Therapeutics for people with COVID-19

For projector – contains no AIC or CIC information

Multiple Technology Appraisal – Third appraisal committee meeting (post appeal)

Technology appraisal committee C [12 December 2023]

Chair: Stephen O'Brien

Evidence assessment group: School of Health and Related Research (ScHARR), Sheffield

Technical team: Rachel Ramsden, Adam Brooke, Ross Dent

Company: Gilead Sciences (other companies involved in MTA are not attending this meeting)

Therapeutics for people with COVID-19

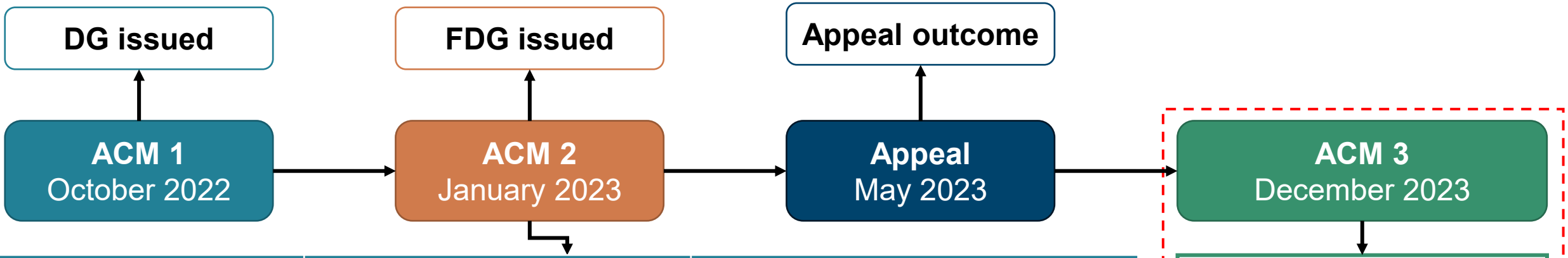
→ **Appraisal recap and appeal outcome**

- Latest evidence and submissions, including EAG critique:
  - clinical rationale for sub-groups
  - clinical evidence for population sub-groups
  - updated economic modelling
- ICERs

NICE National Institute for Health and Care Excellence

Abbreviations: EAG, external assessment group; FDG, final draft guidance; ICERs, incremental cost-effectiveness ratios

Appraisal history



Setting	Recommended	Not recommended
Mild COVID-19 (high risk of progression, also hospital-onset COVID-19)	• nirmatrelvir plus ritonavir • sotrovimab (only if nirmatrelvir plus ritonavir is contraindicated or unsuitable)	• casirivimab plus imdevimab • molnupiravir • remdesivir • tixagevimab plus cilgavimab
Severe COVID-19 (w/out supplemental oxygen)	• no technologies recommended	• casirivimab plus imdevimab
Severe COVID-19 (with supplemental oxygen)	• tocilizumab	• casirivimab plus imdevimab • remdesivir

Outline of meeting:

1. Consider outcome of appeal and latest evidence and submissions
2. Consider rewording of FDG based on suggested clarifications from appeal panel

Abbreviations: ACM, appraisal committee meeting; DG, draft guidance; FDG, final draft guidance

Appeal points

4 of Gilead's appeal points were upheld by the appeal panel, to be discussed

- Appeals submitted by Merck Sharp & Dohme (MSD), Gilead Sciences, and AstraZeneca (AZ)
- MSD have chosen to start a new STA and AZ's appeal points will be addressed by FDG wording changes and a consultation on the IVAG report. **Only upheld appeal points relating to remdesivir will be discussed**
- Gilead (remdesivir) had 8 appeal points heard, 4 of which were upheld by the appeal panel:

NICE acted unfairly because:

1. Lack of time and resource allocated to MTA meant companies were not given the opportunity to make full evidence submission, including an economic model, resulting in important evidence not being considered
2. Lack of time meant 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
3. Committee has not given adequate reasons for why the population requiring "low flow oxygen" was not considered as a potential subgroup

NICE exceeded its powers:

4. 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

Abbreviations: EAG, external assessment group; MTA, multiple technology appraisal; STA, single technology appraisal

Appeal panel conclusion

Appeal panel suggested actions and considerations for committee

Committee asked to:	• Address the unfairness resulting from deviation from NICE's processes for MTA, specifically, the challenges to stakeholder engagement • Consider how best to ensure that that all relevant evidence, including Real World Evidence, is identified, evaluated, and critically appraised • 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 reconsider whether an analysis of this subgroup would be informative • 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
Consider rewording FDG to:	• Provide further explanation why a probabilistic sensitivity analysis was not performed • Clarify what "other differences specific to pandemic setting" (FDG 3.12) means

Abbreviations: FDG, final draft guidance; MTA, multiple technology appraisal

Post appeal considerations

New evidence and submissions from Gilead to be discussed today

Following discussions between NICE and Gilead, Gilead has:

- made a targeted evidence submission which includes:
  - clinical rationale for sub-groups for which they consider remdesivir is most effective
  - clinical evidence for populations, identified by literature searches
  - updated modelling (including Gilead's own model) and cost-effectiveness results
- had an opportunity to engage with the EAG on modelling for remdesivir
- commented on the EAG report following model adaptation.

Abbreviations: ACM, appraisal committee meeting; EAG, external assessment group

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Remdesivir (Veklury, Gilead Sciences)

Table Recap of details of the technology

Marketing authorisation	Remdesivir is indicated for the treatment of 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) • adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19
Mechanism	Remdesivir is an adenosine nucleotide prodrug which inhibits RNA polymerase
Administration	Day 1: IV infusion of 200mg or 5mg/kg for paediatric patients less than 40kg Day 2+: IV infusion of 100mg or 2.5mg/kg for paediatric patients less than 40kg Duration if supplemental oxygen is required: daily for at least 5 days, not more than 10 Duration if supplemental oxygen is not required: daily for 3 days
Price	£340.00 for one vial 100mg powder for concentrate for solution for infusion £2,040 for a treatment duration of 5 days if supplemental oxygen is required

Table Recap of rationale for committee recommendations for remdesivir at ACM2

Mild COVID-19	ICERs not cost-effective, even for people contraindicated to nirmatrelvir plus ritonavir
Severe COVID-19 (with oxygen)	Not possible to reliably estimate remdesivir's cost effectiveness due to substantial uncertainty about effectiveness (in terms of mortality benefit)

NICE

Abbreviations: ACM, appraisal committee meeting; ICERs, incremental cost-effectiveness ratio; RNA, ribonucleic acid

Clinical rationale for population sub-groups

Sub-groups in which Gilead consider remdesivir to be most effective

Table Definition of population sub-groups identified by Gilead

Low-flow oxygen	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
Children	Paediatric population as per the marketing authorisation indication (previous slide)
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

Table EAG summary of the clinical rationale for the selected sub-groups provided by Gilead

Low-flow oxygen	• Subgroup considered as distinct and readily defined population • ESCMID Guidelines conditionally recommend remdesivir for use in hospitalised patients requiring no or LFO but not in patients requiring high-flow oxygen
Children	• Remdesivir is the only available licensed treatment option • Inequity of access to comprehensive clinical care for this group
Immunocompromised patients	• Considered to experience worse clinical outcomes than others; make up less than 1% of people but account for large proportion of COVID-19 hospitalisations/deaths • Nirmatrelvir and ritonavir is the only recommended antiviral and is not appropriate for all immunocompromised patients

Abbreviations: ESCMID, European Society of Clinical Microbiology and Infectious Diseases; LFO, low-flow oxygen.

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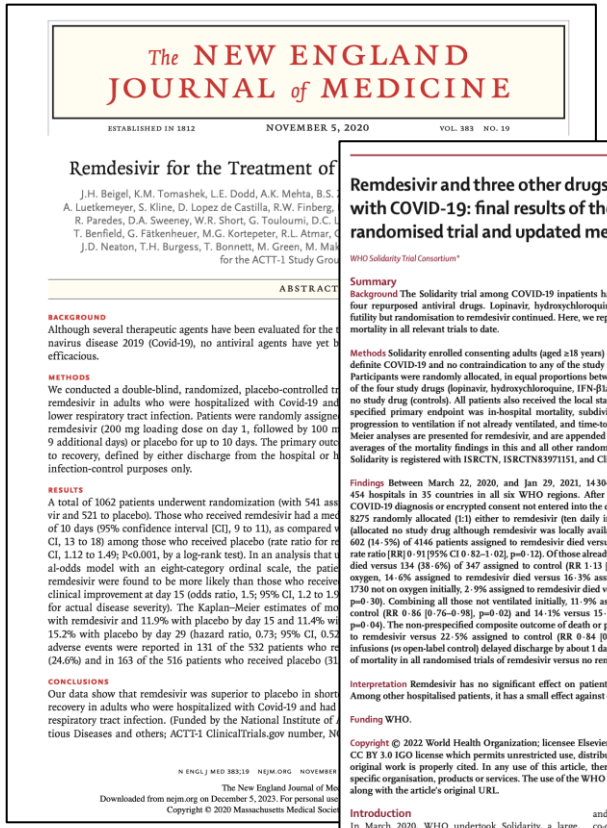
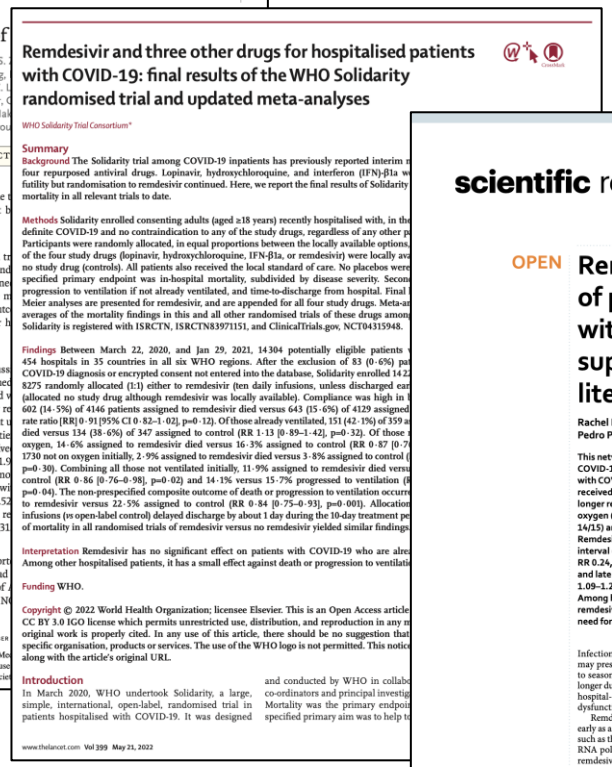
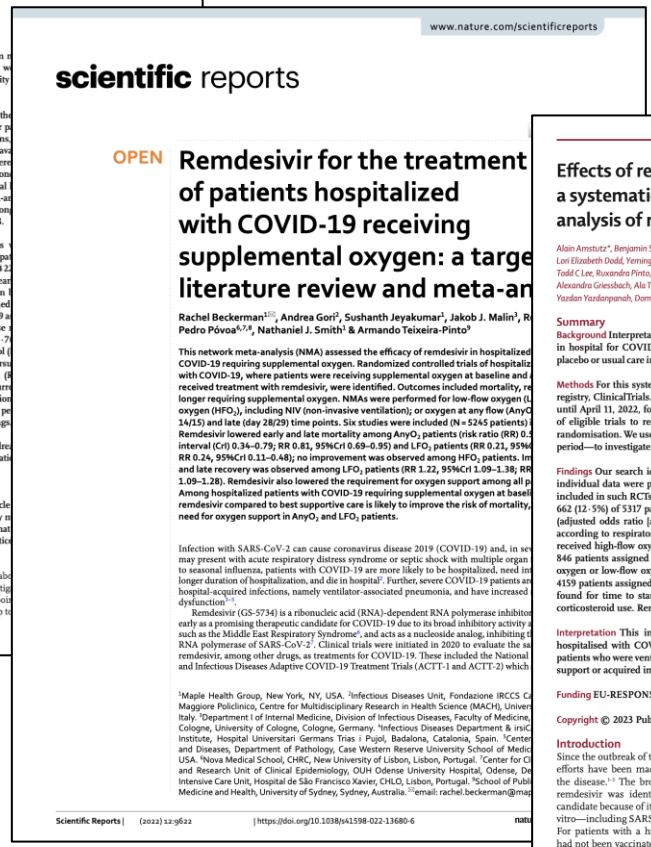


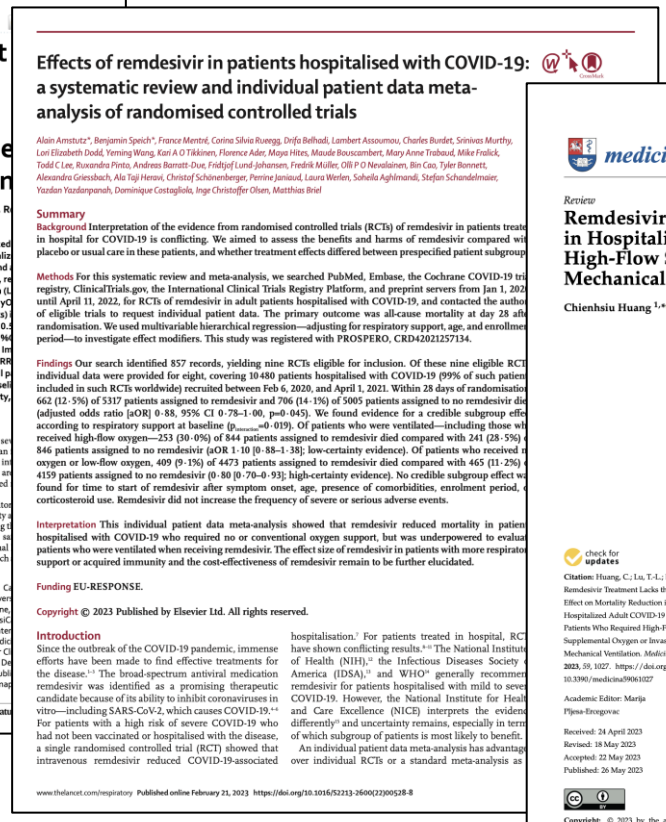
Beigel, Nov 2020
ACTT-1



Solidarity, May 2022



Beckerman, June 2022

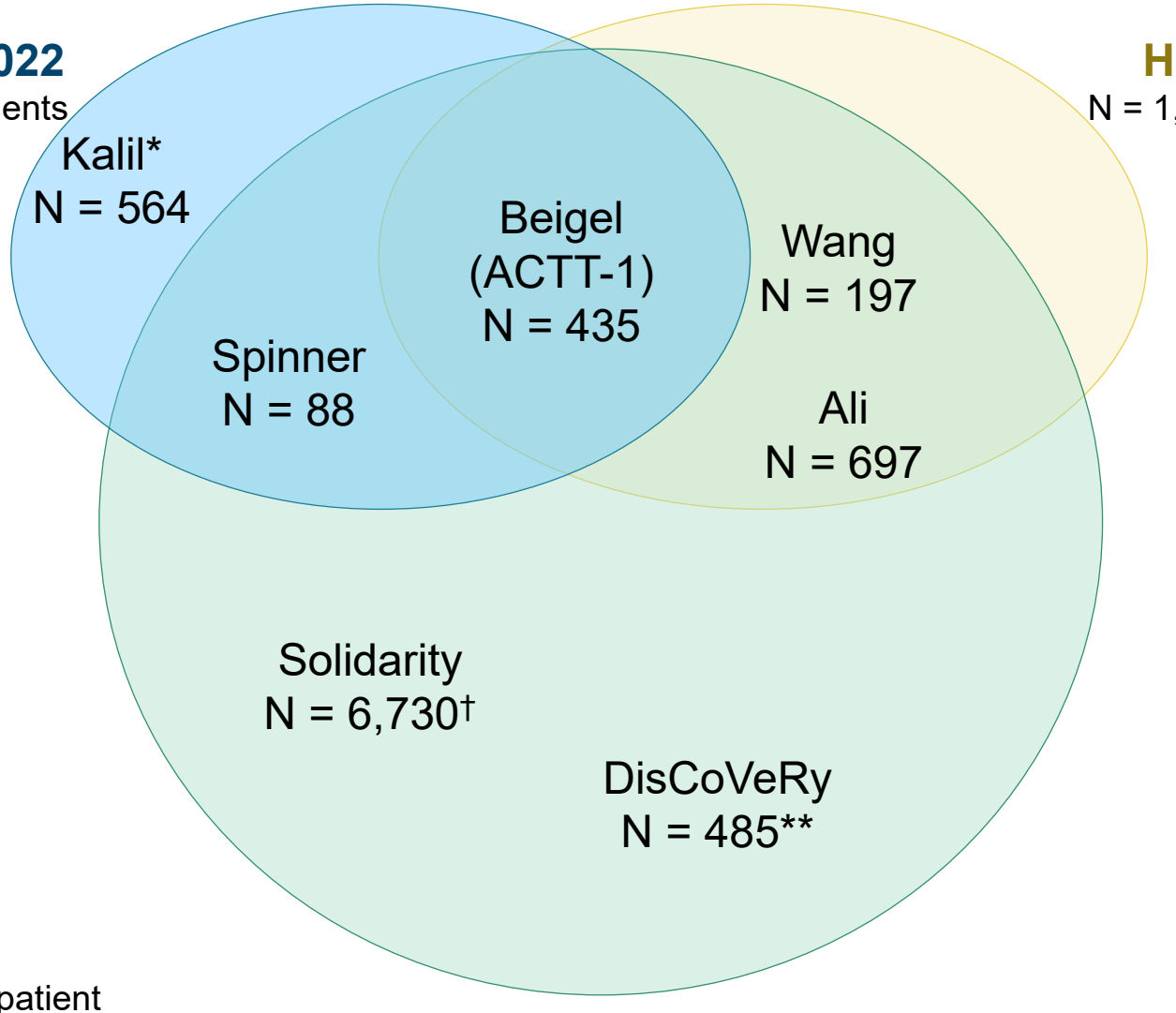


Amstutz, Feb 2023

Huang, May 2023

NICE

NMAs included in Gilead targeted evidence submission for 28-day mortality in low-flow oxygen patients



*Remdesivir versus baricitinib plus remdesivir

**Tech team assumed n with ordinal scale 4 at baseline, as reported in Ader et al. 2021

†Calculated

Abbreviations: IPD, individual patient level data; LFO, low-flow oxygen; NMA, network meta-analysis; RR, risk ratio

Remdesivir 28-day mortality in low-flow patients: RCT evidence

Study	Evidence type	Oxygen requirement	Treatment arm	Mortality		Data period
				Event/Total	Outcome [95% CI]	
Beigel et al. 2020 (ACTT-1)	RCT	LFO	Remdesivir	9/232 (4%)	HR 0.30 [0.14, 0.64]	Enrolment: Feb to April 2020
			Placebo	25/203 (12%)		
Solidarity†	RCT	High-flow or LFO	Remdesivir	426/2918 (14.6%)	RR: 0.87 [0.76, 0.99]	Enrolment: March 2020 to Jan 2021
			Control	476/2921 (16.3%)		
Beckerman et al. 2022*	SLR / NMA (RCT)	LFO	Remdesivir	21/560 (4%)	RR: 0.24 [0.11, 0.48]	Searches: Up to April 2021
			BSC	29/239 (12%)		
Amstutz et al. 2023	SLR / NMA (RCT)	No oxygen or low-flow oxygen	Remdesivir	409/4473 (9%)	aOR: 0.80 [0.70, 0.93]	Searches: Up to Apr 2022
			No Remdesivir	465/4159 (11%)		
Huang et al. 2023	SLR / NMA (RCT)	LFO	Remdesivir	56/695 (8%)	RR: 0.59 [0.43, 0.80]	Searches: Jan 2020 to Feb 2023
			Control	90/634 (14%)		

†All known deaths were before day 150; *Reflects the later mortality assessment

NICE

Abbreviations: aOR, adjusted odds ratio; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; LFO, low flow oxygen; NMA, network meta-analysis; RCT, randomised controlled trial; RR, risk ratio; SLR, systematic literature review

Remdesivir 28-day mortality in low-flow patients: RWE

Study	Evidence type	Setting	Treatment arm	Mortality	
				Event/Total	Outcome [95% CI]
Mozaffari et al. 2023 (CROI)	RWE	USA	Remdesivir	NR/135,164	aHR 0.79 [0.73, 0.85]
			No Remdesivir		
Jeyapalina et al. 2022	RWE	USA	Remdesivir	NR/2,126	HR 0.58 [0.42, 0.80]
			No Remdesivir		
Chokkalingam et al. 2022	RWE	USA	Remdesivir	677/5,523 (12%)	HR 0.81 [0.73, 0.90]
			Control	725/5,523 (13%)	
Garibaldi et al. 2022	RWE	USA	Remdesivir	865/10,314 (8.4%)	aHR 0.85 [0.77, 0.92]
			Control	1,334/10,652 (12.5%)	
Mozaffari et al. 2022	RWE	USA	Remdesivir	NR/13,808	HR 0.77 [0.68, 0.86]
			No Remdesivir	NR/13,808	
Olender et al. 2021	RWE	US, Europe, and Asia	Remdesivir	9/210 (4.3%)	OR 0.29 [0.14, 0.58]
			No Remdesivir	101/803 (12.5%)	

For most recent Omicron variant of concern, aHR is 0.74 [0.66, 0.82])

Abbreviations: aHR, adjusted hazard ratio; OR, odds ratio; CI, confidence interval; CROI, Conference on Retroviruses and Opportunistic Infections; HR, hazard ratio; NR, not reported; RWE, real-world-evidence; SOC, standard of care

SOLIDARITY and ACTT-1

Recap on SOLIDARITY from the FDG

- Inclusion of SOLIDARITY in the NMA resulted in a statistically significant but smaller mortality benefit for remdesivir compared with standard care (HR of 0.85 [95% CI 0.76 to 0.95])
  - The committee considered the inclusion of SOLIDARITY in the NMA important and appropriate
- Generalisability concerns:
  - Recruitment started before predominance of omicron variants (and widespread vaccination)
  - Standard care (including dexamethasone use, and the hospital practices of escalation to mechanical ventilation) differed within and across countries included in the study
  - Standard care has considerably changed since the start of the pandemic
- Because of the generalisability issues, the applicability of the mean-efficacy estimate from SOLIDARITY to the current NHS setting was considered highly uncertain and likely to be the ceiling efficacy estimate
- Committee concluded there was insufficient evidence to show meaningful difference in mortality benefit versus standard care

Recap on ACTT-1 from the FDG

- AG scenario informed time to discharge for remdesivir by ACTT-1, resulting in a large reduction in ICERs
- Generalisability concerns: time to discharge evidence was collected during the early stages of the pandemic
- Committee was uncertain about the treatment benefit on time to discharge in the endemic setting and concluded it was reasonable to remove these treatment effects

Abbreviations: AG, assessment group; CI, confidence interval; FDG, final draft guidance; HR, hazard ratio; NMA, network meta-analysis

Generalisability of the clinical evidence (1/2)

Appeal

- Gilead appeal point 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
- Appeal panel concluded committee decision was not unreasonable considering the evidence submitted to NICE

Generalisability concern (FDG 3.12)	Appeal panel conclusions
Changes in population immunity	• Reasonable to assume that vaccination status may have some impact on the severity of COVID-19 infection, even in hospitalised patients
Changes in pathogenicity	• Not presented with any evidence to support Gilead's assertion that differing pathogenicity of COVID-19 variants had no impact on efficacy of remdesivir • The data on viral neutralisation did not really address questions about changing viral pathogenesis
Changes in supportive care	• Reasonable that changes in supportive care through the pandemic may have had an impact on the relative efficacy of therapies for COVID-19, and this may affect the generalisability of clinical trial data
Other changes specific to the setting	• Revise the FDG to better define other changes (included staff shortages, personal protective equipment, data collection, fear, less interaction)

Abbreviations: FDG, final draft guidance

Generalisability of the clinical evidence (2/2)

Company submission (post appeal)

- Evidence for remdesivir is generalisable to an endemic setting

Generalisability concern (FDG 3.12)	Company response
Changes in population immunity	• A patient hospitalised with severe COVID-19 requires treatment • Data from latest ICNARC report suggests 28-day mortality is not significantly different comparing the latest dataset (Jan 2022 to Mar 2023) versus older datasets (e.g. May 2021 to Dec 2021)
Changes in pathogenicity	• No evidence provided by EAG or committee to support the assertion that changes in the pathogenicity of the virus affected the efficacy of remdesivir
Changes in supportive care	• No data produced by EAG or committee which demonstrates that changes in best supportive care over time affect generalisability
Other changes specific to the setting	• "Other changes" were never specified and no quantitative evidence was provided on how this would impact the generalisability of the evidence

Abbreviations: EAG, external assessment group; FDG, final draft guidance; ICNARC, Intensive Care National Audit & Research Centre

Low-flow oxygen: Mortality

Background

- Underlying mortality rate in the model was changed to account for company positioning remdesivir only for patients receiving LFO

Company

- LFO patients receiving remdesivir had significantly improved 28-day mortality compared to patients receiving SOC, as proven by several studies spanning across multiple COVID variants of concern
- Of the 3 NMAs, the company selected 28-day mortality data from Huang et al. to inform the base case because it published most recently; used a risk ratio as the outcome measure (aligns with EAG model); the estimate is in between the 28-day mortality results of the 3 NMAs
    - Amstutz et al. not recommended as a base case input as it focused on a slightly different patient population, i.e. patients with no or LFO requirements

EAG

- Prefers individual patient data meta-analysis results, conducted by Amstutz et al., to inform base case
- EAG used results from LFO and no oxygen groups combined, to reduce the uncertainty in the estimate of the efficacy of remdesivir, because:
    - Amstutz et al. sensitivity analysis found that patients receiving no oxygen at baseline derived a similar relative benefit to patients receiving LFO
    - NICE rapid guideline stated that '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'

Abbreviations: EAG, external assessment group; LFO, low-flow oxygen; NMA, network-meta-analyses; SOC, standard of care

Low-flow oxygen: Clinical improvement

Committee conclusion in FDG (paragraph 3.23)

- Committee was uncertain about the treatment benefit in the endemic setting and concluded it was reasonable to remove treatment effects on time to discharge and clinical improvement at 28 days

Company (post appeal)

- Study by Garibaldi et al. showed LFO patients on remdesivir have superior outcomes for clinical improvement (aHR 1.23 [95% CI 1.19, 1.27])
- Beckerman et al. report similar outcome ('recovery'), defined as either recovery from COVID-19 or discharge from hospital, and results are consistent with Garibaldi et al. (RR 1.17 [95% CI 1.09, 1.28])
- Company selected Garibaldi et al. for modelling the clinical improvement outcome due to large sample size

EAG

- Garibaldi et al. noted limitations including being unable to match ~half of remdesivir patients, unmeasured confounders and that the study was conducted prior to the widespread use of vaccines and emergence of variants such as Delta and Omicron, which could impact generalisability
- EAG 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 was used as previously assumed by the EAG

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; EAG, external assessment group; FDG, final draft guidance; LFO, low-flow oxygen; NMA, network meta-analysis; RR, risk ratio

Low-flow oxygen: time to discharge

Committee conclusion in FDG (paragraph 3.23)

- Committee was uncertain about the treatment benefit in the endemic setting and concluded it was reasonable to remove treatment effects on time to discharge and clinical improvement at 28 days

Company (post appeal)

- In ACTT-1, patients in 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)
- Company preferred using outcomes from the ACTT-1 trial to inform the model due to larger sample size compared to an alternative RCT that reported time to discharge data, Spinner et al.
- Neither ACTT-1 nor the results from Spinner et al. for the TTD outcome were analysed for a LFO population

EAG

- Unclear how, if at all, the National Early Warning Score is currently being used to safely discharge patients from UK hospitals
- EAG 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, as did the company

Abbreviations: CI, confidence interval; EAG, external assessment group; FDG, final draft guidance; HR, hazard ratio; LFO, low-flow oxygen; RCT, randomised controlled trial; TTD, time to discharge

Children: evidence for paediatric patients

Company (post appeal)

- Remdesivir is a safe and well tolerated treatment for children, providing the only viable treatment option for patients aged <12 years with severe COVID-19
- A treatment option is important due to rare nature of COVID-19 in children, which consequently would cause minimal burden on overall NHS resources (of all children/adolescents who had a recorded SARS-CoV-2 infection between July 2020 and Feb 2022, <1% were admitted to hospital)

Study	Population	Results for remdesivir
CARAVAN (NCT04431453)	Children aged 28 days – <18 years	• Clinical improvement (≥2 point increase on the ordinal scale: 75% at Day 10, 85% at last assessment
Goldman et al.	Hospitalised patients <18 years old via a compassionate use program (March 21 to April 22)	• Most recovered; rate of serious adverse events was low • Clinical improvement of ≥1 point by baseline oxygen support status: 90% (category 5), 85% (category 4), 100% (category 3 [LFO]) and 75% (category 2)
Samuel et al.	Patients admitted to a US academic medical centre	• No significant adverse effects
Chera & Tanca	Physicians' experience of treating children	• Concluded many studies/case reports show good results in favour of using remdesivir for the treatment in children

Abbreviations: LFO, low flow oxygen

Evidence for immunocompromised patients

Company (post appeal)

- RWE study by Mozaffari et al., remdesivir showed a significant mortality benefit across all variants, including Omicron
  - 28-day mortality benefit is particularly strong in people 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
- Reported analyses of 3 hospitals in Spain, showing a significant mortality benefit for patients with pneumonia (HR of 0.63 [0.49, 0.81])
- Akinosoglou et al. 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”

	N	aHR [95% CI]	P value
14-day mortality			
Overall	28,338	0.70 [0.62 - 0.78]	<0.0001
Pre-Delta	8,958	0.59 [0.48 - 0.71]	0.0100
Delta	11,084	0.77 [0.65 - 0.92]	0.0035
Omicron	8,296	0.75 [0.63 - 0.90]	0.0020
28-day mortality			
Overall	28,338	0.75 [0.68 - 0.83]	<0.0001
Pre-Delta	8,958	0.65 [0.56 - 0.76]	<0.0001
Delta	11,084	0.79 [0.68 - 0.91]	0.0013
Omicron	8,296	0.84 [0.72 - 0.97]	0.0203

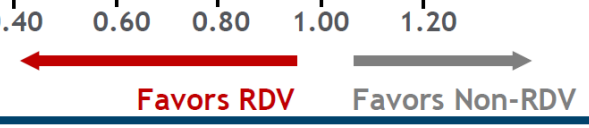


Table: 14-and 28-day mortality across variant periods for immunocompromised patients (Mozaffari et al.)

NICE

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; RDV, remdesivir; RWE, real world evidence

Other considerations: is tocilizumab a comparator for remdesivir?

EAG

Unclear whether tocilizumab would be a comparator

- Final draft guidance stated that tocilizumab was an option for adults with COVID-19 who are having systemic corticosteroids and need supplemental oxygen or mechanical ventilation
- So there is potential for adults on LFO to have tocilizumab
- Company's implied statement that treatments were only compared with SoC is incorrect as all treatments could be compared with each other via the use of NMB in the MTA

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

Company response

- Treatments previously recommended as part of the MTA (including tocilizumab, nirmatrelvir plus ritonavir and sotrovimab) have been compared against SOC. Deviating from SOC as comparator of choice would invalidate and question previous recommendations on other treatments and so is not appropriate
- Cost-effectiveness results for remdesivir versus tocilizumab are unfit for decision making and have the potential to bias the committee given no dedicated search was run to inform the effectiveness parameters applied in the EAG model. **EAG:** Results are in a appendix which may be dismissed by committee

*HR for time to death; RR for clinical improvement; HR for time to discharge

Abbreviations: EAG, external assessment group; HR, hazard ratio; LFO, low flow oxygen; MTA, multiple technology appraisal; NMB, net monetary benefit; SOC, standard of care

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Recap of EAG's original model

The model was accepted by committee as appropriate for decision making

Committee conclusion in FDG (paragraph 3.21)

- Relative treatment effect, and reduced hospitalisation and mortality rates are key drivers of benefit, model was not sensitive to other benefits of treatment like faster resolution of symptoms
- Model broadly appropriate to capture most important outcomes and appropriate for decision making given available evidence base for COVID-19

Figure: Community decision tree model structure

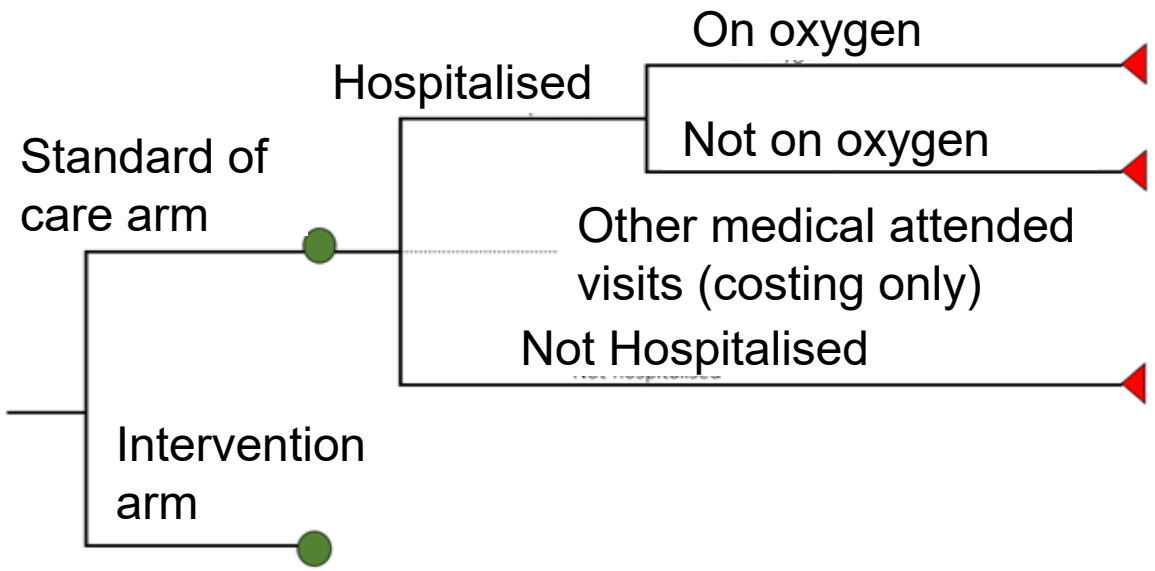
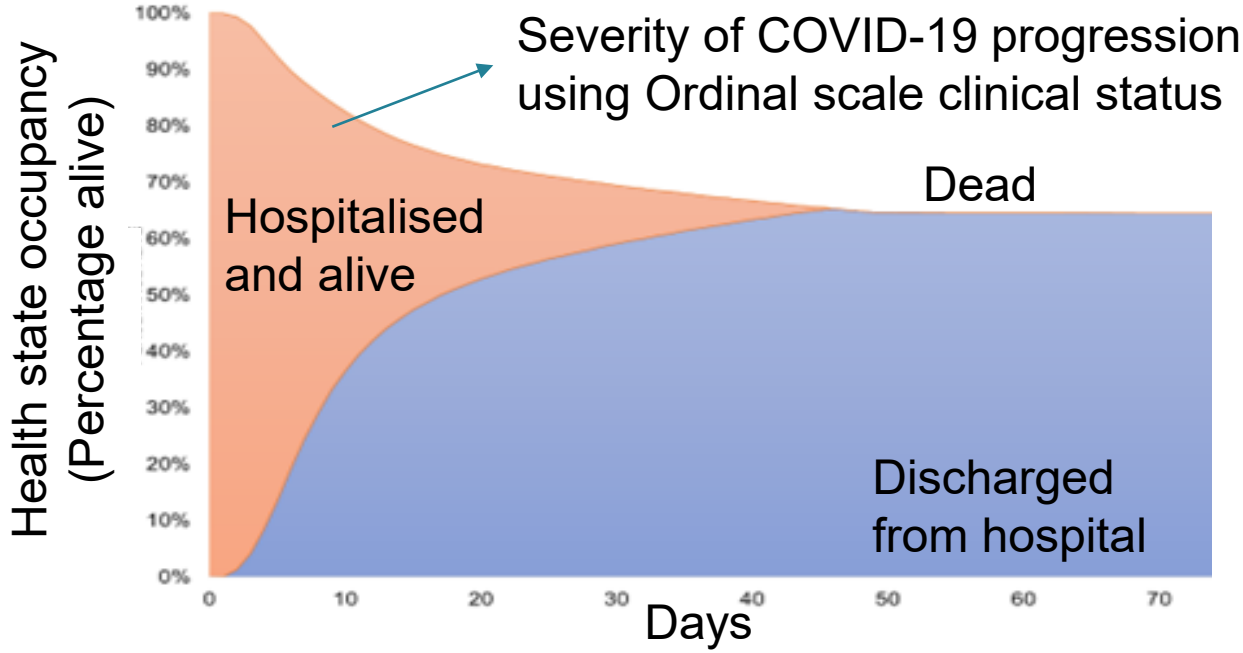


Figure: Hospital partitioned survival model structure

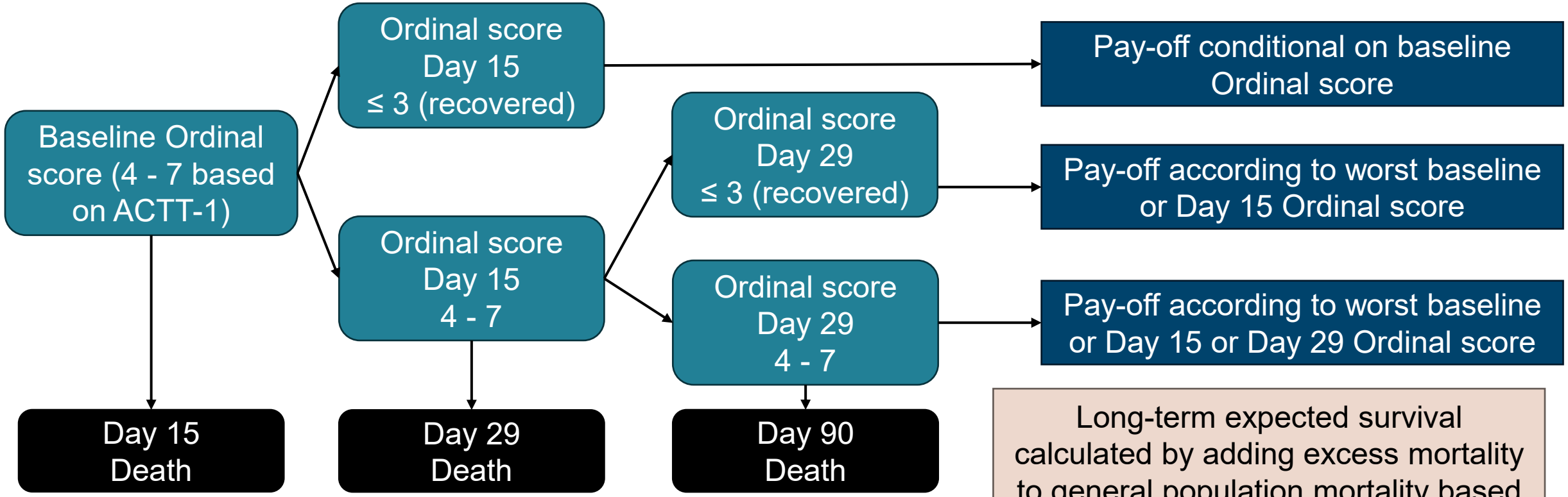


Abbreviations: EAG, external assessment group; FDG, final draft guidance

Overview of company's model

The company developed a model and shared it post appeal

- 90-day outcomes are estimated, to which long-term outcomes are assigned based on whether patients survive, having been in intensive care or non-intensive care in-hospital
- Comparator arms are best supportive care, dexamethasone, and remdesivir (with dexamethasone)
- The primary data source to support the modelling of in-hospital outcomes is the ACTT-1 study



Long-term expected survival calculated by adding excess mortality to general population mortality based on nature of hospital stay

EAG comments on most appropriate modelling

ICERs moderately lower in EAG's model versus the company's with similar inputs

- EAG had insufficient time to critique the company's model as it was shared after the initial submission
- EAG noted that ICERs were moderately lower in the EAG's model versus the company's with similar inputs
- EAG maintains use of its model (which may favour remdesivir) as it has been scrutinised by companies, discussed at previous committee meetings, and it has additional flexibility versus the company's model

Amendments to EAG model to reflect updated positioning of remdesivir

Low flow oxygen

- Patients placed at Ordinal scale 5 instead of distributed from 5 to 7
- Company suggested updated mortality rate of 10% at 15 days based on SOLIDARITY
- EAG used mortality rate of 14% at 28 days based on Amstutz et al

Children

- Assumed efficacy values used in LFO patients are generalisable to children
- Average age of hospitalised patients was arbitrarily reduced to 15 years
- Mortality rate at 28 days set to 0.19% (Wilde et al) and 0.45% (Ward et al)
- 5 days hospital stay modelled (minimum possible) though Wilde et al reported median stay of 2 days (IQR 1 to 4)

Immunocompromised

- Assumed efficacy values used in LFO patients are generalisable
- Evans at al. reported 24.98% of hospitalisations resulting in death
- Figure may be overestimated as this includes deaths following hospitalisation
- Age and length of stay in hospital unchanged due to lack of data

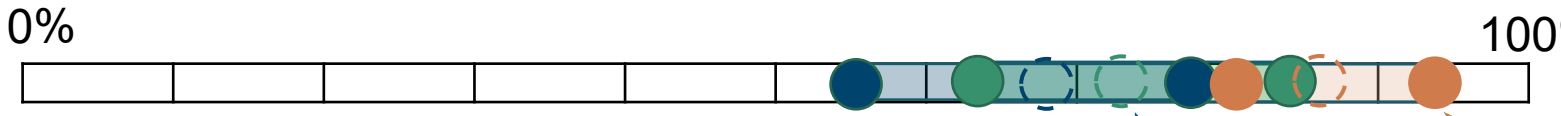
EAG consider as exploratory analyses due to non-systematic data sources and potentially incorrect assumptions

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; IQR, interquartile range; LFO, low flow oxygen

EAG approach to modelling scenarios (1/2)

Exploring mortality, time to discharge and clinical improvement

e.g. mortality
(HR for time to death)



Amstutz et al (excluding SOLIDARITY) mean, mean-low and low scenarios

Huang mean, mean-low and low scenarios

Amstutz (including solidarity) mean, mean-low and low scenarios

Mean: expected mean from the specified distribution (calculated by the EAG)
Low: more unfavourable 95% confidence limit
Mean-low: average value from the mean and low scenarios

EAG

- As ICERs for remdesivir for adult patients receiving LFO were <£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
- Rationale for exploring worse mortality benefit than observed 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

Abbreviations: EAG, external assessment group; HR, hazard ratio; ICER, incremental cost effectiveness ratio; LFO, low flow oxygen; SOC, standard of care

EAG approach to modelling scenarios (2/2)

Key: ICER (including PAS for remdesivir) in adults requiring LFO

>30k
Within 20-30k
Below 20k

All 27 scenarios assume a positive impact of remdesivir on mortality

		HR for time to death, RR for clinical improvement, HR for time to discharge		
Study used for remdesivir	**Efficacy scenario**	**Differences in mortality only**	**Differences in mortality and clinical improvement**	**Differences in mortality and time to discharge but not in clinical improvement***
Amstutz *et al* (including SOLIDARITY data)**	Mean	**1)** 0.817, unity, unity	**10)** 0.817, 1.040, unity	**19)** 0.817, unity, 1.270
	Low	**2)** 0.930, unity, unity	**11)** 0.930, 0.990, unity	**20)** 0.930, unity, 1.100
	Mean-Low	**3)** 0.865, unity, unity	**12)** 0.865, 1.015, unity	**21)** 0.865, unity, 1.187
Huang *et al*	Mean	**4)** 0.635, unity, unity	**13)** 0.635, 1.040, unity	**22)** 0.635, unity, 1.270
	Low	**5)** 0.839, unity, unity	**14)** 0.839, 0.990, unity	**23)** 0.839, unity, 1.100
	Mean-Low	**6)** 0.723, unity, unity	**15)** 0.723, 1.015, unity	**24)** 0.723, unity, 1.187
Amstutz *et al* (excluding SOLIDARITY data)	Mean	**7)** 0.559, unity, unity	**16)** 0.559, 1.040, unity	**25)** 0.559, unity, 1.270
	Low	**8)** 0.773, unity, unity	**17)** 0.773, 0.990, unity	**26)** 0.773, unity, 1.100
	Mean-Low	**9)** 0.682, unity, unity	**18)** 0.682, 1.015, unity	**27)** 0.682, unity, 1.187

*due to the risk of double-counting in ACTT-1;
**Patients with no or LFO requirements analysed as a single patient population

Abbreviations: EAG, external assessment group; HR, hazard ratio; ICER, incremental cost effectiveness ratio; LFO, low flow oxygen; PAS, patient access scheme; RR, relative risk

Therapeutics for people with COVID-19

- Appraisal recap and appeal outcome
- Latest evidence and submissions, including EAG critique:
  - clinical rationale for sub-groups
  - clinical evidence for population sub-groups
  - updated economic modelling

→ **ICERs**

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Abbreviations: EAG, external assessment group; FDG, final draft guidance; ICERs, incremental cost-effectiveness ratios

Cost-effectiveness results

All results for remdesivir are reported in PART 2 slides because they include confidential PAS discounts.

Summary

- For remdesivir compared with SOC in adult patients requiring LFO when using the EAG's model, the ICERs (including the PAS for remdesivir):
  - were <£20,000 per QALY gained in 23 out of 27 scenarios
  - were <£30,000 per QALY gained in 4 out of 27 scenarios
  - No ICERs were >£30,000 per QALY gained
- Key drivers in the EAG's model 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
  - Whether any benefit in time to discharge should be assumed
- For remdesivir compared with tocilizumab, the intervention with the highest NMB varies depending on the scenario chosen
- Company's ICER using its own model: £2,331 (without the PAS for remdesivir)

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Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; LFO, low flow oxygen; NMB, net monetary benefit; PAS, patient access scheme; SOC, standard of care

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Thank you.