Remdesivir Associated with Decreased Mortality in Hospitalized COVID-19 Patients - A Real-world Evidence Study using Natural Language Processing*. 2023; Available from: hiips://www.askgileadmedical.com/docs/conference/Lopez_ECCMID2023_Remdesivir%20associated%20with%20decreased@pdf.
37. Akinosoglou, K., et al., *Remdesivir Use in the Real-World Setting: An Overview of Available Evidence.* Viruses, 2023. **15**(5): p. 1167.
38. Consortium, W.S.T., *Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses.* The Lancet, 2022. **399**(10339): p. 1941-1953.
39. Harrison, D.A., et al., *Impact of vaccination on COVID-19-associated admissions to critical care in England: a population cohort study of linked data.* medRxiv, 2022: p. 2022.10.03.22280649.
40. Ara, R. and J.E. Brazier, *Populating an economic model with health state utility values: moving toward better practice.* Value in Health, 2010. **13**(5): p. 509-518.

41. Sheinson, D., et al., *A cost-effectiveness framework for COVID-19 treatments for hospitalized patients in the United States.* Advances in therapy, 2021. **38**: p. 1811-1831.
42. ICNARC. *Report on COVID-19 in critical care: England, Wales and Northern Ireland 3 December 2021*. 2021; Available from: hiips://www.icnarc.org/ .
43. ONS. *National life tables – life expectancy in the UK: 2018 to 2020*. 2021; Available from: hiips://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/latest.
44. Lone, N.I., et al., *Five-year mortality and hospital costs associated with surviving intensive care.* American journal of respiratory and critical care medicine, 2016. **194**(2): p. 198-208.
45. NIH, *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines - July 2023*. 2023.
46. Wilde, H., et al., *Hospital admissions linked to SARS-CoV-2 infection in children and adolescents: cohort study of 3.2 million first ascertained infections in England.* bmj, 2023. **382**.
47. Reiffel, J.A., *Propensity Score Matching: The 'Devil is in the Details' Where More May Be Hidden than You Know.* The American Journal of Medicine, 2020. **133**(2): p. 178-181.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

10 Appendix

Appendix 1: Email sent by Gordon Lundie (Gilead) to Ross Dent (NICE) on the 25th of July 2023, outlining requirements for a potential third committee meeting

From: Gordon Lundie <Gordon.Lundie@gilead.com>
Sent: Tuesday, July 25, 2023 5:45 PM
To: Ross Dent <Ross.Dent@nice.org.uk>
Cc: Mirko Von Hein <Mirko.VonHein@gilead.com>; Kathryn Coville <Kathryn.Coville@gilead.com>; Leena Sathia <Leena.Sathia@gilead.com>; James Jarrett <james.jarrett@gilead.com>
Subject: COVID MTA and response from Gilead to proposed resolution
Importance: High

Dear Ross,

Thanks again for taking the time recently to discuss the two proposals presented to us to address the COVID MTA appeal outcome.

We have carefully considered the two options, with a view to identifying the best option that would:

- remedy the significant flaws in the MTA process, as clearly identified by the Appeal Panel in its decision – including, generally, "*the unfairness resulting from NICE's processes for the MTA, specifically the challenges to stakeholder engagement resulting from the re-sequencing of the appraisal process and the abbreviation of the usual time frame*"; and
- reach a decision in time for winter 2023/2024, so that remdesivir can be made available, as appropriate, for patients in need

On this basis, our preference is for a third committee meeting, provided that the following steps are taken to address the previous procedural flaws in the MTA:

1. Gilead will be able to make a targeted evidence submission before the third appraisal committee meeting; this evidence submission would comprise relevant evidence and analysis including some not previously submitted to NICE, such as real-world evidence and the cost-effectiveness model (CEM) developed by Gilead (for cross validation to the EAG CEM).
   This is to address in particular the Appeal Panel's finding on Gilead's appeal point 1(a).1

2. Gilead will have the opportunity to engage with the EAG to understand the changes required to the EAG CEM so that it can generate results for a low-flow oxygen patient population. This might take the form of one or more touch-point meetings.
   This is to address the Appeal Panel's general finding of unfairness arising from challenges to stakeholder engagement, and its finding on Gilead's appeal point 1(a).2 in particular. It is also necessary to ensure that the committee can appropriately follow the Appeal Panel's direction to reconsider whether an analysis of patients requiring low-flow oxygen would be informative, and consider the position with regard to children.

3. Gilead will be able to review and comment on the EAG report supplied to the committee ahead of the 3rd appraisal committee meeting.
   This is to address the Appeal Panel's general finding of unfairness arising from challenges to stakeholder engagement.
   We believe it is crucial to be able to comment on the EAG report and to have adequate time to do so

4. If the appraisal committee will consider two or more products, the agenda for the appraisal committee meeting will be structured to ensure that the review of remdesivir can be given adequate and meaningful discussion, with opportunity for open discussion of all material issues. (For example, the agenda could set a separate part of the meeting for each manufacturer).
   This is to address the Appeal Panel's general finding of unfairness arising from challenges to stakeholder engagement and previous lack of consultation on key issues.

Please let us know if these conditions can be accommodated by NICE, so that we can work on a more specific timetable of events leading to a third committee meeting.
We believe that the full implementation of the above conditions are the minimum required to remedy the deficiencies identified, and the directions given, by the Appeal Panel.

We do not see an STA as a suitable or reasonable alternative, given that this would both further delay access to remdesivir to patients in need and also further exacerbate the already significant cost and delay to Gilead.

We would like to understand the decisions taken by other companies in the MTA, as to their options, before a final decision is concluded, and a timetable agreed.

Best regards,

Gordon

Appendix 2: Summary of key study characteristics included in this evidence submission

Author	Year	Number of patients (RDV)*	Number of patients (SOC)*	Data collection period
Ahmed et al. (CARAVAN) [31]	2022	53	n.a.	not reported
Amstutz et al. [11]	2023	4,473	4,159	Feb 2020 – Jan 2021
Beckerman et al. [8]	2022	560	239	not reported
Beigel et al. [12]	2020	232	203	Feb 2020 – Apr 2020 (enrolment)
Boglione et al. [30]	2022	163	n.a.	Mar 2020 – Jan 2021
Chokkalingam et al. [15]	2022	24,856	24,856	May 2020 – May 2021
Finn et al. [26]	2022	748**	1531**	Feb 2020 – Dec 2020
Garibaldi et al. [9]	2022	42,473 (18,328***)	54,386 (18,328***)	Feb 2020 – Feb 2021
Goldman et al. [32]	2021	77	n.a.	Mar 2020 – Apr 2020
Huang et al.[10]	2023	695	634	Feb 2020 – Apr 2021
Jeyapalina et al. [14]	2022	2126****	2126****	Jan 2021 – Dec 2021
Mozaffari et al. [16]	2022	41,816 (28,855***)	34,230 (28,855***)	Aug 2020 – Nov 2020
Mozaffari et al. [35]	2023	19,184 (14,169***)	11,213 (14,169***)	Dec 2020 – Apr 2021
Mozaffari et al. (CROI) [13]	2023	197,817 (164,791***)	102,783 (164,791***)	Dec 2020 – Apr 2021
Mozaffari et al. (CROI) [28]	2023	115,923	68,389	May 2020 – April 2022
Olender et al. [25]	2021	298	816	Mar 2020 – Apr 2020
Olender et al. [17]	2021	368	1399	n.a.
Paules et al. [29]	2022	435 (ordinal scale 5 patients)		Feb 2020 – Apr 2020 (enrolment)
Wiley et al. [27]	2022	7155 (total population)		Mar 2020 – Dec 2020
* Where subgroup specific data was available, this data is reported instead of the total patient number; ** Number of hospitalizations; *** Propensity score matched group; **** No breakdown provided by remdesivir / SOC patient numbers – numbers represent the total number of patients analysed; n.a.: not applicable				

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Gilead targeted submission following the decision of the appeal hearing for the multiple technology assessment for COVID-19 treatments [ID6261] – addendum

Addendum to the evidence submission to support the resolution of the upheld Gilead appeal points

Drug	Remdesivir (Veklury)
Therapeutic indication	Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in: • adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment). • adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
Appraisal number	ID6261
Company representative	Mirko von Hein Associate Director, Market Access UK & Ireland Mirko.vonhein@gilead.com
2nd company representative	Gordon Lundie Executive Director, Market Access UK & Ireland Gordon.lundie@gilead.com
Date of submission	Thursday, 28 September 2023

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Table of Contents

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

List of tables

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

List of abbreviations

Abbreviation	Definition
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
BSC	Best supportive care
CI	Confidence interval
CROI	Conference on retroviruses and opportunistic infections
EAG	Evidence assessment group
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IMV	Invasive mechanical ventilation
LFO	Low flow oxygen
LOS	Length of stay
MTA	Multiple technology assessment
NICE	National institute for health and care excellence
NMA	Network meta-analysis
OR	Odds ratio
PSM	Propensity score matching
QALY	Quality adjusted life year
RCT	Randomized controlled trial
RR	Risk ratio
RWE	Real world evidence
SLR	Systematic literature search
SOC	Standard of care
STA	Single technology appraisal
TTD	Time to discharge
VOC	Variant of concern
WTP	Willingness to pay

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

1 Executive summary

In an email sent to Gilead on the 11th of September 2023, NICE has outlined concerns the evidence assessment group (EAG) has raised with NICE following the submission of the Gilead targeted evidence submission for remdesivir as part of the COVID-19 multiple technology appraisal (MTA) process [ID6261]. This addendum to the Gilead targeted submission aims to address the concerns raised by the EAG.

In section 2 Gilead provides more detail on the methodology used to select relevant studies to inform the appraisal of remdesivir for the use in patients with low-flow oxygen (LFO), immunocompromised patients and children.

Section 3 focuses on the differences in the meta-analyses submitted to support the LFO population, providing a comprehensive overview of the characteristics of these publications. Furthermore section 4 discusses the Cochrane review identified by the EAG and provides an argumentation for why this review has not been referenced in the initial Gilead targeted submission.

Section 5 adds further context and background to the real-world evidence (RWE) presented in the Gilead targeted submission. Details on the methodology of those studies – including aspects such as propensity score matching (PSM) and data sources – are provided as requested by the EAG.

Lastly section 6 describes the rationale for the selection of the studies to inform the three key input parameters to be used in the EAG economic model. These parameters include 28-day mortality, clinical improvement and time to discharge (TTD) from hospital. Gilead provides reasons for why certain studies have been preferred over others.

Gilead is convinced that the provided evidence represents the most comprehensive synthesis of all relevant trials for remdesivir patients who require LFO, who are immunocompromised as well as paediatric patients. Should further information be required for the EAG to conduct their assessment of the available evidence, Gilead is open to collaborating with the EAG to facilitate a rapid appraisal, ultimately making remdesivir available again for patients.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

2 Clarification on the methods to select studies and outcomes

The EAG has raised concerns about the systematic review conducted by Gilead to summarize the available evidence for studies on remdesivir in LFO, immunocompromised and paediatric patients. To eradicate these concerns, Gilead would like to clarify the approach which was taken to summarize the clinical evidence.

As a dedicated systematic literature review (SLR) for patients receiving LFO was not feasible due to time constraints, Gilead leveraged existing SLRs conducted for inpatients with COVID-19. Gilead conducted both a clinical and economic SLR for inpatients with COVID-19 and shared the technical reports as well as the extraction grid with NICE on the 15th of September 2023.

The technical reports of the clinical and economic SLR contain all relevant information required and expected of a high-quality systematic search, including a full description of the identification of studies, search strategy, search terms used and study selection criteria. Furthermore, the SLRs reported a PRISMA flow chart for the identified studies, a summary of the included clinical studies as well as a risk of bias assessment using the York Centre for Reviews and Dissemination checklist.[1]

To complement the SLRs which focus on the inpatient sector, Gilead has conducted additional targeted searches for LFO, immunocompromised and paediatric patients specifically. These searches were conducted using Google scholar and leveraged search terms derived from the PICO framework, targeting LFO, immunocompromised and paediatric patients specifically.[2]

3 Differences in the submitted meta-analyses for remdesivir

One of the comments made by the EAG in the email sent to Gilead on the 11th of September questioned the results of the three distinct network-meta-analyses (NMA) which were submitted by Gilead in the targeted submission. In the words of the EAG, these three NMAs provided "markedly different results", referring to the outcomes on 28-day mortality in LFO patients comparing remdesivir against standard of care (SOC). For simplicity, the results for 28-day mortality of the three cited NMAs are depicted again below in Table 1.

Table 1: Overview of the three distinct NMAs cited in the Gilead targeted evidence submission and their mortality outcomes

Study	**Evidence type**	**Outcome [95% CI]**
Huang et al. 2023 [3]	SLR / NMA (RCT)	RR 0.59 [0.43, 0.80]
Beckerman et al. 2022 [4]	SLR / NMA (RCT)	RR 0.24 [0.11, 0.48]
Amstutz et al. 2023 [5]*	SLR / NMA (RCT)	aOR 0.80 [0.70, 0.93]
aOR: adjusted odds ration; CI: Confidence interval; NMA: network meta-analysis; RCT: Randomized controlled trial; RR: risk ratio; SLR: systematic literature review * Amstutz et al. analyse patients with no or low-flow oxygen requirements as a single patient population		

Even though the outcomes reported in Table 1 differ, Gilead believes that they indicate a strong beneficial effect of remdesivir on mortality in LFO patients. All outcomes reported in the three distinct NMAs show a significant mortality benefit for remdesivir, with all the upper confidence intervals reported clearly below one.[3-5]

Given that one of these outcomes needs to inform the base case of the adapted version of the EAG economic model, it is valid to investigate further what factors impact the magnitude of the reported mortality outcomes. Gilead has previously recommended to use the outcome from Huang et al. to

inform 28-day mortality in the EAG model, given that this paper was published most recently, used a risk ratio as the outcome measure – which aligns with the EAG model – and reports a result that falls in between the results reported by both Beckerman et al. and Amstutz et al., therefore representing a more balanced outcome for assessment in the face of uncertainty.[3-5] To provide more information on these NMAs to both the EAG and NICE, study characteristics of these NMAs are reported in Table 2, which should help assess differences in the reported outcomes.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Table 2: Study characteristics of the NMAs included in the Gilead targeted evidence submission

NMA	Year	LFO definition	Included studies	Analysis type	Sample size (n/N)	Data search	Population details
Huang et al. [3]	2023	Four category ordinal scale: (1) not requiring supplemental oxygen; (2) requiring supplemental low-flow oxygen; (3) requiring non-invasive ventilation or high-flow oxygen; (4) requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).	Ali et al. [6] Beigel et al. [7] Wang et al. [8]	Aggregate	RDV: 56/695[d] Control: 90/634[d]	January 2020 to February 2023	Unvaccinated[f]
Beckerman et al. [4]	2022	Low-flow oxygen defined as either hospitalized and requiring any supplemental oxygen or hospitalized requiring low-flow supplemental oxygen, depending on the study	Beigel et al. [7][a] Spinner et al. [9][a] (Kalil et al. [10])[a, b]	Aggregate	RDV: 21/560[d, e] BSC: 29/239[d, e]	Up until April 2021	Unvaccinated[f]
Amstutz et al. [5]	2023	WHO ordinal scale levels (no distinction between no and low flow oxygen)	Beigel et al. [7] Wang et al. [8] Spinner et al. [9] Ali et al. [6] SOLIDARITY [11][c] DisCoVeRy [12, 13]	Individual patient level data (10,480 patients)	RDV: 409/4473[d] No RDV: 465/4159[d]	Up until April 2022	Unvaccinated
a: Based on list of study presented in table 3 of the Beckerman et al. paper; b: Results reported separately for remdesivir + baricitinib; c: SOLIDARITY data cited individually in the Amstutz paper, including FIN-Solidarity, NOR-Solidarity and additional WHO-Solidarity; d: Event/ total; e: Sample size data reported in this table reflects the later mortality assessment; f: Study does not report distinctively that it assess an unvaccinated population, but no vaccination can be assumed							

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

As can be seen from Table 2, the three NMAs differ in terms of their study characteristics. While Huang et al. and Beckerman et al. conducted their meta-analysis using aggregate data, Amstutz et al. instead used individual patient level data.[3-5]

The NMAs also differed with regards to the patient populations which they assessed. Huang et al. and Beckerman et al. report results for LFO patients, while Amstutz et al. report results for patients receiving no oxygen or LFO (as a combined group). Consequently, Amstutz et al. assess a broader patient population compared to Huang et al. and Beckerman et al., thus potentially explaining some of the differences in the magnitude in effect between the studies.[3-5]

Further differences are present in the sample sizes of the NMAs. Amstutz et al. report results for over 10,000 patients treated within an RCT context, while Huang et al. and Beckerman report results for 1,300 and 800 total patients respectively. These differences in sample size are due to the aforementioned differences in the definition of the patient population (i.e. LFO vs. no oxygen or LFO).

Out of the three NMAs, Amstutz et al. is the only one which reports explicitly that the entire patient population is unvaccinated. Nonetheless, it can be assumed that both Huang et al. and Beckerman et al. assess a similarly unvaccinated patient population, given the trials which they included in their analysis are from a time during which widespread vaccination was not yet available.

Amstutz et al. include the broadest set of studies, summarizing results from 6 separate trials, while Huang et al. and Beckerman et al. summarize results of 3 and 2 studies respectively.[3-5] All NMAs include the key ACTT-1 trial but differ otherwise. Huang et al. also includes Ali et al. and Wang et al., while Beckerman et al. include Spinner et al. in their analysis.[3, 4, 6, 8, 9]

The RCT conducted by Wang et al., which is included in the meta-analyses by Huang et al., used exclusively data from hospitals in China while Spinner et al. leveraged data from a mix of different geographical regions, including the United States, Europe and Asia, thus potentially contributing towards the differences in effect size reported in the two NMAs focused on LFO patients only.[8, 9] Huang et al. also include the CATCO trial conducted by Ali et al., which analysed data from 52 Canadian hospitals.[6] Given that Beckerman et al. conducted their data searches up until April 2021, this explains why the CATCO trial – which was published in January 2022 – was not included in their NMA.[4, 6]

As outlined in the targeted submission submitted by Gilead on the 1st of September 2023, Gilead believes that the results of Huang et al. should be used as the base case results for mortality in the adapted EAG model. Given the differences in study characteristics, the other two NMAs might be used in explorative sensitivity analysis to reflect the uncertainty in the magnitude of the mortality estimate.

4 Comment on the Cochrane review for remdesivir

In the email sent to Gilead on the 11th of September 2023, NICE has shared concerns of the EAG with regards to the evidence submission from Gilead. One of these concerns focused around "the possibility that other relevant studies have been missed" as part of the methods used to identify studies for LFO, immunocompromised and paediatric patients. In particular, the email highlights a Cochrane review published by Grundeis et al., which has not been referenced in the Gilead targeted submission.[14]

As already outlined in section 2, the targeted searches conducted by Gilead focused on identifying studies for LFO, immunocompromised and paediatric patients. The paper by Grundeis et al. however

focused on remdesivir in patients treated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and therefore had a different scope compared to the Gilead targeted submission.[14] Given the different scope of the analysis in the Grundeis et al. paper, the Cochrane review has not been referenced in the Gilead targeted submission.

In line with other publications on LFO patients, Grundeis et al. have conducted sensitivity analysis in the subgroup with LFO at baseline, and found that "the evidence suggests a benefit for remdesivir compared to placebo or standard care alone", referring back to results from ACTT-1 (RR 0.32, 95% CI 0.15 to 0.66).[7, 14] The authors also conducted tests for subgroup differences which revealed high heterogeneity (Chi^2 = 8.32, df = 2, P = 0.02, I^2 = 75.7%).[14]

5 Additional detail on the submitted real-world evidence studies

One of the concerns raised by the EAG relates to a lack of details on "the methods used within real-world evidence studies (RWE) to obtain comparative efficacy values", as outlined in the email sent by NICE on the 11th of September. Gilead would like to take the opportunity to provide additional information on the RWE studies which are referenced in the Gilead targeted submission.

A key method used to derive comparative results in several RWE studies is propensity score matching (PSM). This technique has been applied in the studies conducted by Mozaffari et al., Jeyapalina et al., Chokkalingam et al., Garibaldi et al. and Olender et al. to reduce bias due to confounding variables and to estimate a treatment effect.[15-21]

Propensity scores are used as they allow to design and analyse an observational (nonrandomized) study so that it mimics some of the characteristics of a randomized controlled trial.[22] In a way propensity scores balance treatment groups, as the distribution of observed baseline covariates will be similar between treated and untreated subjects.[22]

For example, Mozaffari et al. used propensity scores to match patients which received remdesivir to those patients not receiving remdesivir.[15] In particular, Mozaffari et al. estimated a propensity score using separate logistic regression model for LFO at baseline. As outlined by Mozaffari et al., variables included in PS models were demographics (age group, sex, race, ethnicity, primary payor), key comorbidities, hospital characteristics, admission from skilled nursing facility, admission month, hospital ward upon admission, other indicators of severity based on admission diagnoses (such as hypoxemia, sepsis, respiratory failure, and pneumonia), and concomitant COVID-19 treatment with anticoagulants, corticosteroids, and convalescent plasma at baseline.[15] More information on the propensity score matching implementation can be found in the full publication from Mozaffari et al. as well as in the supplementary material the authors provide online.[15]

Several of the RWE studies for remdesivir relied on retrospective data from the Premier Healthcare Database, which captures approximately 20% of all hospitalisations across 45 states and Washington, DC in the United States.[15] In the absence of RWE data specific to the UK context for the targeted patient population, Gilead assumes the data from the Premier Healthcare database be generalisable, given its large sample size.

Further information on the submitted real-world evidence studies included in the Gilead targeted submission can be found in the technical report of the Gilead SLR.[23]

The EAG has also commented that table 4 of the targeted submission omits "studies that were identified in Barnieh et al.", which they argue limits the validity of the Gilead search strategy.[24]

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Gilead would like to clarify that RWE studies depicted in the forest plot from Barnieh et al. were only used as supplementary evidence to demonstrate that a mortality benefit for patients on remdesivir has been observed in other patients populations. As outlined by the authors, the study from Barnieh et al. evaluated the real-world effectiveness of remdesivir versus non remdesivir treatments in patients hospitalized with COVID-19. Given that Barnieh et al. do not report results specifically for LFO patients, these studies should have not been identified in the search regardless, and therefore do not invalidate the Gilead search strategy.

6 Rationale for selecting input parameters for the EAG model

As already outlined in the Gilead targeted submission, Gilead recommends using the key data inputs for remdesivir in a LFO population as outlined in Table 3. In their email to Gilead the EAG has highlighted that "there is insufficient text to explain why the results" of the selected studies are preferred to the results of other available studies. This section provides further information on why the selected studies have been chosen.

Table 3: Data inputs for the low-flow oxygen patient population to be used in the EAG economic model

Input parameter	Effect estimate	95% confidence interval	Reference
28-day mortality	RR 0.59	0.43, 0.80	Huang et al. [3]
28-day clinical improvement	aHR 1.23	1.19, 1.27	Garibaldi et al. [20]
Time to hospital discharge	HR 1.27	1.10, 1.46	ACTT-1 [25]

6.1 Mortality

For the 28-day mortality outcome three meta-analyses were identified which provided results on the LFO patient population. Systematic reviews and meta-analyses of RCTs represent the best available evidence compared to other study designs.[26]

As outlined in section 3, Gilead has carefully compared the three available meta-analyses and provided arguments for why Huang et al. was the preferred choice.[3] One of the reasons why Huang et al. has been selected was the fact that the study was published most recently and therefore includes the most recent time horizon for their data search (until February 2023). Furthermore, the Huang et al. reported 28-day mortality as a risk ratio, which aligns with the input parameter used in the EAG model. Lastly, Huang et al. report a more conservative estimate of the 28-day mortality outcome compared to Beckerman et al. (RR 0.59 vs. RR 0.24).[3, 4]

Amstutz et al. was not recommended as a base case input for 28-day mortality as it focused on a slightly different patient population, i.e. patients with no oxygen or LFO requirements.[5]

To account for any study selection bias, Gilead suggests conducting sensitivity analysis using both the 28-day mortality outcome form Beckerman et al. and Amstutz et al. to provide a range of plausible cost-effectiveness results to the NICE committee.

Nonetheless, all three meta-analyses show a significant mortality benefit for remdesivir, with all the reported upper confidence intervals clearly below one.

6.2 Clinical improvement

Gilead previously recommended to use outcomes from Garibaldi et al. to inform the clinical improvement endpoint in the EAG model.[20] The study by Garibaldi et al is a retrospective,

multicentre comparative effectiveness study, which compared data for almost 20,000 remdesivir patients to a matched control group. Due to the large sample size of this trial, Gilead selected Garibaldi et al. for the clinical improvement outcome.

It should be noted that Beckerman et al. report results for a similar outcome, which they label "recovery", defined as "either recovery from COVID-19 or discharge from hospital".[4] Given the similarity to the clinical improvement outcome, the outcome from Beckerman et al. might also be considered as additional evidence. Regardless, both Garibaldi et al. and Beckerman et al. report similar results, thus indicating high consistency across the two different studies (aHR 1.23, 95% CI 1.19, 1.27; RR 1.17, 95% CI 1.09, 1.28).

6.3 Time to hospital discharge

For hospital TTD, Gilead previously suggested using outcomes from the ACTT-1 trial.[7] The only other RCT which had reported data on TTD for remdesivir is Spinner et al., who provided TTD curves in a supplementary analyses.[9] Gilead preferred the ACTT-1 results over the results from Spinner et al. due to larger sample size in the ACTT-1 trial compared to the sample size in the paper by Spinner et al. (N=1062 vs. N=584).

Gilead is aware of the committee's preference to exclude TTD effects for all treatments following the last two appraisal committee meetings and is conscious that TTD effects for remdesivir might not be considered by the committee to be aligned to previous recommendations made for tocilizumab, Paxlovid and Sotrovimab.

7 Conclusion

Gilead has conducted a thorough review of the available evidence for remdesivir and provided additional clarifying information based on the request of the EAG. Alongside this addendum of the Gilead targeted submission, Gilead has provided NICE and the EAG with the technical reports and associated extraction grid of both the clinical and economic SLR focused in COVID-19 inpatients. This information should hopefully enable the EAG to conduct their review, amend the economic model and facilitate a third committee meeting within a reasonable timeframe.

Remdesivir remains a highly beneficial treatment option for patients with COVID-19, with particularly strong clinical outcomes for patients receiving LFO or patients who are immunocompromised. Similarly, remdesivir is a safe and well tolerated treatment for children, providing the only viable treatment option for severe paediatric patients aged <12 years.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

8 References

1. Tacconelli, E., *Systematic reviews: CRD's guidance for undertaking reviews in health care.* The Lancet Infectious Diseases, 2010. **10**(4): p. 226.
2. Amir-Behghadami, M. and A. Janati, *Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews.* Emergency Medicine Journal, 2020.
3. Huang, C., T.-L. Lu, and L. Lin, *Remdesivir Treatment Lacks the Effect on Mortality Reduction in Hospitalized Adult COVID-19 Patients Who Required High-Flow Supplemental Oxygen or Invasive Mechanical Ventilation.* Medicina, 2023. **59**(6): p. 1027.
4. Beckerman, R., et al., *Remdesivir for the treatment of patients hospitalized with COVID-19 receiving supplemental oxygen: a targeted literature review and meta-analysis.* Scientific Reports, 2022. **12**(1): p. 9622.
5. 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.
6. Ali, K., et al., *Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial.* Cmaj, 2022. **194**(7): p. E242-E251.
7. Beigel, J.H., et al., *Remdesivir for the Treatment of Covid-19 — Final Report.* New England Journal of Medicine, 2020. **383**(19): p. 1813-1826.
8. Wang, Y., et al., *Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.* The lancet, 2020. **395**(10236): p. 1569-1578.
9. Spinner, C.D., et al., *Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial.* Jama, 2020. **324**(11): p. 1048-1057.
10. Kalil, A.C., et al., *Baricitinib plus remdesivir for hospitalized adults with Covid-19.* New England Journal of Medicine, 2021. **384**(9): p. 795-807.
11. Consortium, W.S.T., *Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses.* The Lancet, 2022. **399**(10339): p. 1941-1953.
12. Ader, F., et al., *Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial.* The Lancet Infectious Diseases, 2022. **22**(2): p. 209-221.
13. Ader, F., et al., *Final results of the DisCoVeRy trial of remdesivir for patients admitted to hospital with COVID-19.* The Lancet Infectious Diseases, 2022. **22**(6): p. 764-765.
14. Grundeis, F., et al., *Remdesivir for the treatment of COVID-19.* Cochrane Database of Systematic Reviews, 2023(1).
15. Mozaffari, E., et al., *Remdesivir treatment in hospitalized patients with coronavirus disease 2019 (COVID-19): a comparative analysis of in-hospital all-cause mortality in a large multicenter observational cohort.* Clinical Infectious Diseases, 2022. **75**(1): p. e450-e458.
16. Mozaffari, E., et al., *Remdesivir reduced mortality in immunocompromised patients hospitalized for COVID-19 across variant waves: Findings from routine clinical practice.* Clin Infect Dis, 2023.
17. CROI. *REMDESIVIR REDUCES MORTALITY IN HOSPITALIZED COVID-19 PATIENTS ACROSS VARIANT ERAS*. 2023 [cited 2023; Available from: hiips://www.croiconference.org/abstract/remdesivir -reduces-mortality-in-hospitalized-covid-19-patients-across-variant-eras/.
18. Jeyapalina, S., et al. *1127. Effectiveness of Remdesivir as Treatment for COVID-19 Positive US Veterans*. in *Open Forum Infectious Diseases*. 2022. Oxford University Press US.
19. Chokkalingam, A.P., et al., *Association of remdesivir treatment with mortality among hospitalized adults with COVID-19 in the United States.* JAMA Network Open, 2022. **5**(12): p. e2244505-e2244505.

20. 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.
21. Olender, S.A., et al., *Remdesivir for severe coronavirus disease 2019 (COVID-19) versus a cohort receiving standard of care.* Clinical Infectious Diseases, 2021. **73**(11): p. e4166-e4174.
22. Austin, P.C., *An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies.* Multivariate Behav Res, 2011. **46**(3): p. 399-424.
23. Gilead Sciences, *Clinical SLR - technical report - inpatient treatment with remdesivir - data on file*. 2023.
24. Barnieh, L., et al., *Real-world effectiveness of remdesivir for hospitalized patients with COVID-19: systematic review and meta-analysis.* European Respiratory Journal, 2022. **60**(suppl 66): p. 4498.
25. Gilead Sciences, *ACTT-1 clinical study report - data on file*. 2020.
26. OpenMD. *Levels of Evidence*. 2023; Available from: hiips://openmd.com/guide/level s-of-evidence.

Gilead Sciences Ltd 280 High Holborn, London WC1V 7EE
Tel +44 (0)20 3681 4681 Fax +44 (0)20 3681 4699
Registered in England No 2543818
www.gilead.co.uk

Molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261]: EAG critique of the post-appeal evidence submitted for remdesivir

Produced by	Sheffield Centre of Health and Related Research (SCHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK Andrew Metry, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Abdullah Pandor, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Shijie Ren, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK
Date completed	20th of October 2023

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135564.

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. These provide more details on the work which has been undertaken for the treatments assessed in-hospital for severe COVID-19, which was NICE ID4038.

The final draft guidance for ID4038[4] did not recommend the use of molnupiravir, remdesivir and tixagevimab plus cilgavimab and the manufacturers of these interventions appealed the decision. In order for expediency with respect to the remaining interventions in ID4038, NICE provided a new ID number, ID6261 for molnupiravir, remdesivir and tixagevimab plus cilgavimab, with these appraisals to be concluded after the appeal.

The appeal panel upheld the appeal on multiple appeal points made by the three companies with the evaluation returned to the appraisal committee who must '*take all reasonable steps to address the following issues before publishing final guidance.*' Full details of the appeal decision are available online.[5]

NICE has entered into discussions with all three companies. The first re-appraisal is that of remdesivir. Following discussions between NICE and Gilead (the manufacturers of remdesivir) an agreement was reached that was summarised by Gilead as follows: "*NICE has agreed that four aspects must be addressed, namely (1) the opportunity for Gilead to make a targeted evidence submission, (2) an opportunity for engagement with the evidence assessment group (EAG) on economic modelling for remdesivir, (3) the ability for Gilead to comment on the EAG report following model adaptation and (4) an agenda for the third appraisal committee meeting (ACM) which allows appropriate room for discussion of the relevant evidence for remdesivir*".[6]

Section 2 summarises the targeted evidence review (and multiple subsequent documents) submitted by the company in response to the Appeal decision to assess the clinical effectiveness of remdesivir in three subgroups of patients with severe COVID-19 that required hospitalisation. These subgroups were patients requiring low-flow supplemental oxygen; children, and immunocompromised patients. Section 3 provides the EAG critique of the clinical evidence submitted by Gilead and its search strategy and proposes alternative evidence sources that the EAG thinks may be more appropriate.

As the EAG was writing up its report, Gilead sent its own economic model to the EAG. There was insufficient time to critique the implementation of the model, but the EAG noted that when a comparison was made between incremental cost-effectiveness ratios (ICERs) in terms of cost per quality-adjusted

life years (QALYs) gained generated by the company's model and the EAG's model, with attempts to ensure comparable input parameters, that the ICER was moderately lower in the EAG's model. Given that the EAG's model had been scrutinised by multiple companies, had been discussed at previous committee meetings, and the EAG believes it has additional flexibility to that of the company's model the EAG has maintained the use of its model which may be favourable to the intervention.

Section 4 details the changes introduced to the model by the EAG to consider the new evidence and selected subgroups. Section 5 provides the cost-effectiveness results generated by the EAG. The EAG's model produces ICERs for remdesivir compared with standard of care (SoC). Section 6 provides a discussion on the results generated by the EAG.

It is unclear whether tocilizumab would be a comparator. The NICE final draft guidance for ID4038[4] stated that tocilizumab was an option for treating adults with COVID-19 who are having systemic corticosteroids and need supplemental oxygen or mechanical ventilation, and thus there is potential for adult patients receiving low-flow oxygen (LFO) to have tocilizumab. Discussions with NICE did not provide a definitive conclusion on whether tocilizumab was a comparator and therefore, following guidance from NICE, the EAG has provided the results comparing remdesivir with tocilizumab in appendices should the Appraisal Committee find these results informative. There is a confidential patient access scheme (PAS) for tocilizumab which, following NICE guidance, is not considered within the report. A confidential appendix incorporating the PAS for tocilizumab has been provided to the NICE appraisal committee.

2 A summary of the company's targeted submission

The company submitted new evidence on remdesivir for the treatment of COVID-19 in the form of a targeted evidence submission (TS) on the 6th of September 2023. The EAG deemed that there were insufficient details in the TS and relayed this to NICE who scheduled a meeting between the company, the EAG and NICE representatives. Following this additional evidence was provided by the company in stages. On the 15th of September 2023, the company provided a draft clinical systematic literature review (SLR) technical report and an extraction grid relating to hospitalised patients. On the 9th of October 2023, the company further provided the clinical rationale for selecting the subgroups on which it focussed and a bias assessment using NICE-preferred tools in the form of an extraction grid.

Given the report deadline of the 20th of October 2023, the EAG could not follow best practice and independently undertake a systematic review and meta-analysis of the clinical evidence relevant to the decision problem. Following discussions with NICE, a pragmatic, alternative approach was undertaken relying on a brief critique of the company's TS (including additional supporting information) of the clinical evidence.

2.1 Critique of the company's targeted submission

Although remdesivir (Veklury) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19

the scope of the TS focused on populations in which the company considered remdesivir to be most effective. These populations included patients requiring LFO, children and immunocompromised patients. A definition of each of these patient populations, as provided by the company in the TS is reproduced in Table 1.

Table 1: Definition of relevant patient populations for remdesivir (reproduced from Table 3, TS)

Patient population	Definition
Low-flow oxygen (LFO)	Patients requiring oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min as per the NICE COVID-19 rapid guidelines[7]
Children	The paediatric patient population includes: • paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) • paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 as outlined in the summary of product characteristics (SmPC) for remdesivir[8]
Immunocompromised patients	Patients who have a weakened immune system due to a particular health condition or patients who are on medication or treatment that suppresses their immune system

Following a request from NICE, the company provided a detailed rationale for the selected subgroups.[9] The EAG has briefly summarised the company's rationale.

- The LFO subgroup was considered as a distinct and readily defined population[7, 10-13] and the European Society of Clinical Microbiology and Infectious Diseases Guidelines[11, 12] conditionally recommend remdesivir for use in hospitalised patients requiring no or LFO but not in patients requiring high-flow oxygen.
- In paediatric patients, remdesivir is the only available licensed treatment option for COVID-19 and there is inequity of access to comprehensive clinical care for this group.
- The immunocompromised subgroup was considered to experience worse clinical outcomes with COVID-19 than the general population and comprise less than 1% of the UK population, but account for a large proportion of those hospitalised with, of dying from, COVID-19. In addition, nirmatrelvir and ritonavir (Paxlovid) is the only recommended antiviral and is not appropriate for all immunocompromised patients (including immunocompromised patients requiring supplemental oxygen).

As noted in the addendum to the TS (page 6), the company states that a '*dedicated systematic literature review (SLR) for patients receiving LFO was not feasible due to time constraints, Gilead leveraged existing SLRs conducted for inpatients with COVID-19... The technical reports of the clinical and economic SLR contain all relevant information required and expected of a high-quality systematic search, including a full description of the identification of studies, search strategy, search terms used and study selection criteria. Furthermore, the SLRs reported a PRISMA flow chart for the identified studies, a summary of the included clinical studies as well as a risk of bias assessment using the York Centre for Reviews and Dissemination checklist.[14] To complement the SLRs which focus on the inpatient sector, Gilead has conducted additional targeted searches for LFO, immunocompromised and paediatric patients specifically. These searches were conducted using Google scholar and leveraged search terms derived from the PICO framework, targeting LFO, immunocompromised and paediatric patients specifically.[15]*'

Whilst the EAG acknowledges the limitations and time constraints to undertake a full systematic review following the Appeal decision, the review methods, and processes in the TS (and accompanying technical report) are neither fully transparent nor reproducible, and the strengths and limitations of the company's review process are not fully acknowledged. For example, in the absence of clear and explicit review eligibility criteria in the TS (including supporting information), it is unclear how the company's broader systematic review of COVID-19 treatments in the inpatient setting was used and informed the TS, which focused on a subgroup of patients requiring LFO, children and immunocompromised patients; the advantages and disadvantages of using Google Scholar as a standalone source for the TS (the EAG notes that the use of Google Scholar as a standalone source for systematic review searches is not usually recommended or considered a replacement for traditional academic citation databases);[16-18] and how many (and which) primary studies met the review inclusion criteria (including a table of excluded studies with reasons) for the TS. The EAG further notes that the broader review only included primary studies (interventional and observational studies) and excluded existing systematic reviews and (network) meta-analyses (Company's Clinical SLR Technical report, Table 7, page 18-19) – a critique of the search strategy for the broader review is contained in Appendix 1. In contrast, the TS appears to have included existing systematic reviews and (network) meta-analyses and other studies (TS, Table 4, page 17; Figure 6, page 18). It is unclear why the selection of study designs was notably different between the broader review and the TS.

Although no narrative or statistical synthesis of the results was undertaken or reported in the broader review, the TS summarised the results of selected systematic reviews and primary studies. These included data on mortality, clinical improvement, time to discharge, recovery, hospital readmission, progression to invasive mechanical ventilation or death, and long COVID syndrome for patients requiring LFO, for children and for immunocompromised patients (TS, page 17-28). The EAG was

unable to undertake independent quality assessments of all included / reported studies, due to the multiple submissions and varied timing of the company's additional supporting information and the deadline for this report.

In the subsequent subsections, the EAG critique has been limited to key data inputs in the economic model for remdesivir in the LFO population, namely: mortality; clinical improvement; and time to hospital discharge. No critique of the evidence has been provided for the paediatric and immunocompromised populations (see TS, page 25-28 for details of supporting evidence) as the TS (page 38) states that, *'the evidence for the paediatric patient population receiving remdesivir does consist of non-comparative, single arm trials. Given this lack of comparative data, deriving incremental cost-effectiveness estimates against a SOC comparator are not feasible*.' No comment in the TS was made for the immunocompromised population where ICERs were also not provided.

2.1.1 LFO population and mortality

As noted earlier, it is unclear how the company's broader systematic review was used to inform the TS and which primary studies were potentially eligible for inclusion. Nevertheless, the TS (page 17) and TS addendum (page 6) identified three potentially relevant systematic reviews (network meta-analyses of RCTs)[19-21] which provided data on relevant primary studies and mortality outcomes in hospitalised adult COVID-19 patients receiving LFO. A summary of each systematic review is provided in Table 2 and an assessment of methodological quality is provided in Appendix 2.

The company selected the 28-day mortality data from the Huang *et al.*[19] review to inform the base case of the EAG economic model, as the '*…paper was published most recently, used a risk ratio as the outcome measure – which aligns with the EAG model – and reports a result that falls in between the results reported by both Beckerman et al. and Amstutz et al., therefore representing a more balanced outcome for assessment in the face of uncertainty'* [TS addendum, page 7]. In addition, using the AMSTAR-2 critical appraisal tool for systematic reviews,[22] the company considered the Huang *et al.*[19] review '*…to have more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review* [TS addendum, Bias assessment using NICE preferred tools, Excel Spreadsheet]'. In contrast, the company considered the Beckerman *et al.*[20] review to have a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. However, the EAG notes that purely based on the details provided in Appendix 2 which provides a summary of the company's AMSTAR-2 ratings for included systematic reviews, the company's assessment gradings appear to look similar for Beckerman *et al*.[20] and Huang *et al*.[19] across most critical domains (question 2, 4, 7, 9 and 15), except questions 11 and 13, which suggest both studies may have a one potential critical flaw.

Table 2: Summary of systematic reviews informing mortality outcomes (adapted, TS addendum, Table 1, page 6 and Table 2, page 8)

Author, year	LFO definition	Included studies	Analysis type	Data search	Population details	Mortality outcomes	
Huang *et al.*[19]	Four category ordinal scale: (1) not requiring supplemental oxygen; (2) requiring supplemental low-flow oxygen; (3) requiring non-invasive ventilation or high-flow oxygen; (4) requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).	Ali *et al.*[23] Beigel *et al.*[24] Wang *et al.*[25]	Aggregate	January 2020 to February 2023	Unvaccinated[f]	Remdesivir: 56/695[d] Control: 90/634[d]	Risk ratio: 0.59 (95% CI: 0.43, 0.80)
Beckerman *et al.*[20]	Low-flow oxygen defined as either hospitalized and requiring any supplemental oxygen or hospitalized requiring low-flow supplemental oxygen, depending on the study	Beigel *et al.* [24a] Spinner *et al.*[26 a] (Kalil *et al.* [27])[a, b]	Aggregate	Up until April 2021	Unvaccinated[f]	Remdesivir: 21/560d, [e] Best Supportive Care: 29/239d, [e]	Risk ratio: 0.24 (95% CrI: 0.11, 0.48)
Amstutz *et al.*[21]	WHO ordinal scale levels (no distinction between no, and low flow, oxygen)	Beigel *et al.*[24] Wang *et al.*[25] Spinner *et al.*[26] Ali *et al.*[23] SOLIDARITY[28 c] DisCoVeRy [29, 30]	Individual patient level data (10,480 patients)	Up until April 2022	Unvaccinated	Remdesivir: 409/4473[d] No Remdesivir: 465/4159[d]	Adjusted odds ratio: 0.80 (95% CI: 0.70, 0.93) (Analysis includes patients with no or low-flow oxygen requirements as a single patient population)

a: Based on list of study presented in table 3 of the Beckerman *et al.* paper; b: Results reported separately for remdesivir + baricitinib; c: SOLIDARITY data cited individually in the Amstutz paper, including FIN-SOLIDARITY, NOR-SOLIDARITY and additional WHO-SOLIDARITY; d: Event/ total; e: Sample size data reported in this table reflects the later mortality assessment; f: Study does not report distinctively that it assesses an unvaccinated population, but no vaccination can be assumed
CI – confidence interval; CrI – credible interval

The EAG prefers to use the individual patient data (IPD) meta-analysis results, conducted by Amstutz *et al*.[21], to better inform the base case of the EAG economic model. An IPD meta-analysis approach has advantages over a standard meta-analysis based on aggregate data by: increasing the quantity and quality of the data available; standardising outcome and subgroup definitions across trials; maximising power to assess the heterogeneity of the treatment effect across subgroups, and by allowing adjustment for baseline differences.[31, 32] The company's critical appraisal, using the AMSTAR-2 tool,[22] also considered this systematic review to have more than one weakness but no critical flaws and considered it to provide an accurate summary of the results of the included studies (TS addendum, Bias assessment using NICE preferred tools, Excel Spreadsheet).

Although the Amstutz *et al.* review[21] included the broadest set of studies, summarising results from 8 RCTs (6 separate trials), while Huang *et al.*[19] and Beckerman *et al.*[20] summarised results of 3 and 2 trials respectively (see Table 2), the company states that '*Amstutz et al. was not recommended as a base case input for 28-day mortality as it focused on a slightly different patient population, i.e. patients with no oxygen or LFO requirements*' (TS addendum, page 11). However, the EAG notes that Amstutz *et al*.[21] undertook a sensitivity analysis, which investigated oxygenation in more detail (Amstutz *et al.*[21] Appendix Figure S8, page 36 – summarised in Appendix 3), and found that '*patients who were receiving no oxygen at baseline derived a similar relative benefit (adjusted odds ratio [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 (aOR 0·79, 0·68–0·92 with and aOR 0·59, 0·43–0·82 without additional WHO Solidarity data).*' As Amstutz *et al*.[21] did not show a significant difference between the no oxygen and the LFO groups and the NICE rapid guideline[7] (p100) stated that the '*for the WHO-SOLIDARITY trial, the panel agreed to include people having supplemental oxygen in the meta-analyses for people having low-flow or no oxygen at baseline*' the EAG used the results from the LFO and no oxygen groups combined, to reduce the uncertainty in the estimate of the efficacy of remdesivir. However, the EAG has also run analyses excluding data from SOLIDARITY[28] and used data only for patients requiring LFO. Odds ratios were transformed into hazard ratios (HRs) as described in Section 4.

2.1.2 LFO population and clinical improvement

The TS (page 19 and TS addendum page 11) appears to have identified and included one potential study by Garibaldi *et al*.[33] to inform the clinical improvement endpoint for LFO patients in the EAG model. This retrospective, multicentre comparative effectiveness study from the US, examined the effectiveness of remdesivir administration in hospitalised COVID-19 patients between the 23rd of February 2020 and the 11th of February 2021. The primary outcome was time to clinical improvement from the first day of remdesivir treatment (defined as a 2-point decrease in the 8-point WHO severity score or discharged alive from the hospital without worsening of the WHO severity score within 28 days). Remdesivir recipients were matched to controls using time-dependent propensity scores and cox

proportional hazards regression models were applied to estimate the treatment effect on the outcomes of interest. Of the 20,966 matched individuals receiving LFO (10,314 patients received remdesivir and 10,652 matched controls) remdesivir recipients were statistically significantly more likely to achieve clinical improvement by 28 days (adjusted HR 1.23, 95% CI: 1.19–1.27; median of 6 days for remdesivir compared to 7 days in controls).[33]

Although the company provided an assessment using the criteria reported in the NICE real-world evidence framework[34] and a tabulated summary of the methods used to minimise the risk of bias in the study by Garibaldi *et al*.[33] (reproduced in Appendix 4), a full critique of the strengths and limitations of this study was not adequately discussed. Garibaldi *et al*. [33] highlighted a number of limitations, most notably being unable to match approximately half of the remdesivir patients, unmeasured confounders and that the study was conducted prior to the widespread use of vaccines and the emergence of variants such as Delta and Omicron, which could impact generalisability. Despite these limitations, the company selected Garibaldi *et al*.[33] for the clinical improvement outcome due to the large sample size of the study (TS addendum, page 12).

Moreover, the TS addendum (page 12) states that *'It should be noted that Beckerman et al. report results for a similar outcome, which they label "recovery", defined as "either recovery from COVID-19 or discharge from hospital".[20] Given the similarity to the clinical improvement outcome, the outcome from Beckerman et al. might also be considered as additional evidence. Regardless, both Garibaldi et al. and Beckerman et al. report similar results, thus indicating high consistency across the two different studies (aHR 1.23, 95% CI 1.19, 1.27; RR 1.17, 95% CI 1.09, 1.28*)'. The company's TS does not provide sufficient details of these reviews, including: the individual RCTs that provided data for the recovery endpoint, including meta-analysis results; the quality, strengths and limitations of this evidence; and why this evidence was not considered relevant. However, as mentioned earlier, the EAG notes that the company considered the Beckerman *et al*. review[20] to have a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

The EAG has conducted analyses with, and without, a positive impact on remdesivir in terms of clinical improvement. When a positive impact was assumed, data from Covid-NMA[35] was used as previously assumed by the EAG.

However, as in the original modelling,[3] the EAG assumed no benefit in clinical improvement for remdesivir when an improvement in time to discharge was assumed as the ACTT-1 values incorporated clinical improvement as the time to discharge relative risk (RR) was for discharge or National Early

Warning Score ≤2 for 24 hours. Therefore, a RR of unity was assumed for clinical improvement in all 3 efficacy scenarios to reduce the possibility of double counting.

2.1.3 LFO population and time to hospital discharge

The TS (page 19-21 and TS addendum page 12) appears to have identified 2 RCTs that reported data on time to discharge from hospital: the ACTT-1 study[24] (n=1062), and Spinner *et al*.[26] (n=584; which only provided time to discharge curves in a supplementary analysis). The TS provided limited details of these studies (no quality appraisals appear to have been conducted for the Spinner *et al*. study[26]) and stated (page 20) that '*It should be noted that neither the ACTT-1 nor the results from Spinner et al.[26] for the TTD outcome were analysed for a patient population receiving low-flow oxygen, which is the patient population in which remdesivir is most effective*.' In summary, the company selected the time to hospital discharge data from the ACTT-1 study[24] (n=1062) to inform the EAG model, primarily due to larger sample size. No further rationale was provided, and a full critique of the strengths and limitations of this study was not adequately discussed. In the ACTT-1 study,[24] patients in the remdesivir group had a shorter time to discharge or to a National Early Warning Score of 2 or lower than those in the placebo group (median, 8 days vs. 12 days; HR, 1.27; 95% CI: 1.10-1.46). The EAG notes that the National Early Warning Score includes six physiological measures with total scores ranging from 0 to 20, with higher scores indicating greater clinical risk. It is unclear how, if at all, the National Early Warning Score is currently being used to safely discharge patients from UK hospitals. The company also notes that it '*…is aware of the committee's preference to exclude TTD effects for all treatments following the last two appraisal committee meetings and is conscious that TTD effects for remdesivir might not be considered by the committee to be aligned to previous recommendations made for tocilizumab, Paxlovid and Sotrovimab'*.

The EAG has conducted analyses with, and without, a positive impact on remdesivir in terms of time to hospital discharge. When a positive impact was assumed, the EAG used data from ACTT-1,[24] as did the company.

3 The EAG's critique of the company's search strategies and selected clinical evidence

For a critique of the use of Google Scholar for obtaining estimates of clinical efficacy, see Section 2. A critique of the broader search strategy is contained in Appendix 1.

The systematic reviews of economic evidence (comprising reviews of cost-effectiveness, health-related quality of life and cost and resource use) were originally conducted in July 2020 (then updated in May 2021 and December 2022). Databases covered MEDLINE and EMBASE plus international HTA websites, conference proceedings and registries of cost-effectiveness and utility studies. While the ERG usually recommends searching EconLit for the purpose of economic SLRs, this is not essential. Study design terms are based on the unvalidated (but widely used) Scottish Intercollegiate Guidelines Network filters, with terms added.

Unusually, the company have included terms relating to the interventions of interest in all three of the reviews. For reviews of cost or utility data (HRQoL), guidance recommends excluding interventions and using population terms only, with the addition of an appropriate filter.

The ERG speculates that the decision to include intervention terms may have been taken for practical reasons (due to the high prevalence of COVID-19 during the acute phase of the pandemic) although this could perhaps have been addressed more effectively for the review of HRQoL evidence by limiting the population to inpatients.

The net result of this approach is that papers containing useful data about the costs of standard of care (e.g. hospitalisation) or other drugs (outside of the company's scope) will be missing from the models proposed in the TS. The impact of this is unknown although the EAG expects that this will not be a significant limitation given that the EAG model has been scrutinised by many stakeholders and costs associated with hospital care were amended followign stakeholder comments.

4 Amendments to the EAG's model and the analyses undertaken

Section 4 is subdivided into the amendments required within the model in order to assess the subgroups put forward by the company and the analyses which were undertaken.

4.1 Amendments made to the EAG's model

The model required changing to take into consideration the fact that the company was positioning remdesivir only for patients receiving LFO. This meant that all patients were placed at ordinal scale 5 rather than divided amongst ordinal scales 5 to 7 as modelled previously.

Patients receiving LFO are less severe than patients receiving high-flow oxygen or mechanical invasive ventilation and the underlying mortality rate used previously needed to be changed to take this into account. The company suggested a value of 10% at 15 days for patients on LFO, based on 14% mortality in SOLIDARITY[28] at day 15, however the EAG used an alternative value of 14.0% at 28 days (432 deaths out of 3076 patients who needed oxygen but without ventilation who did not receive remdesivir as reported at Amstutz *et al*.[21])

The 28-day mortality data from Amstutz *et al*.[21] and Huang *et al*.[19] were reported as ORs and RRs, however the EAG's model uses HRs. To estimate HRs, the goal seek function of Excel was used to calculate the HRs that would generate the same clinical outcomes as reported in Amstutz *et al*.[21] and Huang *et al*.[19]. Table 3 provides the mortality data from the studies and the corresponding HRs calculated by the EAG. The ORs and RRs reported are midpoints with 95% CIs, with the values used for the mean, mean-low and low efficacy scenarios calculated by the EAG. These scenarios, and the rationale for choosing them, are described in Section 4.2.

Table 3: ORs/RRs of the mortality data used in the EAG's model with the corresponding calculated HRs time to death

Source for mortality data relating to remdesivir	ORs/RRs calculated by the EAG or reported in study	HR calculated by the EAG
Amstutz *et al.*[21] including SOLIDARITY[28] (mean efficacy)	0.792	0.817
Amstutz *et al.*[21] including SOLIDARITY[28] (low efficacy)	0.919	0.930
Amstutz *et al.*[21] including SOLIDARITY[28] (mean-low efficacy)	0.856	0.865
Amstutz *et al.*[21] excluding SOLIDARITY[28] (mean efficacy)	0.598	0.635
Amstutz *et al.*[21] excluding SOLIDARITY[28] (low efficacy)	0.817	0.839
Amstutz *et al.*[21] excluding SOLIDARITY[28] (mean-low efficacy)	0.707	0.723
Huang *et al.*[19] (mean efficacy)	0.597	0.559
Huang *et al.*[19] (low efficacy)	0.800	0.773
Huang *et al.*[19] (mean-low efficacy)	0.699	0.682

OR – odds ratio; RR – relative risk; HR – hazard ratio.

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. This subgroup was chosen as the EAG was aware that the European Society of Clinical Microbiology and Infectious Diseases Guidelines[11, 12] conditionally recommend remdesivir for use in hospitalised patients requiring no or low-flow oxygen, but not in patients requiring high-flow oxygen. The analyses undertaken by the EAG have assumed that the efficacy values used in LFO patients are generalisable to children and the immunocompromised which may not be correct. Further, these analyses are populated with some values identified from non-systematic reviews, however, the EAG believes that these analyses will be informative to the Appraisal Committee.

For children, the average age of hospitalised patients was arbitrarily reduced to 15 years. The underlying probability of death at 28 days was set to two alternate values. The first value was that reported in Ward *et al.*[36] of 48 deaths from 10,540 hospitalisations within 28 days (0.45%) with the second value being that associated with Wilde *et al.*[37] of 55 deaths at any time during the study period from 29,230 patients with a first SARS-CoV-2-related hospitalisation (0.19%). The average length of stay for children was considerably shorter than for adults with Wilde *et al.*[37] reporting a median length of stay of 2 days, with an interquartile range of 1 to 4 days. Due to the structure of the model, which adjusted the Kaplan-Meier plot from the control arm of the RECOVERY study[38] 100% of children patients with need of supplemental oxygen were assumed to be discharged at 28 days resulting in an average length of stay of around 5 days, which was the minimum length of stay that could be modelled.

For immunocompromised patients, the EAG identified a paper that provided data on the outcomes of immunocompromised patients during the Omicron SARS-CoV-2 variant.[39] This reported that from 4585 patients broadly-defined as immunocompromised there were 4585 hospitalisations and 1145 deaths resulting in 24.98% of hospitalisations resulting in death. This percentage was broadly similar for patients stringently-defined as immunocompromised and whether or not the patient had three doses of a COVID-19 vaccine. The EAG notes that the definition of death included patients who did not die in hospital and may therefore overestimate the probability of deaths following hospitalisation, but the extent of the overestimation is unknown. Due to the absence of data the average age of hospitalised patients and average length of stay was left unchanged from previous modelling.

4.2 The scenarios undertaken

The EAG has run 27 scenarios all of which assume a positive impact of remdesivir on mortality; these are provided in Table 4. The values assumed for tocilizumab in each scenario are contained in Appendix 5. Appendices 6 and 7 contain the comparative results between remdesivir and tocilizumab.

Scenarios 1-9 assume no differences in either clinical improvement or time to discharge; Scenarios 10-18 assume differences in clinical improvement; Scenarios 19-27 assuming differences in time to discharge but not in clinical improvement due to the risk of double-counting in ACTT-1.[24] Scenarios 25 and 26 most closely resemble that of the company's base case with the differences being that the company uses Garibaldi *et al*.[33] for clinical improvement the EAG analysis assumes no clinical improvement benefit and that in the mean scenario the company assumes the midpoint value whereas the EAG has used the calculated mean from the distribution.

Each block of nine scenarios are the combinations of three mortality estimates for remdesivir (Amstutz *et al*.[21] with SOLIDARITY[28], Amstutz *et al*.[21] without SOLIDARITY[28] and Huang *et al.*[19]) and three assumed efficacies levels (mean, low and mean-low). The efficacy values related to mortality for these studies are shown in Table 3.

The mean efficacy value was the expected mean from the specified distribution (calculated by the EAG) whilst the low efficacy value used the more unfavourable 95% confidence limit. As the ICERs for remdesivir for adult patients receiving LFO were below £20,000 using the mean values, analyses using the more favourable 95% confidence limit were not undertaken, and instead mean-low efficacy analyses were run which averaged the value from the mean and low scenarios. This approach was deemed by the EAG to provide useful granularity between the mean and low scenarios and not result in data overload for the Appraisal Committee. The rationale for exploring worse mortality benefit from that observed in the studies is due to the change in circumstances since the studies were conducted which

include changes in: the SARS-CoV-2 variant in circulation; the vaccination status of patients; the prior infection status of patients; and improvements in SoC across time.

Previously, the EAG capped values in the low efficacy scenarios when it was assumed there was no benefit for mortality in order that the treatments evaluated do not, on balance, harm patients. That is, at the very worst, the treatments would produce identical QALYs to SoC. However, as the HRs used for the risk of mortality for remdesivir are all below 1, no capping was applied as the EAG believes it plausible that other aspects such as time to discharge and clinical improvement could be worse as a by-product of preventing death.

Table 4: Parameter values used in the EAG's analyses

Scenario	Study used for remdesivir	Efficacy scenario	Remdesivir parameters*
1	Amstutz *et al.*[21†]	Mean	0.817, unity, unity
2	Amstutz *et al.*[21†]	Low	0.930, unity, unity
3	Amstutz *et al.*[21†]	Mean-Low	0.865, unity, unity
4	Amstutz *et al.*[21]	Mean	0.635, unity, unity
5	Amstutz *et al.*[21]	Low	0.839, unity, unity
6	Amstutz *et al.*[21]	Mean-Low	0.723, unity, unity
7	Huang *et al.*[19]	Mean	0.559, unity, unity
8	Huang *et al.*[19]	Low	0.773, unity, unity
9	Huang *et al.*[19]	Mean-Low	0.682, unity, unity
10	Amstutz *et al.*[21†]	Mean	0.817, 1.040, unity
11	Amstutz *et al.*[21†]	Low	0.930, 0.990, unity
12	Amstutz *et al.*[21†]	Mean-Low	0.865, 1.015, unity
13	Amstutz *et al.*[21]	Mean	0.635, 1.040, unity
14	Amstutz *et al.*[21]	Low	0.839, 0.990, unity
15	Amstutz *et al.*[21]	Mean-Low	0.723, 1.015, unity
16	Huang *et al.*[19]	Mean	0.559, 1.040, unity
17	Huang *et al.*[19]	Low	0.773, 0.990, unity
18	Huang *et al.*[19]	Mean-Low	0.682, 1.015, unity
19	Amstutz *et al.*[21†]	Mean	0.817, unity, 1.270
20	Amstutz *et al.*[21†]	Low	0.930, unity, 1.100
21	Amstutz *et al.*[21†]	Mean-Low	0.865, unity, 1.187
22	Amstutz *et al.*[21]	Mean	0.635, unity, 1.270
23	Amstutz *et al.*[21]	Low	0.839, unity, 1.100
24	Amstutz *et al.*[21]	Mean-Low	0.723, unity, 1.187
25	Huang *et al.*[19]	Mean	0.559, unity, 1.270
26	Huang *et al.*[19]	Low	0.773, unity, 1.100
27	Huang *et al.*[19]	Mean-Low	0.682, unity, 1.187

† Including data from SOLIDARITY[28]

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

5 The results generated by the EAG

Results are presented for the three patient subgroups: adults requiring LFO; children (also assumed to require LFO) and immunocompromised patients (also assumed to require LFO). The EAG highlights that time to discharge is much more influential on the ICERs and patient outcomes than changes in clinical improvement. As such, there are only small differences between the results obtained in Scenarios 1 to 9 and those obtained in Scenarios 10 to 18.

The comparative results between tocilizumab and remdesivir are contained in Appendix 6 and Appendix 7. These results use the list price for tocilizumab; results with the PAS discount applied for tocilizumab are reported in a confidential appendix.

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

Figure 1 shows the incremental net monetary benefit (NMBs) values for remdesivir when compared to SoC for treating patients requiring LFO at an ICER threshold of £20,000, whilst Figure 2 presents these values at the £30,000 threshold. The ICERs for remdesivir compared with SoC are reported in Appendix 6.

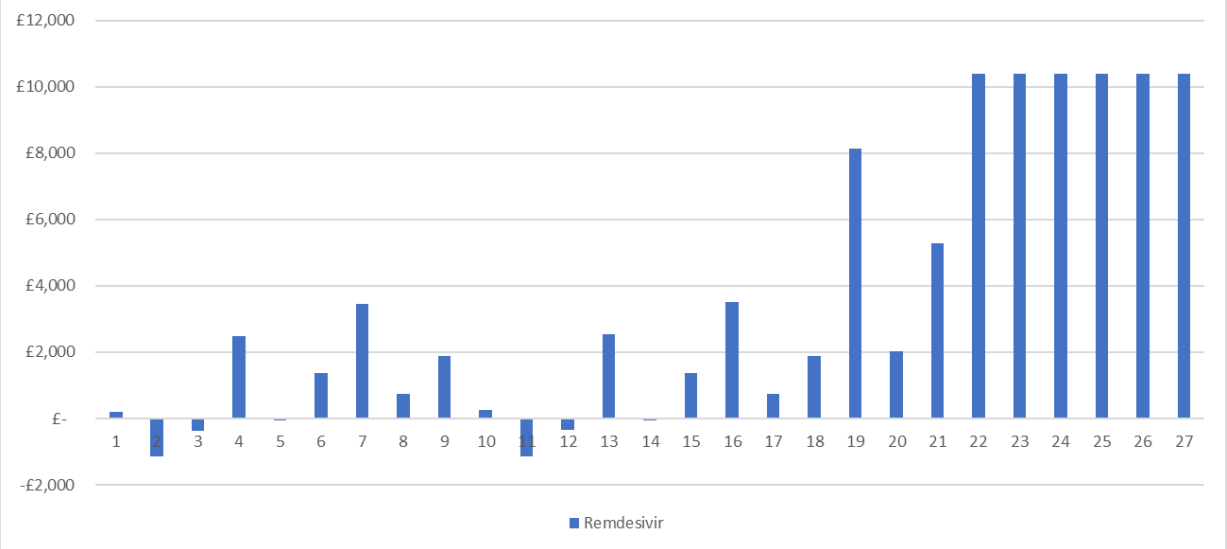


Figure 1: Incremental NMB results for adults receiving LFO at an ICER threshold of £20,000

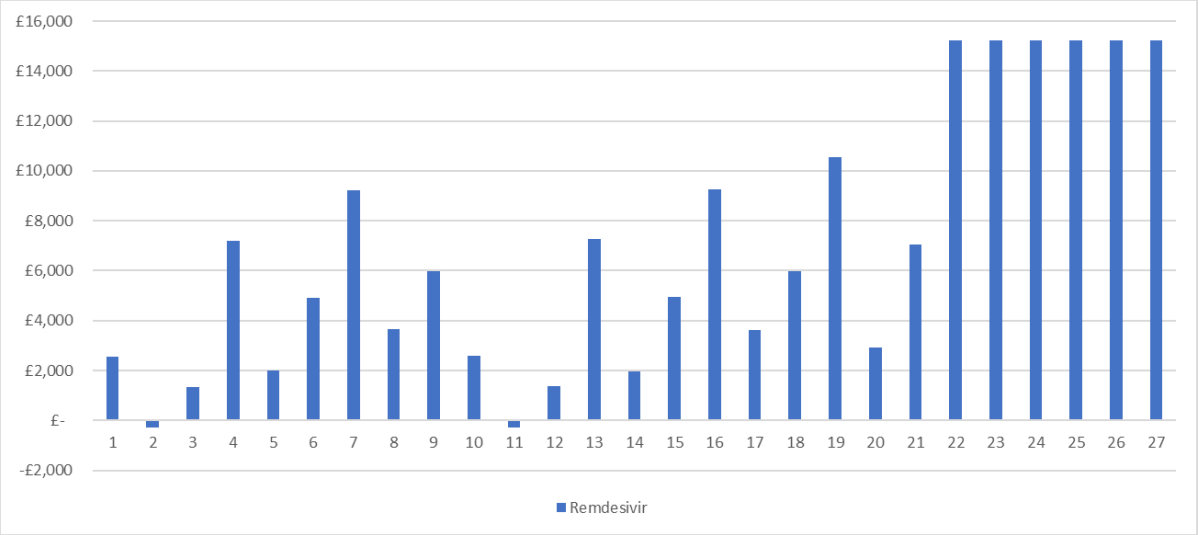


Figure 2: Incremental NMB results for adults receiving LFO at an ICER threshold of £30,000

In the EAG analyses, remdesivir has an ICER compared with SoC above £30,000 in Scenarios 2 and 11, these scenarios both assume low efficacy taken from Amstutz *et al*.[21] when data from SOLIDARITY[28] was included, and that remdesivir has no benefit on time to discharge.

Scenarios 3, 5, 12 and 14 are estimated to have ICERs compared with SoC above £20,000. Scenarios 3 and 12 both assume mean-low efficacy taken from Amstutz *et al*.[21] when data from SOLIDARITY[28] was included and that remdesivir has no benefit on time to discharge. Scenarios 5 and 14 both assume low efficacy taken from Amstutz *et al*.[21] when data from SOLIDARITY[28] was excluded and that remdesivir has no benefit on time to discharge.

5.2 Exploratory ICERs estimated for children

Figure 3 shows the NMBs values for remdesivir when compared to SoC for treating children requiring LFO at an ICER threshold of £20,000, whilst Figure 4 presents these values at the £30,000 threshold. The ICERs are reported in Appendix 8. Both figures present NMBs using probability of death taken from in Ward *et al*.[36] (0.45%) and from Wilde *et al*.[37] (0.19%).

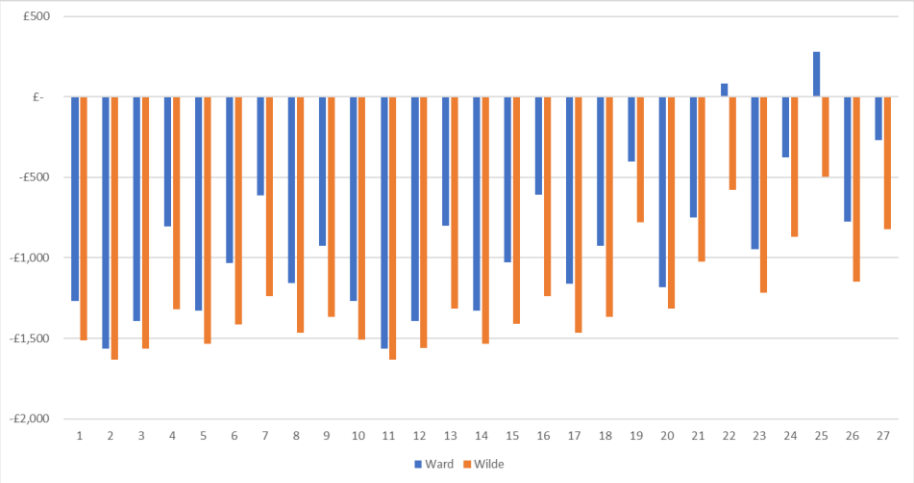


Figure 3: Incremental NMB results for children receiving LFO at an ICER threshold of £20,000

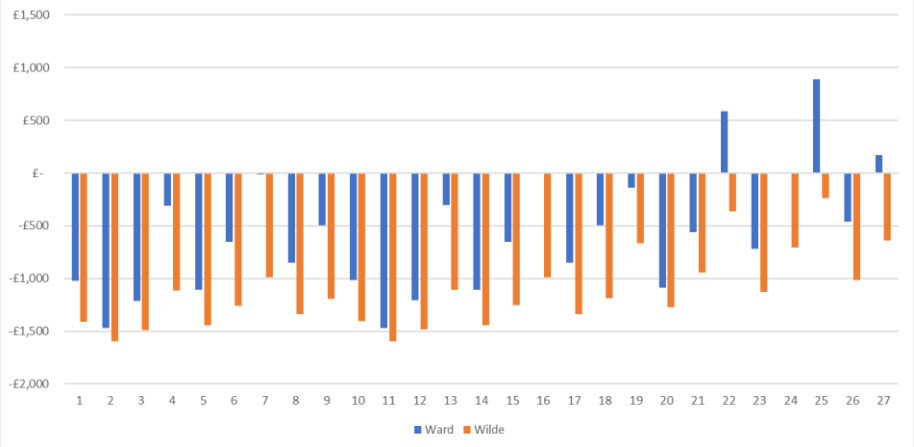


Figure 4: Incremental NMB results for children receiving LFO at an ICER threshold of £30,000

No ICERs were below £30,000 when the probability of death from Wilde *et al*.[37] was used. When the probability of death from Ward *et al*.[36] was used the ICER for remdesivir was below £20,000 in two scenarios (22 and 25) and scenario 27 had an ICER below £30,000. All three scenarios assumed that remdesivir had a beneficial impact of time to discharge; Scenarios 22 and 25 assumed mean efficacies from Amstutz *et al*.[21] and Huang *et al*.[19] respectively, whereas Scenario 27 uses the mean-low estimate from Huang *et al*.[19]

5.3 Exploratory ICERs estimated for immunocompromised patients.

Figure 5 shows the incremental net monetary benefit (NMBs) values for remdesivir when compared to SoC for treating patients requiring LFO at an ICER threshold of £20,000, whilst Figure 6 presents these values at the £30,000 threshold. The ICERs are reported in Appendix 7.

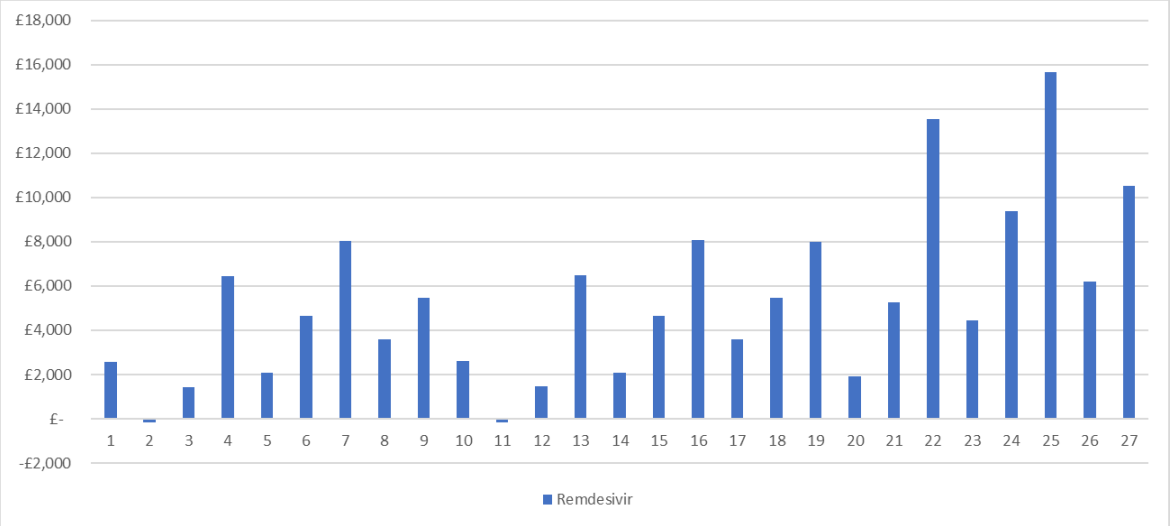


Figure 5: Incremental NMB results for immunocompromised patients receiving LFO at an ICER threshold of £20,000

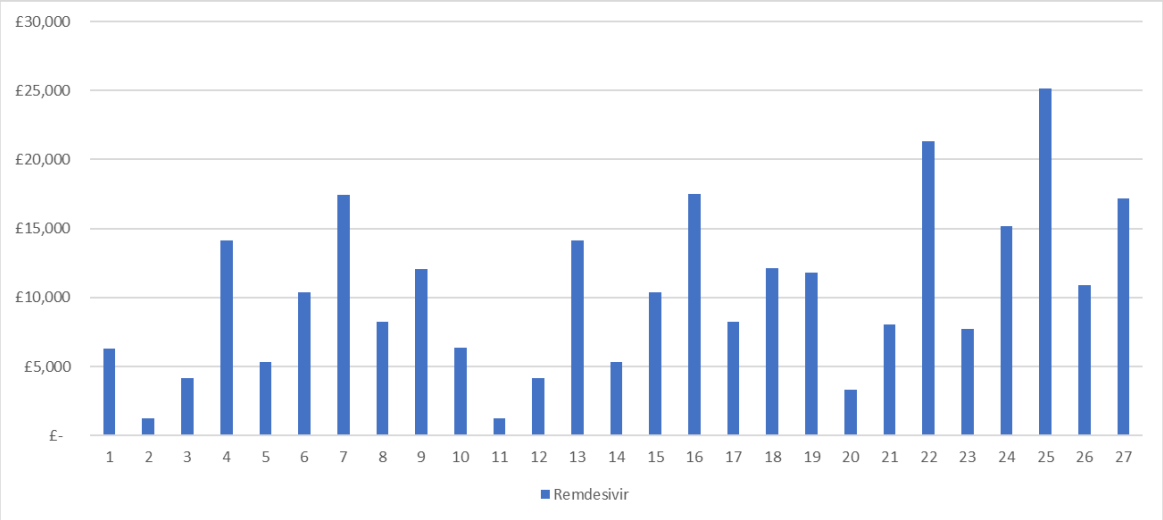


Figure 6: Incremental NMB results for immunocompromised patients receiving LFO at an ICER threshold of £30,000

Remdesivir had an ICER below £30,000 in all scenarios. Two scenarios (2 and 11) had ICERs slightly above £20,000. Both scenarios assumed low efficacy from Amstutz *et al*.[21] with data from SOLIDARITY[28] included for mortality and no impact on time to discharge.

6 Discussion of the results generated by the EAG

The EAG has provided 27 scenarios for each of the three subgroups which produce a wide range in the ICER. Considering remdesivir compared with SoC only the ICER in adult patients requiring LFO ranged from dominating to £33,130; for children requiring LFO the ICERs ranged from £15,413 to £183,524; and for adult patients requiring LFO who are immunocompromised the ICERs ranged from dominating to £21,225. Results for children and immunocompromised adult patients have additional uncertainty due to the necessity of assuming that the treatment effects associated with adult patients requiring LFO are generalisable to these groups.

Key drivers in the ICERs are: which study should provide the estimate of mortality benefit associated with remdesivir; whether the mean estimate of effect should be used or a lower estimate; and whether any benefit in time to discharge should be assumed.

The EAG believes that the Amstutz *et al*.[21] paper provides the best estimate as it included the broadest set of studies and used individual patient data. There is uncertainty over whether data from SOLIDARITY[28] should be included as this also included patients not requiring supplemental oxygen, although the EAG notes that the SOLIDARITY data were used in the NICE rapid guideline.[7] If Amstutz *et al*.[21] is used for the source of mortality benefit then this generates ICERs that are less favourable to remdesivir, being most unfavourable when data from SOLIDARITY[28] are included.

The level of reduction in benefit associated with remdesivir due to changes in the SARS-CoV-2 variant in circulation; the vaccination status of patients; the prior infection status of patients; and improvements in SoC across time is uncertain and has been left for Appraisal Committee discussion. The EAG has aimed to provide sufficient data points such that the Committee has a good idea of the ICER associated with its preferred decision. When less favourable assumptions are made the ICERs increase.

Similarly, whether or not remdesivir provides a benefit in time to discharge has been left for Appraisal Committee discussion. The EAG notes that the final draft guidance for ID4038 states that the Committee concluded that it was reasonable to remove these treatment benefits (Section 3.2.3).[4] Assuming that remdesivir does not improve time to discharge increases the ICERs.

If tocilizumab were considered a comparator, then the comparison of remdesivir and tocilizumab is complex as the intervention with the highest NMB varies depending on the scenario chosen and it is plausible that the Appraisal Committee prefer different scenarios for each intervention. As stated, the tocilizumab results do not include the confidential PAS.

7 References

1. Metry A, Pandor A, Ren S, Shippam A, Clowes M, Dark P*, et al.* Therapeutics for people with COVID-19. An economic evaluation. University of Sheffield; 2022.
2. Metry A, Stevenson M. Therapeutics for people with COVID-19. An economic evaluation. University of Sheffield; 2022.
3. Metry A, Pandor A, Ren S, Stevenson M. Therapeutics for people with COVID-19. An economic evaluation: EAG additional analysis post NICE Appraisal Consultation Document. In; 2023.
4. National Institute for Health & Care Excellence (NICE). Therapeutics for people with COVID-19. *Final draft guidance* 2023.
5. Nice. Molnupiravir, remdesivir and tixagevimab plus cilgavimab for treating COVID-19 [ID6261] - final judgement by the appeal panel; 2023.
6. Sciences G. ID6261 COVID-19 Gilead targeted submission post appeal. In; 2023.
7. NICE. COVID-19 rapid guideline: Managing COVID-19; 2023.
8. EMC. Veklury 100 mg powder for concentrate for solution for infusion. 2023. https://www.medicines.org.uk/emc/product/11597/smpc#gref (Accessed
9. Gilead. Response to NICE request. In; 2023.
10. NIH. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines - July 2023; 2023.
11. Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R*, et al.* European society of clinical microbiology and infectious diseases guidelines for coronavirus disease 2019: an update on treatment of patients with mild/moderate disease. *Clin Microbiol Infect* 2022;28:1578-90.
12. Bartoletti M, Azap O, Barac A, Bussini L, Ergonul O, Krause R*, et al.* ESCMID COVID-19 living guidelines: drug treatment and clinical management. *Clin Microbiol Infect* 2022;28:222-38.
13. World Health Organisation (WHO. Clinical management of COVID-19: Living guideline, 18 August 2023. In; 2023.
14. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *The Lancet Infectious Diseases* 2010;10:226.
15. Amir-Behghadami M, Janati A. Population, Intervention, Comparison, Outcomes and Study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews. *Emergency Medicine Journal* 2020.
16. Gusenbauer M, Haddaway NR. Which academic search systems are suitable for systematic reviews or meta-analyses? Evaluating retrieval qualities of Google Scholar, PubMed, and 26 other resources. *Res Synth Methods* 2020;11:181-217.
17. Haddaway NR, Collins AM, Coughlin D, Kirk S. The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching. *PLoS One* 2015;10:e0138237.
18. Bramer WM, Giustini D, Kramer BM, Anderson P. The comparative recall of Google Scholar versus PubMed in identical searches for biomedical systematic reviews: a review of searches used in systematic reviews. *Syst Rev* 2013;2:115.
19. Huang C, Lu T-L, Lin L. Remdesivir Treatment Lacks the Effect on Mortality Reduction in Hospitalized Adult COVID-19 Patients Who Required High-Flow Supplemental Oxygen or Invasive Mechanical Ventilation. *Medicina* 2023;59:1027.
20. Beckerman R, Gori A, Jeyakumar S, Malin JJ, Paredes R, Póvoa P*, et al.* Remdesivir for the treatment of patients hospitalized with COVID-19 receiving supplemental oxygen: a targeted literature review and meta-analysis. *Scientific Reports* 2022;12:9622.
21. Amstutz A, Speich B, Mentré F, Rueegg CS, Belhadi D, Assoumou L*, 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.
22. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J*, et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.

23. Ali K, Azher T, Baqi M, Binnie A, Borgia S, Carrier FM, *et al.* Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *Cmaj* 2022;194:E242-E51.
24. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, *et al.* Remdesivir for the Treatment of Covid-19 — Final Report. *New England Journal of Medicine* 2020;383:1813-26.
25. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, *et al.* Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet* 2020;395:1569-78.
26. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, *et al.* Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA* 2020;324:1048-57.
27. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, *et al.* Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med* 2021;384:795-807.
28. Consortium WHOST. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *The Lancet* 2022;399:1941-53.
29. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Mentré F, Burdet C, *et al.* Final results of the DisCoVeRy trial of remdesivir for patients admitted to hospital with COVID-19. *The Lancet Infectious Diseases* 2022;22:764-5.
30. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Poissy J, Belhadi D, *et al.* Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *The Lancet Infectious Diseases* 2022;22:209-21.
31. Simmonds MC, Higgins JPT, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clinical trials (London, England)* 2005;2:209-17.
32. Tierney JF, Vale C, Riley R, Smith CT, Stewart L, Clarke M, *et al.* Individual Participant Data (IPD) Meta-analyses of Randomised Controlled Trials: Guidance on Their Use. *PLoS Med* 2015;12:e1001855.
33. Garibaldi BT, Wang K, Robinson ML, Betz J, Caleb Alexander G, Andersen KM, *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:e516-e24.
34. National Institute for Health & Care Excellence (NICE). NICE real-world evidence framework. In; 2022.
35. Initiative CN. Living COVID-19 NMA. 2023. https://covid-nma.com/metacovid/ (Accessed
36. Ward JL, Harwood R, Kenny S, Cruz J, Clark M, Davis PJ, *et al.* Pediatric Hospitalizations and ICU Admissions Due to COVID-19 and Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 in England. *JAMA Pediatr* 2023;177:947-55.
37. Wilde H, Tomlinson C, Mateen BA, Selby D, Kanthimathinathan HK, Ramnarayan P, *et al.* Hospital admissions linked to SARS-CoV-2 infection in children and adolescents: cohort study of 3.2 million first ascertained infections in England. *Bmj* 2023;382:e073639.
38. Recovery Collaborative Group, Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, *et al.* Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet* 2022;399:665-76.
39. Evans RA, Dube S, Lu Y, Yates M, Arnetorp S, Barnes E, *et al.* Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study. *The Lancet Regional Health - Europe* 2023; https://doi.org/10.1016/j.lanepe.2023.100747:100747.

8 Appendices

8.1 *Appendix 1: Critique of broader search strategy to identify clinical evidence*

Searches for clinical effectiveness evidence were conducted in two phases, in January and December 2022 respectively. Databases included all the core sources required by NICE (MEDLINE; Embase; Cochrane Library) plus clinical trial registries and the proceedings of relevant conferences. The search strategies from both iterations of the search are well-designed, incorporating subject headings and free text terms for the population, intervention and comparators of interest. The strategies used differ slightly between the two iterations, with the December searches including some additional terms relating to interventions for outpatients (outside the scope of this review) and non-RCT evidence.

A search filter was used to identify RCT evidence, with the addition of terms to identify other eligible study types including real world and observational studies. The added terms are appropriate, however it is unclear whether any formal validation of this filter has ever taken place to measure its accuracy in the retrieval of these types of study. No search terms relating to systematic reviews and network meta-analyses were included, though these were eligible for inclusion at the title/abstract stage as a source of relevant studies (but subsequently excluded unless they contained primary data). If relevant reviews were intended to be retrieved as a means of identifying primary studies, it might have been prudent to search for them.

Searches were limited to evidence from 2019 onwards, which is appropriate given the disease area (first cases of COVID-19 were reported in late 2019). The ERG considers the clinical searches unlikely to have missed relevant primary studies eligible for inclusion.

8.2 *Appendix 2: Summary of the company's AMSTAR-2 ratings for included systematic reviews*

Table 5 : Summary of the company's AMSTAR-2 ratings for included systematic reviews (reproduced and adapted for presentation, Company Bias assessment using NICE preferred tools – extraction grid)

	Huang *et al.*[19]	**Beckerman *et al.*[20]**	**Amstutz *et al.*[21]**
Q1 Did the research questions and inclusion criteria for the review include the components of PICO?	**Y**	**Y**	**Y**
Q1 Notes	RCTs were eligible for inclusion if they directly compared the clinical effectiveness of remdesivir to a placebo in the treatment of hospitalized adult COVID-19 patients. Studies that had any one or more of the following outcomes were included: hospital mortality or 28-day mortality, and ordinal scale of the patients at the start of treatment.	The SLR included the population (patients hospitalized with COVID-19 requiring supplemental oxygen at baseline); the intervention (at least one arm of the trial must have been treated with remdesivir); the comparator (any); and the outcomes (mortality; recovery [defined as recovery from COVID-19 or discharge from hospital]; no longer requiring supplemental oxygen; progressing to non-invasive ventilation or mechanical ventilation).	Eligible studies were RCTs (unpublished or published, any format, in any language) that randomly assigned adult patients (aged ≥16 years) who were treated in hospital for COVID-19 to receive either remdesivir or no remdesivir (i.e., usual care as defined by the local context, with or without placebo). The primary outcome was mortality at 28 days
Q2 Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	**N**	**N**	**Y**
Q2 Notes	The authors did not include an explicit statement to establish that the review methods were determined prior to the initiation of review.	There is no explicit statement that review methods were established prior to the conduct of the review.	The study protocol is available on PROSPERO (CRD42021257134), Open Science Framework (https://osf.io/7a4wf), and in the appendix. It states the review question, search strategy, inclusion criteria and risk of bias assessment. Also, under the data-analysis section a synthesis plan

			is reported. To assess heterogeneity in interaction estimates across trials, forest plots were used.
Q3 Did the review authors explain their selection of the study designs for inclusion in the review?	**N**	**N**	**Y**
Q3 Notes	The authors did not explain their choice to only include RCTs.	Authors did not explain limiting their inclusion to only randomised controlled trials.	There are conflicting results in RCTs on patients treated with remdesivir in hospital for COVID-19, and so the focus on RCTs is justified
Q4 Did the review authors use a comprehensive literature search strategy?	**Partial Y**	**Partial Y**	**Y**
Q4 Notes	The authors detail that the search strategy included PubMed, Web of Science, and Cochrane Library databases searched from 1 January 2020 and 28 February 2023. The following search terms were used: “Remdesivir”, “Veklury”, “GS-5734”, “COVID-19”, “coronavirus" and “SARS-CoV-2.” The authors did not provide details on any additional searching (i.e., grey literature, trial registries, reference lists of included studies), nor on any consultation with experts in the field.	The authors searched at least two databases (MEDLINE (PubMed), medRxiv, EMBASE and Cochrane Trials), provided the search strategy (see supplement), and did not apply publication restrictions according to the publication (e.g., language).	Multiple databases searched (PubMed, Embase, the International Clinical Trials Registry Platform [ICTRP] from WHO, and medRxiv), search strategies given in appendix. No publication restrictions (unpublished and non-English studies included). To ensure literature saturation, reference lists of relevant reviews and original articles identified through the search were scanned. Finally, results with trials identified by other published or registered systematic searches as well as personal knowledge were included. The protocol was discussed with two patient representatives from Switzerland and two practising infectious disease specialists. Search conducted in 2022 and completed in 2023

Q5 Did the review authors perform study selection in duplicate?	**N**	**N**	**Y**
Q5 Notes	The publication did not specify that a dual-review approach for selection was used.	The number of individuals performing study selection was not reported.	Each title and abstract were assessed for potential eligibility by two independent reviewers. Each full text included was obtained and independently assessed by two further reviewers.
Q6 Did the review authors perform data extraction in duplicate?	**N**	**N**	**Y**
Q6 Notes	The publication did not specify that a dual approach was used for extraction.	Study selection was reported to be completed by one individual.	Two review authors independently extracted data on patient characteristics, randomization methods, interventions and outcomes by using a standardized pre-piloted data extraction form
Q7 Did the review authors provide a list of excluded studies and justify the exclusions?	**N**	**N**	**N**
Q7 Notes	The authors did not provide a list of excluded studies. Figure 1 shows a flow diagram of the study selection process and at which stage articles were excluded but does not provide a reasoning for the exclusion.	A list of potentially relevant studies which were excluded at full-text reviewer was not provided.	A list of excluded studies has not been provided. However, characteristics of randomized trials that could not be included in the individual patient data meta-analysis was provided, with a reason for its exclusion from the analysis.
Q8 Did the review authors describe the included studies in adequate detail?	**Y**	**Partial Y**	**Partial Y**
Q8 Notes	Table 2 provides a comprehensive list of characteristics of the included studies including the author, region, study period, number of patients, mean age of patients, other treatments for patients receiving remdesivir, and the median time of symptoms before first dose of	The study did describe the population, intervention, comparators, outcomes, and research designs sufficiently; although the standard of care arm is not well-defined, the authors acknowledge this is due to poor reporting in those studies.	In Table 2 the population and intervention have been described in detail, study setting, and time frame also given. However, the comparator was just reported as usual care and has not been reported in detail.

	remdesivir. Although study design was not explicitly stated in the chart, all included studies were RCTs.		
Q9 Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	**Y**	**Y (includes only RCTs)**	**Y**
Q9 Notes	The risk of bias for each trial was assessed using the Cochrane Risk of Bias Tool 2.0 for RCTs, which assesses unconcealed allocation, lack of blinding of patients and assessors, randomness of allocation sequence and selection of reported results.	This SLR utilized the RoB 2 checklist, which includes assessing if the allocation request was truly random (see bias arising from the randomisation process domain), if there was selection of the reported result from among multiple measurements or analyses of a specified outcome (see bias in selection of the reported result domain), if there was risk of bias from unconcealed allocation (see bias arising from the randomisation process domain), and if there was lack of blinding of patients and assessors when assessing outcomes (see bias in measurement of the outcome domain).	Bias was assessed using the Cochrane Risk of Bias 2 tool
Q10 Did the review authors report on the sources of funding for the studies included in the review?	**N**	**N**	**N**
Q10 Notes	The authors did not report on the sources of funding for the studies included in the review.	Source of funding for studies included in the review were not reported.	Funding of included studies not reported
Q11 If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	**Y**	**N**	**Y**
Q11 Notes	Statistical analysis was completed using RevMan 5, the Cochrane Review Manager tool. For continuous and categorical variables,	Methods for adjusting for heterogeneity within the meta-analysis are not reported by the study.	Justification for IPD meta-analysis reported in protocol and a full break down of techniques reported in the data analysis

	the relative risk (RR) and mean difference with a 95% confidence interval (CI) were calculated, respectively. Significant heterogeneity I2 between the studies was defined as an greater than 50% and a p value for the Q-test less than 0.10 for each study. When effects were thought to be homogenous, the fixed effects model was applied, and when they were heterogeneous, the random-effects model was applied.		section of the protocol, with a mixed effects logistic regression model used for the primary outcome
Q12 If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	**N**	**N**	**Y**
Q12 Notes	In Section 4.5 (Limitations) the authors note that two of the studies included in the meta-analysis had a high risk of bias. However, the authors did not investigate the possible impact of this bias on the results.	Some studies with high risk of bias were included in the meta-analysis, but there were no reported analyses investigating the impact of RoB on summary estimates of effect.	A scenario analysis was conducted of the meta-analysis to only include trials that were judged to have a low risk of bias for all outcomes.
Q13 Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	**N**	**Y**	**Y**
Q13 Notes	Although the authors note that two of the included studies have a high risk of bias, they do not discuss the impact of this on the results other than acknowledging it as a weakness of the review.	In the discussion, authors did briefly discuss the impact of RoB on the interpretation of the results.	A scenario analysis was conducted of the meta-analysis to only include trials that were judged to have a low risk of bias for all outcomes.
Q14 Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	**Y**	**Y**	**Y**
Q14 Notes	Th authors note that the included studies were heterogeneous due to	The authors report heterogeneity in the results for patients receiving high-flow oxygen and	Reported that forest plots would be used to assess heterogeneity, and then reported that they did

	different counties, populations, and study designs.	explain this difference may indicate that patients receiving low-flow oxygen benefit more greatly from remdesivir, or that this may be due to the smaller sample size of high-flow oxygen patients or the confounding effect of including patients on NIV in the high-flow oxygen population.	not find credible evidence for effect modification by age, presence of comorbidities, enrolment period, or corticosteroid use
Q15 If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	**N**	**N**	**N**
Q15 Notes	The authors did not detail the potential for publication bias.	Publication bias was not discussed, and its effect was not evaluated.	Although bias of studies was looked at using the RoB2 and sensitivity analysis that just included studies with low risk of bias, there was no discussion on the likelihood/magnitude of impact of publication bias
Q16 Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	**Y**	**Y**	**Y**
Q16 Notes	The authors declared no conflicts of interest.	Conflicts of interest were reported.	The authors reported no competing interests
Overall confidence level in review results	**Medium**	**Low**	**Medium**
Justification	The systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.	The majority of the questions' responses are no, with some partial yes responses, and few yes responses.	Overall good reporting with full appendices provided making the case for thorough strategies at each step. However, the study did not provide a list of excluded studies nor were the likelihood/magnitude of impact of publication bias discussed.

8.3 *Appendix 3: Data from Amstutz et al.*[21]

Table 6 : Data from Amstutz *et al* .[21] Sensitivity analyses on different subgroup definitions on the primary outcome of mortality at day 28 (adapted from Figure S8)

Subgroup	**Outcome variable: Mortality at day 28**				
	Total number (N)	**Remdesivir (n/N)**	**No remdesivir (n/N)**	**Adjusted odds ratio (95% CI)**	**Interaction p-value**
No oxygen, no ventilation at baseline	2357	34/1274	33/1083	0.86 (0.532, 1.394)	-
Oxygen, but no ventilation at baseline	6274	374/3198	432/3076	0.79 (0.68, 0.919)	0.505
High-flow oxygen or non-invasive ventilation at baseline	741	90/372	91/369	1.04 (0.712, 1.519)	0.764
Mechanical ventilation/ECMO at baseline	949	163/472	150/477	1.15 (0.862, 1.522)	0.439
Without additional WHO- SOLIDARITY[28] data*: No oxygen, no ventilation at baseline	857	14/525	12/332	0.77 (0.338, 1.74)	-
Without additional WHO- SOLIDARITY[28] data*: Oxygen, but no ventilation at baseline	2106	75/1094	114/1012	0.59 (0.431, 0.817)	0.514
Without additional WHO- SOLIDARITY[28] data*: High-flow oxygen or non-invasive ventilation at baseline	741	90/372	91/369	1.04 (0.712, 1.519)	0.539
Without additional WHO-SOLIDARITY[28] data*: Mechanical ventilation/ECMO at baseline	509	54/246	55/263	1.07 (0.695, 1.646)	0.523

ECMO, Extracorporeal membrane oxygenation *These subgroup analyses included data from CATCO, DisCoVeRy, NOR- SOLIDARITY, and FIN- SOLIDARITY, but excluded the additional WHO- SOLIDARITY trial data (n=6167)

8.4 Appendix 4: Summary of the company's NICE Real World Evidence ratings on the methods used by Garibaldi et al.[33]

Table 7 : Summary of the company's NICE Real World Evidence ratings on the methods used by Garibaldi et al.[33] to minimise the risk of bias (reproduced and adapted for presentation, Company Bias assessment using NICE preferred tools – extraction grid)

Study name	Q1 Selection bias at study entry	Q2 Selection bias at study exit	Q3 Addressing confounding	Q4 Detection bias	Q5 Measurement error and misclassification	Q6 Missing data	Q7 Reverse causation
Garibaldi *et al.* 2022[33]	Approximately half of the remdesivir patients were not able to be matched and were therefore excluded from the analysis, potentially introducing bias by selecting a smaller patient population. Symptom onset was not available in the dataset, so we were not able to examine whether or not the benefit of remdesivir differed based on timing of treatment. Because antiviral therapies are likely most effective early in the disease course, differential timing of treatment could bias outcomes toward specific groups.	The primary outcome was time to clinical improvement from the first day of remdesivir treatment or the matched day. Failure of clinical improvement was censored at the last day of follow-up or 28-days, whichever came first. The secondary outcome was time to death from the first day of remdesivir treatment or the matched day Patients who were discharged alive to "home" or "self-care" were censored at 28	The following factors were included in the regression models developed to address confounding: demographics, oxygen delivery device, vital signs, key laboratory data, comorbidities (including the Charleson comorbidity index) and COVID-19-specific medications (e.g., dexamethasone and tocilizumab). The standardized difference between matched cases and controls is presented in the table. The study also uses time-dependent propensity score matching, to create pairs of individuals, one treated with remdesivir and the	HCA Healthcare comprises over 2000 care sites including more than 180 acute-care facilities, and therefore there is substantial risk of bias being introduced as a result of variable clinical practice across hospitals and health systems, particularly for the primary outcome of time to clinical improvement. The authors do not specify how this potential for detection bias was mitigated.	Although the primary outcome of clinical improvement was defined as a 2-point decrease in the 8-point WHO severity score or discharge within 28 days, this assessment was at the discretion of the study physician, which may introduce bias. The secondary outcome was time to death from the first day of remdesivir treatment or the matched day, which is unlikely to be captured incorrectly.	For the laboratory results, missing values were imputed using the last observation carried forward if the last observation was within three days of the missing data, otherwise, using multiple imputation by chained equations (MICE) with a predictive mean matching method. Variables with more than 50% missingness were not included in the models. These precautions pre-	There is unlikely to be a risk from reverse causation

	To account for the variable timing of administration, time-dependent PS matching was utilized to create pairs of individuals, one patient treated with remdesivir and the other the most similar patient eligible for treatment at the time of remdesivir initiation but who did not receive remdesivir. In order to account for changes in the pandemic over time, an individual that received remdesivir prior to 1 October 2020 would be matched to a control patient hospitalized before 1 October 2020. To further mitigate time-related bias, a sensitivity analyses excluding patients hospitalized before 1 July 2020 was conducted, as the early months of the pandemic presented unique challenges to health systems that may have effected results.	days. Patients who were discharged to another healthcare facility without a known death date were censored at last follow-up. There is a low possibility of informative censoring in this study, as time-dependent propensity score matching would eliminate unequal dropouts between the cases and controls.	other the most similar patient eligible for treatment at the time of remdesivir initiation but who did not receive treatment. Notably, the study was conducted prior to the widespread use of vaccines and the emergence of variants such as Delta and Omicron, and therefore their potential for confounding was not investigated.			emptively could mitigate the risk of bias from missing data.	

	A patient who received a certain number of days of remdesivir treatment was matched to a control patient who stayed in the hospital at least that length of time (up to a maximum of five days) beyond the matching day. This time constraint on the matching prevents matching remdesivir patients to individuals would not have been considered candidates for remdesivir treatment as they were healthy enough to be discharged.						

8.5 Appendix 5: The assumed efficacy values for tocilizumab

The efficacy values used in the EAG analyses for are provided in Table 8. The HRs for preventing mortality and time to discharge and the RR for clinical improvement were those used in ID4038 which was sourced from COVID-NMA.[35] As with remdesivir, as the HRs used for the risk of mortality for tocilizumab are all below 1, no capping of parameter values at 1 was applied, as the EAG believes it plausible that other aspects such as time to discharge and clinical improvement could be worse as a by-product of preventing death.

For simplicity, the assumption for remdesivir that there was no clinical improvement when an impact on time to discharge was assumed, was also applied to tocilizumab. This is marginally unfavourable to tocilizumab which has a slight beneficial effect on clinical improvement.

Table 8: Parameter values used in the EAG's analyses for tocilizumab

Scenario number	Efficacy scenario	Tocilizumab parameters*
1, 4, 7	Mean	0.763, unity, unity
2, 5, 8	Low	0.900, unity, unity
3, 6, 9	Mean-Low	0.831, unity, unity
10, 13, 16	Mean	0.763, 1.050, unity
11, 14, 17	Low	0.900, 1.000, unity
12, 15, 18	Mean-Low	0.831, 1.025, unity
19, 22, 25	Mean	0.763, unity, 1.050
20, 23, 26	Low	0.900, unity, 0.880
21, 24, 27	Mean-Low	0.831, unity, 0.967

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

8.6 Appendix 6 ICERs generated by the EAG analyses for adults requiring LFO

Table 9: ICERs generated by the EAG analyses for adults requiring LFO

Scenario number	Remdesivir compared with SoC	Tocilizumab compared with SoC	Remdesivir compared with tocilizumab
1	£19,086	£13,605	Dominated
2	£33,001	£17,800	Dominated
3	£22,146	£14,856	Dominated
4	£14,771	£13,605	£16,847
5	£20,270	£17,800	£24,228
6	£16,169	£14,856	£18,154
7	£14,013	£13,605	£14,467
8	£17,425	£17,800	£17,138
9	£15,427	£14,856	£16,051
10	£18,877	£13,399	Dominated
11	£33,130	£17,800	Dominated
12	£22,042	£14,715	Dominated
13	£14,657	£13,399	£16,897
14	£20,328	£17,800	£24,380
15	£16,115	£14,715	£18,230
16	£13,916	£13,399	£14,490
17	£17,468	£17,800	£17,213
18	£15,379	£14,715	£16,104
19	Dominant	£7,895	£90,372[†]
20	Dominant	£52,896	£222,607[†]
21	Dominant	£20,069	£170,670[†]
22	Dominant	£7,895	Dominant
23	£5,046	£52,896	Dominant
24	£605	£20,069	Dominant
25	£560	£7,895	Dominant
26	£6,670	£52,896	Dominant
27	£1,907	£20,069	Dominant

SoC – Standard of care

[†]Located in Southwest quadrant of cost-effectiveness plane (i.e., remdesivir is cheaper and less efficacious than tocilizumab)

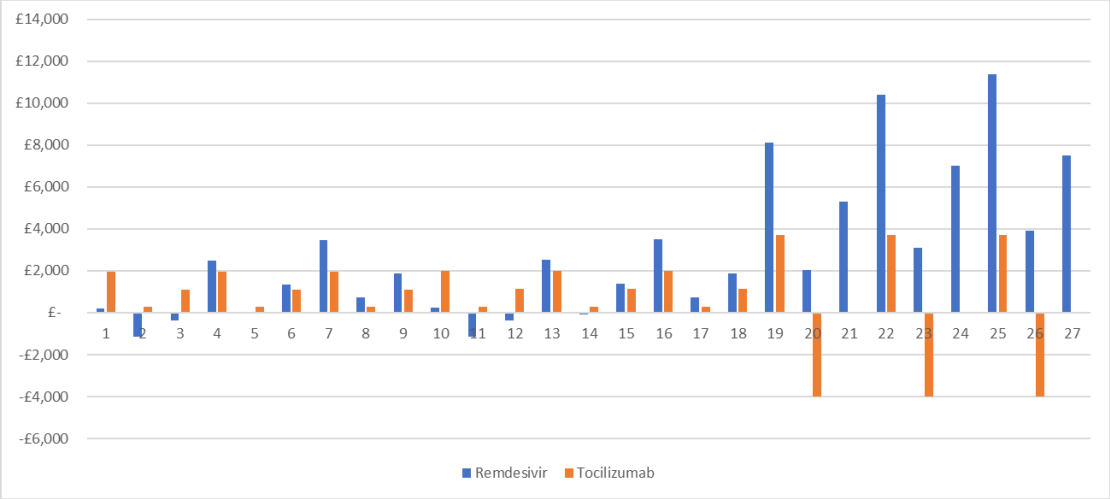


Figure 7: Incremental NMB results for adults receiving LFO at an ICER threshold of £20,000 when tocilizumab is considered a comparator

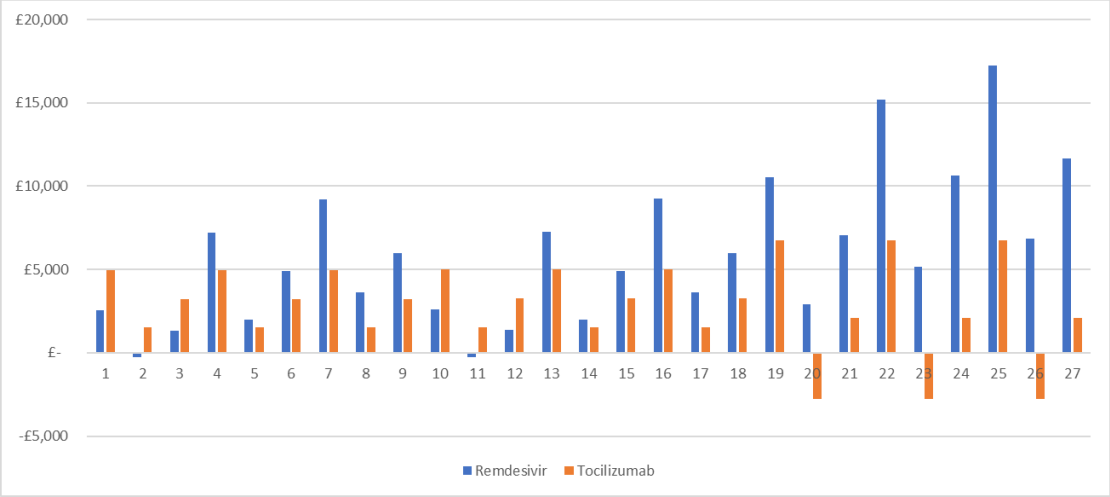


Figure 8: Incremental NMB results for adults receiving LFO at an ICER threshold of £30,000 when tocilizumab is considered a comparator

The comparison of remdesivir and tocilizumab is complex as the intervention with the highest NMB varies depending on the scenario chosen and it is plausible that the Appraisal Committee prefer different scenarios for each intervention. As stated, the tocilizumab results do not include the confidential PAS.

8.7 Appendix 7: ICERs generated by the EAG analyses for immunocompromised adult patients requiring LFO

Table 10: ICERs generated by the EAG analyses for immunocompromised adult patients requiring LFO

Scenario number	Remdesivir compared with SoC	Tocilizumab compared with SoC	Remdesivir compared with tocilizumab
1	£13,036	£9,993	£70†
2	£21,180	£11,770	Dominated
3	£14,670	£10,310	Dominated
4	£11,610	£9,993	£14,397
5	£13,642	£11,770	£16,599
6	£11,878	£10,310	£14,190
7	£11,456	£9,993	£13,017
8	£12,289	£11,770	£12,679
9	£11,735	£10,310	£13,248
10	£12,958	£9,913	Dominated
11	£21,225	£11,770	Dominated
12	£14,633	£10,258	Dominated
13	£11,561	£9,913	£14,402
14	£13,663	£11,770	£16,654
15	£11,857	£10,258	£14,213
16	£11,412	£9,913	£13,011
17	£12,305	£11,770	£12,707
18	£11,715	£10,258	£13,261
19	Dominant	£6,888	£34,658†
20	£6,403	£29,908	£90,599†
21	£901	£13,071	£65,536†
22	£2,529	£6,888	Dominant
23	£6,464	£29,908	Dominant
24	£3,739	£13,071	Dominant
25	£3,487	£6,888	Dominant
26	£6,730	£29,908	Dominant
27	£4,235	£13,071	Dominant

SoC – Standard of care

†Located in Southwest quadrant of cost-effectiveness plane (i.e., remdesivir is cheaper and less efficacious than tocilizumab)

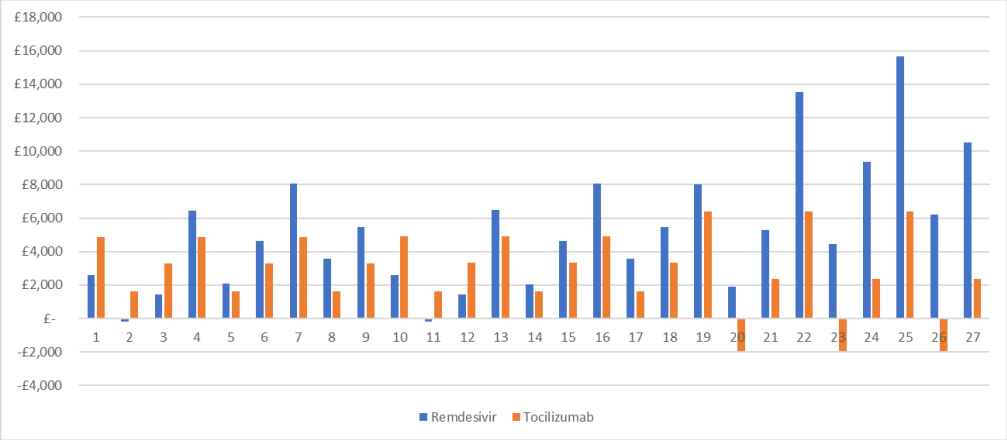


Figure 9: Incremental NMB results for immunocompromised adult patients receiving LFO at an ICER threshold of £20,000 when tocilizumab is considered a comparator

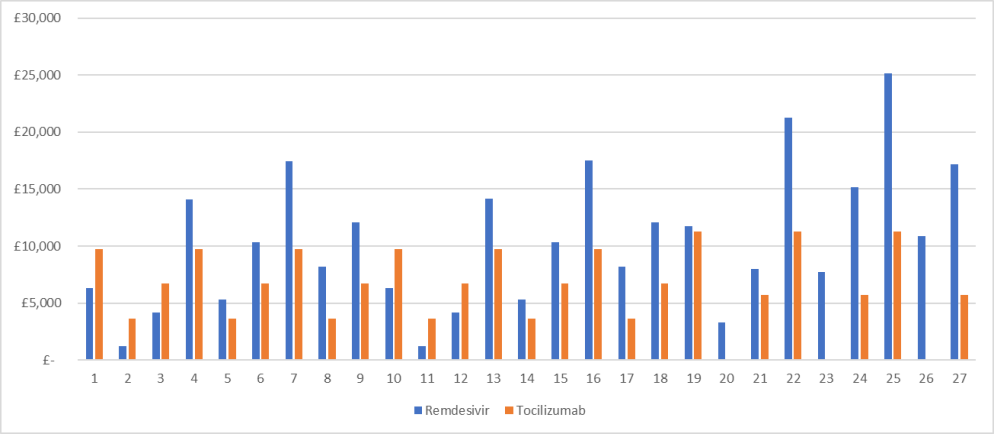


Figure 10: Incremental NMB results for immunocompromised adult patients receiving LFO at an ICER threshold of £30,000 when tocilizumab is considered a comparator

The comparison of remdesivir and tocilizumab is complex as the intervention with the highest NMB varies depending on the scenario chosen and it is plausible that the Appraisal Committee prefer different scenarios for each intervention. As stated, the tocilizumab results do not include the confidential PAS.

8.8 Appendix 8: ICERs generated by the EAG analyses for children requiring LFO

Table 11: ICERs generated by the EAG analyses for children requiring LFO

	Remdesivir compared with SoC	
Scenario number	Probability of death from Ward *et al*.[36] (0.45%)	Probability of death from Wilde *et al*.[37] (0.19%)
1	£70,761	£165,864
2	£183,430	£432,324
3	£95,485	£224,350
4	£36,161	£83,936
5	£80,320	£188,472
6	£47,301	£110,335
7	£30,193	£69,766
8	£57,381	£134,199
9	£41,374	£96,295
10	£70,622	£165,579
11	£183,524	£432,528
12	£95,413	£224,201
13	£36,091	£83,796
14	£80,359	£188,553
15	£47,266	£110,266
16	£30,134	£69,650
17	£57,408	£134,255
18	£41,344	£96,235
19	£35,438	£89,696
20	£138,770	£326,235
21	£59,118	£144,138
22	£18,417	£46,985
23	£62,168	£148,833
24	£29,801	£73,478
25	£15,413	£39,273
26	£44,629	£107,060
27	£26,117	£64,405

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **12pm** on **Monday 30 October** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Tocilizumab is not an appropriate comparator for remdesivir (page 3)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The Evidence Assessment Group (EAG) explains that is "unclear" whether tocilizumab is an appropriate comparator. However, Gilead does not consider tocilizumab to be an appropriate comparator for remdesivir	Any reference to tocilizumab as a potential comparator for remdesivir in should be removed from the EAG report.	Treatments previously recommended as part of the COVID-19 multiple technology appraisal (MTA) – including tocilizumab, nirmatrelvir plus ritonavir and sotrovimab – have been compared against standard of care (SOC) and NICE recommendations were made based on this comparison. Deviating from the use of SOC as the comparator of choice would invalidate and question previous recommendations given by NICE on other treatments and thus is not appropriate. Furthermore, the "comparative" results presented within the EAG report, which present cost-effectiveness estimates of remdesivir versus tocilizumab are flawed, given that no dedicated search was run to inform the effectiveness parameters applied in the amended EAG model. Therefore, the cost-effectiveness results comparing remdesivir to tocilizumab are unfit for decision making and have the potential to bias the NICE committee.	The EAG notes that in the MTA all treatments could be compared with each other via the use of net monetary benefit (NMB). The EAG did not provide multiple ICERs comparing treatments as it was unclear which scenarios the Appraisal Committee would prefer and also because the NMBs were provided. Therefore, the implied statement that treatments were only compared with SoC is incorrect. Currently, the results for the comparison of remdesivir with tocilizumab are contained in an appendix that can be dismissed if the Appraisal Committee agrees with the company. The EAG thinks that it would be a significant omission to remove the results comparing remdesivir with tocilizumab should the Appraisal Committee wish to see these. Therefore, the EAG has not amended the report.

Issue 2 The introduction of a "mean-low" efficacy scenario is arbitrary and potentially misleading (page 13)

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
The EAG has introduced a new efficacy scenario, which they label "mean-low" efficacy. The "mean-low" efficacy scenario lacks scientific justification and represents an arbitrary number	Efficacy estimates should be based on the mean estimate, rather than being informed by various "efficacy scenarios". If a "mean-low" scenario is presented, what is the rationale for omitting a "mean-high" scenario? If the use of efficacy scenarios is desired, both sides of the sensitivity spectrum should be considered, i.e. results should be included for a "mean-high" and a "high" efficacy scenario.	As part of the COVID-19 MTA, the EAG has first introduced its approach of using "efficacy scenarios" to assess uncertainty in efficacy parameters used in the economic model. Previously, the EAG has presented low (less favourable 95% CI), mean (mean estimate) and high (more favourable 95% CI) efficacy scenarios. While Gilead rejects this approach, Gilead agrees that there is some scientific foundation for this approach. However, there is no rationale for calculating an average between a mean and a less favourable 95% CI (as the EAG explain on page 15, they "averaged the value from the mean and low scenarios" to derive the mean-low scenario)	This issue relates to a matter of judgement not factual accuracy. The EAG has been transparent in what the "mean-low" scenario represents. This approach was also included in additional work related to nirmatrelvir and ritonivir[1] and was believed to be informative to the Appraisal Committee. The EAG also comments that no studies have been undertaken in the prevailing circumstances (for example, variant, background therapy, vaccination status) meaning that subjective decisions are required. The EAG believes that the scenarios undertaken are informative to the Appraisal Committee even if they are arbitrary. No change has been made to the report.

[1] NICE. Nirmatrelvir plus ritonavir for treating COVID19 (partial review of TA878). Final Draft guidance. Page 17. Available at: https://www.nice.org.uk/guidance/gid-ta11324/documents/674.

Issue 3 Not presenting results for the "high" efficacy scenario introduces bias (page 15)

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
As explained on page 15, results using the more favourable 95% CI were not presented in the EAG report, given that "ICERs for remdesivir for adult patients receiving LFO were below £20,000 using the mean values". This is a critical point which could easily get overseen by committee members when scanning the EAG report	Amend the EAG report to include results using the more favourable 95% CI (high efficacy scenario).	Justifying the omission of the high efficacy scenario in a half sentence has the potential to bias the decision making of the NICE committee, given that it might only consider the results presented in the report. By presenting results for mean, mean-low and low scenarios, the EAG effectively sets a negative cost-effectiveness anchor, in which it could appear as if the mean efficacy scenario results represent the best-case results for remdesivir, which introduces bias. It is therefore recommended that results of the high efficacy scenario are presented in the EAG report.	This issue relates to a matter of judgement not factual accuracy. It was apparent from the Appraisal Committee's recommendations in the MTA that the high efficacy scenario was not considered appropriate. In Section 3.12 of the FAD. it is stated that '*Therefore, the committee considered that mean efficacy scenarios from these trials likely reflect the highest clinical effectiveness or 'ceiling efficacy' of the treatment.*[2]' The EAG also notes that the omission of a high efficacy scenario was undertaken in the additional analyses for nirmatrelvir and ritonavir[3] with no request from the Appraisal Committee to see more favourable efficacy than the mean from the study. The EAG highlights that the use of mean values produced an ICER below £20,000 for all scenarios and that any high-efficacy scenario would produce more favourable ICERs. This will be confirmed in the Appraisal Committee meeting should this discussion arise. No change has been made to the report.

[2] NICE. Therapeutics for people with COVID-19. Final Draft guidance. Page 20. Available at: https://www.nice.org.uk/guidance/ta878/documents/final-appraisal-determination-document.

[3] NICE. Nirmatrelvir plus ritonavir for treating COVID19 (partial review of TA878). Final Draft guidance. Page 17. Available at: https://www.nice.org.uk/guidance/gid-ta11324/documents/674.

Issue 4 The criticism made by the EAG concerning the review and methods used by Gilead is not justified (page 6)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG criticises the methods used by Gilead to summarize existing evidence for remdesivir in the population of interest by describing them as “neither fully transparent nor reproducible” (page 6). This is not fair, given that Gilead has provided detailed reports outlining the methods applied, and further respond to additional queries made by the EAG	Any reference to lack of transparency and reproducibility in the EAG report shall be removed.	The EAG was involved in all stages following the appeal outcome of the COVID-19 MTA and was therefore informed about all measures taken to present and evaluate the evidence for remdesivir in the population of interest. Gilead has provided detailed reports summarizing the methods used to search the available literature. Furthermore, Gilead responded to requests from the EAG to present an assessment of bias in a different format (using the preferred tools) within a short timeframe and has also respond to additional queries from the EAG.	This issue relates to a matter of judgement not factual accuracy. The EAG has provided clear justification and evidence in the EAG report to support their judgement that ‘…the review methods, and processes in the TS (and accompanying technical report) are neither fully transparent nor reproducible…’ (page 6). The EAG acknowledges the additional work undertaken by Gilead, but this does not negate the EAG’s assessment of the reviews but is likely to be helpful to the Appraisal Committee. No change has been made to the report.

Issue 5 Using the results of the sensitivity analysis on mortality conducted by Amstutz et al.[4] – which included the WHO SOLIDARITY trial[5] – should not be considered for decision making for a low-flow oxygen (LFO) patient population (page 9)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG has outlined that they prefer to use the results of the sensitivity analysis from Amstutz et al.[4], which included individual patient level data (IPD) from the SOLIDARITY trial[2] for mortality as the base case. This is an issue, as the Amstutz et al.[4] themselves explain that the WHO SOLIDARITY trial did not differentiate between LFO and HFO.	Scenario results using the Amstutz et al.[4] mortality odds ratio – which includes results from the SOLIDARITY trial[5] – should not be included in the EAG report	As the EAG elaborates on page 9 of their report, Amstutz et al.[4] report results for a sensitivity analysis for a patient population with "low-flow oxygen (aOR 0·79, 0·68–0·92 with and aOR 0·59, 0·43–0·82 without additional WHO Solidarity[5] data). Out of the two presented sensitivity analysis, the EAG prefers the one which includes results from the SOLIDARITY trial[5]. It should be noted however that the EAG preferred population is not reflective of the patient population currently under assessment as part of the resolution of the COVID-19 MTA appeal. The authors of the meta-analysis themselves clarify in the discussion of their paper, that "data collection regarding respiratory support was not as detailed in the WHO Solidarity trial[5] as in the other seven included trials and did not differentiate between low-flow and high-flow oxygen use." (Amstutz et al.[4] 2023, page 10). Given that NICE was tasked with assessing the use of remdesivir in patients requiring LFO specifically, Gilead requests that only results from Amstutz et al.[4] are considered, which exclude SOLIDARITY[5]. Those results report an aOR of 0·59, 0·43–0·82.	This issue relates to a matter of judgement not factual accuracy. The EAG has been transparent in stating where the data used in the report have been sourced. The EAG has also provided the ICERs for the company's preferred efficacy estimate and thus these values are available to the Appraisal Committee should it agree with the company. No change has been made to the report.

[4] 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.

[5] Consortium, W.S.T., Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. The Lancet, 2022. 399(10339): p. 1941-1953.