Therapeutics for people with COVID-19

Multiple Technology Appraisal

No ACIC
PART 1 slides for public (Update 23/01) FAC check (26/01)

Technology appraisal committee C

Chair: Stephen O'Brien

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

Technical team: Anuja Chatterjee, Adam Brooke, Ross Dent

Companies: AstraZeneca, Eli Lilly, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche

Overview of the day

Section	Data relevant to both appraisals	
1.1	SARS-CoV-2: variant tracking	Public
1.2	*In vitro* data	Public
1.3	Position of various organisations	Public

ID 4038	MTA of COVID-19 treatments	ACM 2
2.1	Community setting (mild COVID-19) – Part 1	Public
3.1	Hospital setting (severe COVID-19) – Part 1	Public
2.2	Community setting – Part 2	Private
3.2	Hospital setting – Part 2	Private

ID 6136	STA of tixagevimab/cilgavimab (Evusheld)	ACM 1
4.1	Prophylaxis in highly vulnerable people – Part 1	Public
4.2	Prophylaxis – Part 2	Private

Recap from ACM1

Three treatments recommended, changing nature of SARS-CoV-2 variants mean clinical evidence remains uncertain

Setting	Recommended	Technologies evaluated and not recommended
Non hospital setting (mild COVID-19) (Referred to as 'community')	• nirmatrelvir plus ritonavir (nirm/rit)	• casirivimab plus imdevimab • molnupiravir • sotrovimab • remdesivir • tixagevimab plus cilgavimab (tix/cil)
Hospital setting (without supplemental oxygen)	• no technologies recommended	• casirivimab plus imdevimab • remdesivir
Hospital setting (with supplemental oxygen)	• tocilizumab • baricitinib	• casirivimab plus imdevimab • remdesivir

ACM1, Appraisal committee meeting 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Committee conclusions on the model

Committee (DG 3.13)

- 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

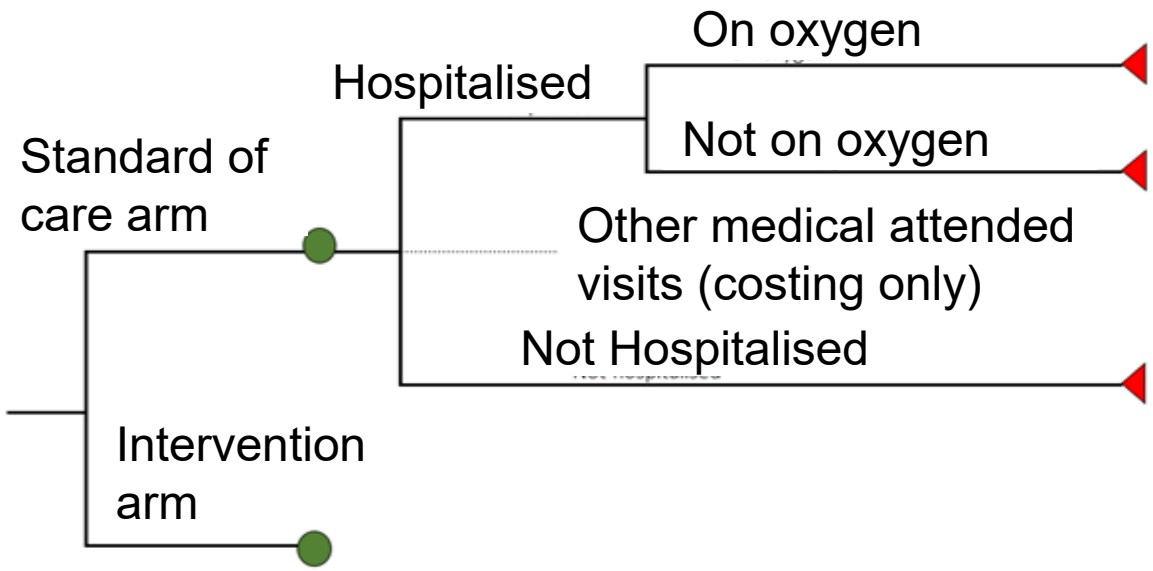
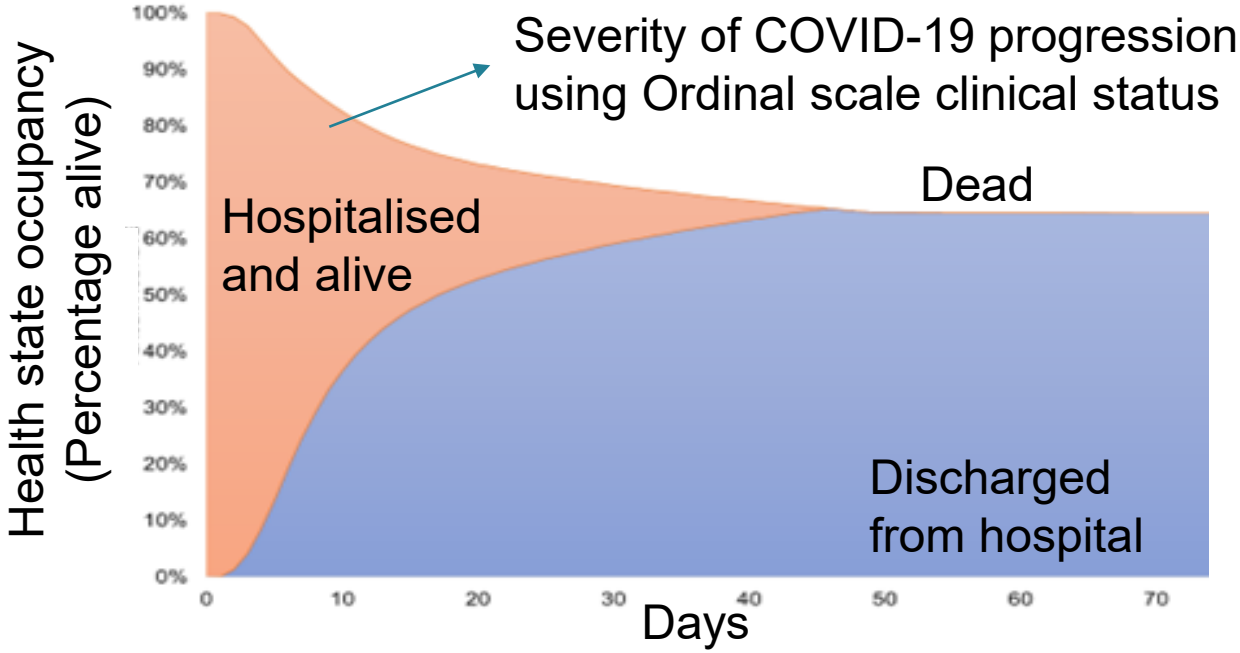


Figure: Hospital partitioned survival model structure



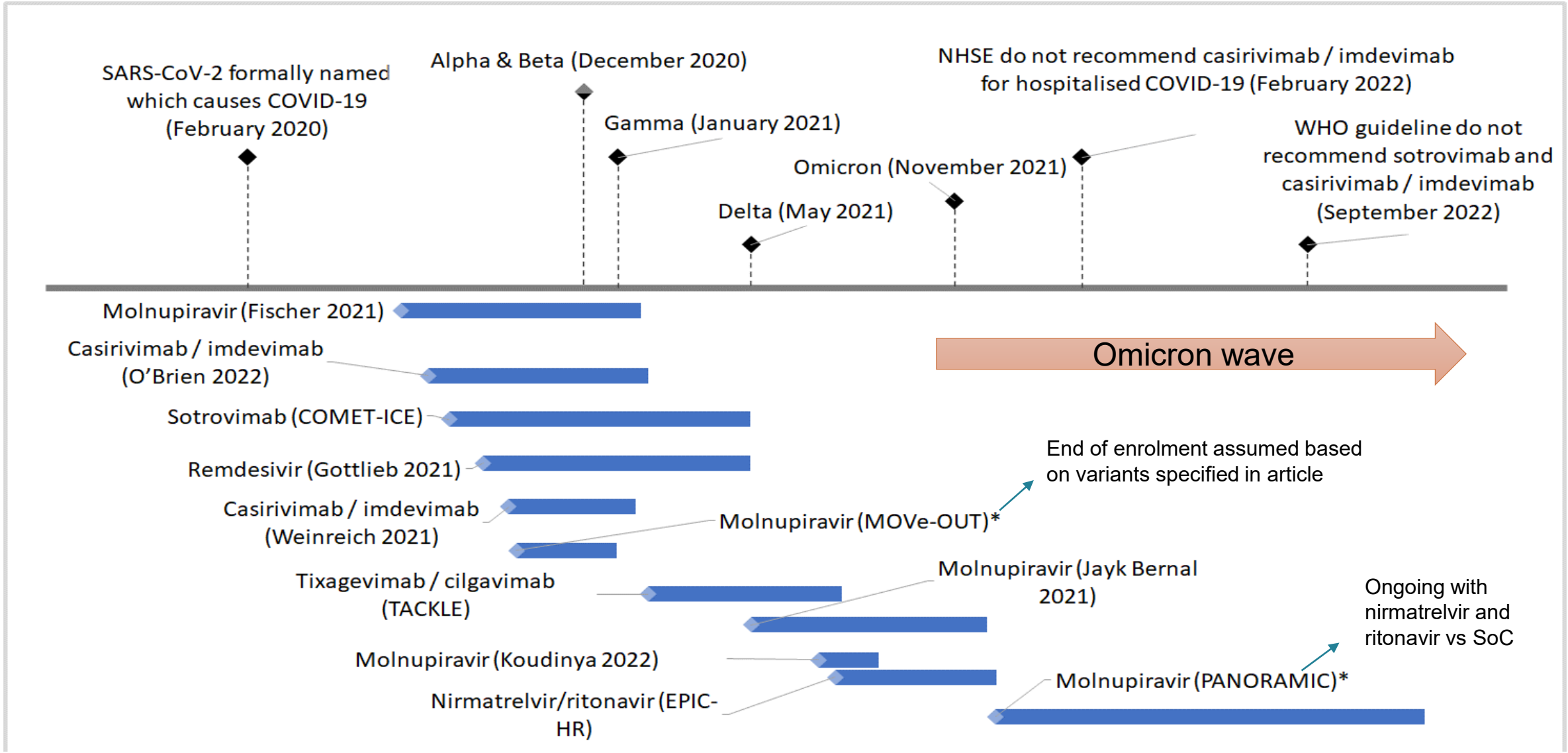
Source: Final AG report pre-DG consult (Figure 10,12)

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Global VOC and clinical trial enrolment dates - Community

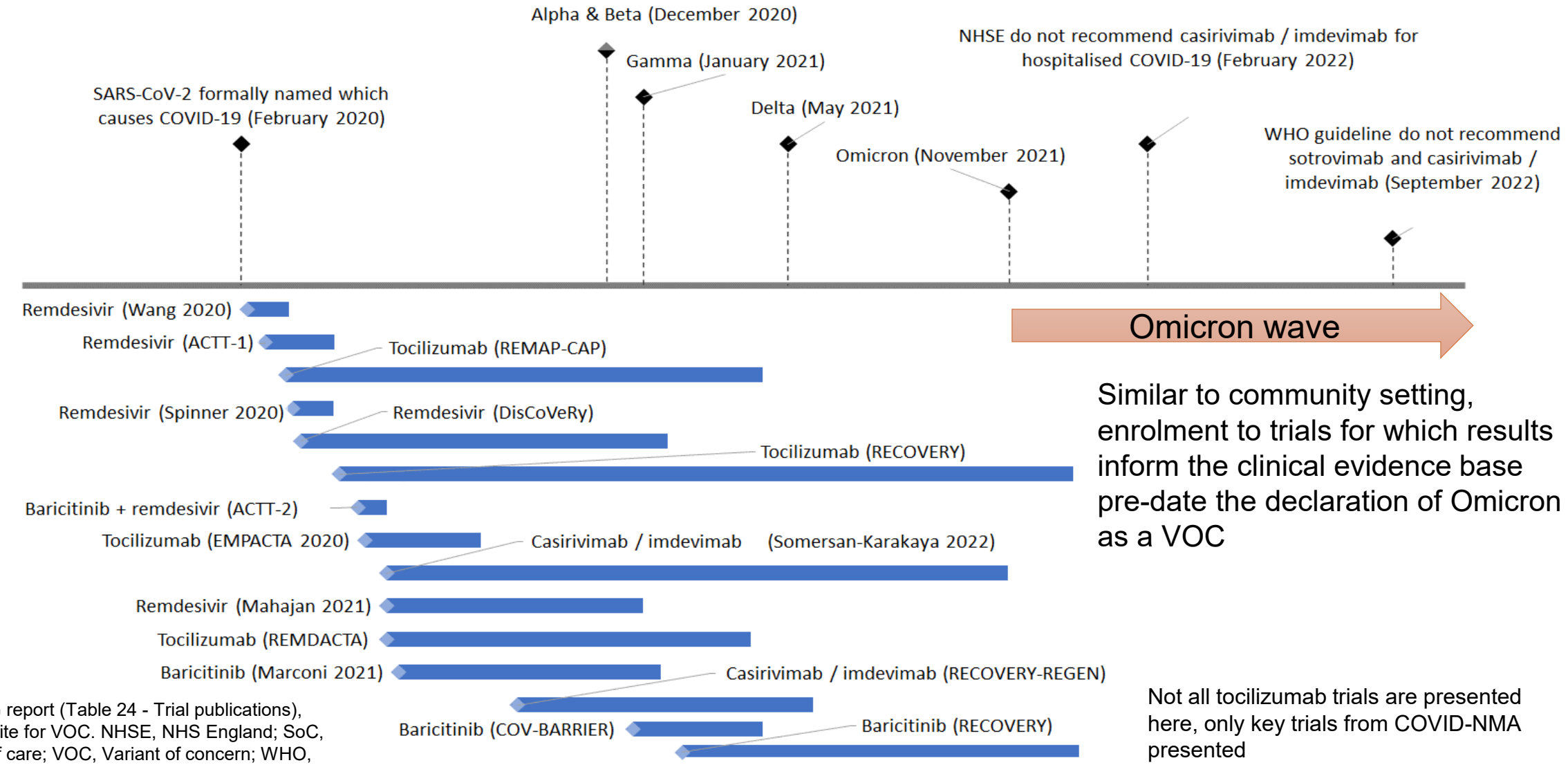
Most of the community trials pre-date the declaration of Omicron as a VOC



Source: AG report (Table 24 - Trial publications), WHO website for VOC. NHSE, NHS England; SoC, Standard of care; VOC, Variant of concern; WHO, World Health Organisation

Global VOC and key clinical trial enrolment dates - Hospital

Most of the hospital setting trials started earlier than the community setting



Similar to community setting, enrolment to trials for which results inform the clinical evidence base pre-date the declaration of Omicron as a VOC

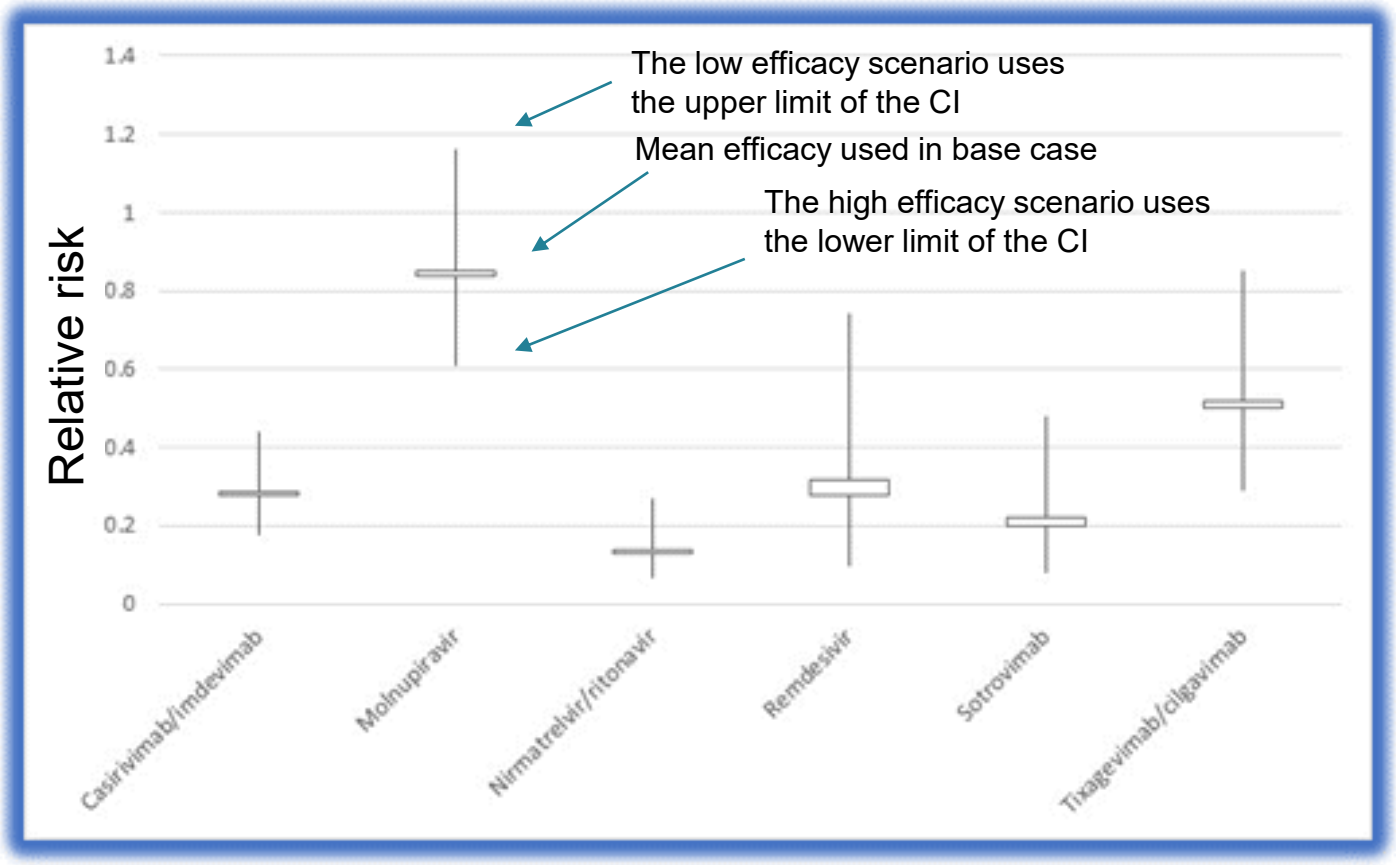
Not all tocilizumab trials are presented here, only key trials from COVID-NMA presented

Source: AG report (Table 24 - Trial publications), WHO website for VOC. NHSE, NHS England; SoC, Standard of care; VOC, Variant of concern; WHO, World Health Organisation

Example of efficacy scenarios and committee conclusions

DG 3.9: Committee understood the limitations of the scenario analysis. It considered scenarios represented an attempt to address some aspects of uncertainty in absence of alternative methods to model uncertainty.

Figure: The relative risk of hospitalisation or death at 28 days



AG response: Mean efficacy - expected if conditions were exactly the same as during the studies in COVID-NMA and metaEvidence

- Approach to low and high efficacy impacted by: number of events or sample size
- 2 identical treatments can have different low and high efficacy outcomes because of sample size

NICE Source: Pre-DG consultation AG report, Post-DG AG report (Section 5.1 – Response 1)

Updated clinical efficacy estimates: Community

Intervention	Estimated efficacy (95% CI)	Mean value from the lognormal distribution
Hospitalisation or death RR:		
Casirivimab/imdevimab	0.28 (0.18 – 0.44)	0.29
Molnupiravir	0.80 (0.56 – 1.15)	0.81
Nirmatrelvir/ritonavir	0.13 (0.07 – 0.27)	0.14
Remdesivir	0.28 (0.10 – 0.74)	0.32
Sotrovimab	0.20 (0.08 – 0.48)	0.22
Tixagevimab/cilgavimab	0.50 (0.29 – 0.86)*	0.52
All-cause mortality RR at 28 days:		
Casirivimab/imdevimab	0.51 (0.09 – 2.95)	0.76
Molnupiravir	0.27 (0.09 – 0.82)	0.32
Nirmatrelvir/ritonavir	0.04 (0.00 – 0.63)	0.15
Remdesivir	1.00 (0.02 – 50.23)**	7.36***
Sotrovimab	0.20 (0.01 – 4.16)	0.65
Tixagevimab/cilgavimab	1.00 (0.32 – 3.06)	1.18***

CI - confidence interval, HR - hazard ratio, RR - relative risk
* An odds ratio was provided in the source and the authors calculated the RR.
** There were no deaths reported in either arm. This estimate is calculated assuming a continuity factor of 0.5 deaths and 1 extra observation was added to each arm
*** A value of 1.00 was used in the modelling

NICE Molnupiravir red text indicates changes from last version of NMA results presented in ACM1. Source: Table 1 Post-DG consultation AG report

Updated clinical efficacy estimates: Hospital (same efficacy applicable for with and without supplemental oxygen settings)

Intervention	Estimated efficacy (95% CI)	Mean value from the lognormal distribution
Time to death HR		
Casirivimab/imdevimab*	0.69 (0.50 – 0.93)	0.70
Tocilizumab*	0.76 (0.64 – 0.90)	0.76
Remdesivir	0.77 (0.57 – 1.04)	0.78
Baricitinib	0.61 (0.47 – 0.78)	0.62
RR for clinical improvement at 28 days		
Casirivimab/imdevimab*	1.03 (0.98 – 1.09)	1.03
Tocilizumab	1.05 (1.00 – 1.11)	1.05
Remdesivir	1.04 (0.99 – 1.10)	1.04
Baricitinib	1.02 (1.00 – 1.05)	1.02
Time to discharge HR		
Casirivimab/imdevimab	1.24 (1.05 – 1.47)	1.24
Tocilizumab	1.05 (0.88 – 1.25)	1.05

*Red indicates changes from last version of NMA results presented in ACM1

Source: Table 2 Post-DG consultation AG report

CI, Confidence interval, HR, Hazard ratio, RR, Relative risk

DG Consultation comments

Responses from:

- Companies: AstraZeneca, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche
- Two patient experts
- NHS England
- 17 patient and professional organisation submissions: Action for Pulmonary Fibrosis, Blood Cancer UK Joint submission from Lymphoma Action-Anthony Nolan-Myeloma UK-Leukaemia Care-Chronic Lymphocytic Leukaemia Support, British Infection Association, British Paediatric Allergy Infection and Immunity Group, British Thoracic Society, British Transplant Society, Cardiothoracic Transplant Patient Group, Faculty of Pharmaceutical Medicine, Kidney Care UK, Kidney Research UK, Long Covid Kids, Long Covid Support, Long Covid SOS, LUPUS UK, Renal Pharmacy Group, Royal College of Physicians, UK Clinical Pharmacy Association,
- Public (Web) comments: 60 submissions

NICE National Institute for Health and Care Excellence

Companies (1/2)

Core theme	Sub themes consultation comments	Action
Limited treatment options for the highest risk group who are contraindicated to nirm/rit	• High unmet need for nirm/rit contraindicated population • Inequalities are potentially worsened • Need for separate high-risk subgroups to account for population difference	Key issue for discussion
Model inputs	• Hospitalisation rates are low and not representative of high-risk population • Administration costs are too high for some treatments. They do not account for contraindications • Hospital cost assumptions should be reconsidered	• Key issue for discussion • AG report includes a response • AG model updates
Modelling assumptions	• Counter-intuitive mortality assumption • Additional outcomes from PANORAMIC study not considered	AG model updates
High-risk population definition to be revisited	• Age not considered which contradicts JCVI's and CDC's approach • Broader population definition should be considered: • McInnes report definition for highest risk and PANORAMIC trial population for high-risk	• Age previously discussed • Key issue for discussion
Suggestions for optimised recommendation for tix/cil and sotrovimab	• Additional evidence should be considered for tix/cil • Optimised recommendations could be made taking account of nirm/rit contraindications	Key issue for discussion

AG, Assessment group; CDC, The US Centers for Disease Control and Prevention; JCVI, The Joint Committee on Vaccination and Immunisation, Nirm/rit, Nirmatrelvir plus ritonavir; Tix/cil, Tixagevimab plus cilgavimab

Companies (2/2)

Core theme	Sub themes consultation comments	Action
Low efficacy scenarios	Considered arbitrary and not evidence based	Response in AG report
Role of antivirals in the hospital setting	• Assumption that antivirals have limited role in hospital needs further scrutiny and evidence. Treatment sequence in hospital misunderstood. • Treatment gaps for access to antivirals for Ordinal scale categories 4+ • No treatment option recommended for people who do not need supplemental oxygen	Key issue for discussion
Use of *in vitro* evidence to conclude on clinical effectiveness	• Generalising neutralising monoclonal antibody *in vitro* evidence is inappropriate • Real world evidence on clinical effectiveness should be considered	Key issue for discussion
Limitations of the indirect comparison	Pooling the results without adjustment for clinical differences should be reconsidered	Previously assessed by committee
Additional equality challenges	No treatment options for children: up to 12 years and young people: between 12 and 17 years	Key issue for discussion
Areas where guidance can be clearer, factual inaccuracies	Companies have flagged a number of areas for clarification	Final draft guidance will address these concerns

Other stakeholders (1/2)

Similar core themes: limited treatment options for nirm/rit contraindicated, high-risk population definition, role of antivirals in hospital. Long Covid assumptions and additional evidence on sotrovimab also flagged.

Core theme	Sub themes consultation comments	Action
Limited treatment options for the highest risk group who are contraindicated to nirm/rit	• Limited choice for people in the community with only 1 mode of treatment administration • Alternative renal dosing of nirm/rit should be considered although currently unlicensed and may result in medicine safety risk • Impact of removing treatment from people not considered • High burden on shielders and its impact on mental well being / quality of life / economic consequences not considered • Opportunity cost of NHS money already spent on people with an immunocompromised state / people with transplants not considered	Key issue for discussion
Modelling assumptions	• Treatment sequencing not considered • Wider NHS benefits from reducing viral load and shortening illness not considered	Previously discussed
Long Covid assumptions	• Duration of long Covid of 108 weeks is an underestimate • Costs are being underestimated • One set of utility estimates may not be appropriate • Excess mortality and morbidity because of long Covid not included • Treatment benefits of reducing duration and probability of long Covid not considered	AG model updates AG report includes a response

AG, Assessment group; Nirm/rit, Nirmatrelvir plus ritonavir

Other stakeholders (2/2)

Core theme	Sub themes consultation comments	Action
High-risk population definition to be revisited	• People left out of McInnes definition should be considered by NICE • Definition excludes impact of long Covid and reinfections leading to higher risk of hospitalisation • Treatment for children: up to 12 years and young people: between 12 and 17 years not adequately considered across all settings	Key issue for discussion
Role of antivirals in the hospital setting	Antivirals play a key role in the hospital setting: • More relevant for people with immunodeficiencies where viral clearance is significantly impaired and also in children who do not reach hyperinflammatory phase • Changing population characteristics, early disease, less severe with high burden of comorbidity, mostly older people presenting at hospital Antiviral efficacy does not alter with variants, anti-inflammatory efficacy argument also applies here Treatment gaps for hospital-onset COVID-19	Key issues for discussion
Evidence that should have been considered	Sotrovimab clinical efficacy from real world studies: Zheng, Green 2022 (OpenSAFELY platform)	Key issue for discussion
Additional evidence to consider	OpenSAFELY Collaborative 2022 (non-hospitalised on kidney replacement therapy)	Key issue for discussion

Key issues

Issue	ICER impact
Consideration of *in vitro* evidence for neutralising monoclonal antibodies	Large / Unknown

Challenges with limited treatment options for the high-risk population:
• Should the hospitalisation rates be reconsidered based on newer evidence?
• Is nirm/rit cost effective in a broader high-risk group?
• Are any of the alternative treatments clinically effective and cost effective?
  • Molnupiravir evidence from PANORAMIC trial – Is the evidence generalisable to the high-risk population as defined by the McInnes report?
  • Should evidence from tix/cil treatment within 5 days of symptom onset be considered?
	Large

Challenges with treatment gaps in the hospital setting: • Consideration of remdesivir evidence - Should NMA include SOLIDARITY trial evidence? • Were the conclusions regarding role of antiviral biological plausibility in the hospital setting clinically relevant?	Large
No treatment options recommended in children: • Are any of the licensed treatments effective and cost effective for children?	Unknown

NMA, Network meta-analysis; Nirm/rit, Nirmatrelvir plus ritonavir, Tix/cil, tixagevimab plus cilgavimab

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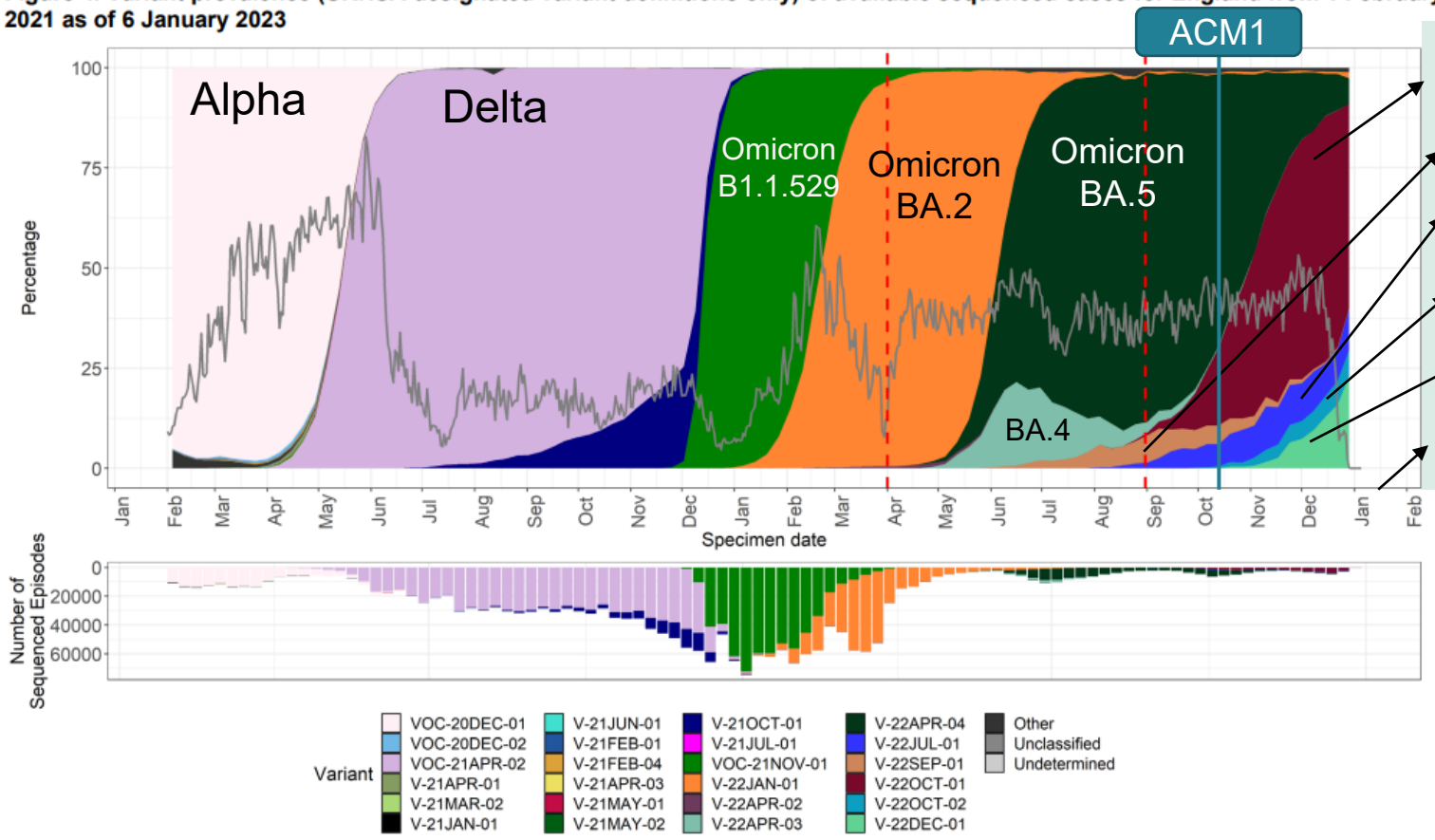
Circulating variants change and difficult to predict

*Possible only to predict prevalence of variants from trajectories of **currently circulating** variants in the near future*

Figure 4. Variant prevalence (UKHSA designated variant definitions only) of available sequenced cases for England from 1 February 2021 as of 6 January 2023

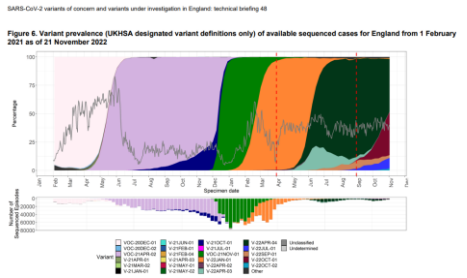


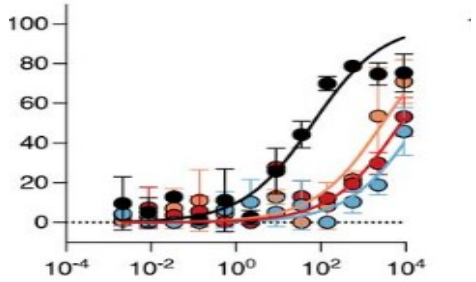
- Omicron BQ.1 (51.3%)
- Omicron BA.4.6 (0.12%)
- Omicron BA.2.75 (4.9%)
- XBB recombinant (3.6%)
- Omicron CH.1.1 (19.5%)
- XBB.1.5 (V-23JAN-01) (4.5%)

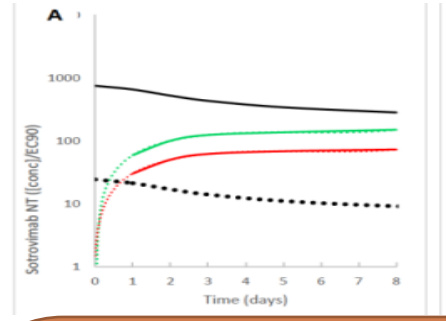
Predicting change in currently circulating variants limited only to the ‘near future’ (1-2 months)

Source: UKHSA Technical briefing 49 (11 January 2023). Variant prevalence (Page 4).

Conceptual framework for decision-making







IVAG

Epidemiology – currently circulating variants

In vitro neutralisation of drugs in reference variant from RCT vs. current variants

Yes

Data in people
Pharmacokinetic PK
Pharmacodynamics
PD

No

No neutralisation – likely no clinical effect

NICE TA committee

Clinical outcome e.g. infection rate + hospitalisation

Cost-utility analysis QALY benefit, costs

Decision

◉ *trial data and observational data*

NICE

Non-randomised evidence consideration

- Companies, patient and professional organisations suggest committee should take account of non-randomised (observational/real world) evidence.
- Non-randomised evidence presented during consultation has not been quality assessed.
- The AG and a recent peer reviewed paper highlight the challenges of using non-randomised studies for COVID-19:
    - Hill and Mirchandani 2022 compared outcomes of RCTs with non-randomised studies for 6 COVID-19 treatments (including remdesivir and molnupiravir). Statistically significant benefits were observed in non-randomised studies and not the RCTs. The paper questions the validity of non-randomised studies when it contradicts the outcomes from RCTs and cautions against its use.
- Consultation comments state that despite confounding bias commonly associated with non-randomised studies, the OpenSAFELY study should be considered because the authors have used well tested methodologies to remove such bias from their analysis.

AG, Assessment group; RCT, Randomised controlled trials

Latest OpenSAFELY data

Analyses conducted within the OpenSAFELY platform - consists of primary-care database, covers 40% of English GP practices. Data linked to multiple national databases (includes UK Renal Registry (UKRR)).

Sotrovimab shows lower risk of severe outcomes than molnupiravir:

- Dec 2021-Feb 2022: (Hazard ratio (HR) 0.54, 95% CI 0.33-0.88, P=0.01). Similar results seen for BA.2 analysis.
- Advanced renal kidney diseases: (HR=0.35, 95% CI: 0.17-0.71; P=0.004). No key differences in effect estimates between earlier and later time periods.

BA.2 and BA.5 eras: No evidence of a difference in all-cause hospitalisation or death between sotrovimab and nirm/rit groups (HR 0.89 95% CI 0.67-1.18)

Table: 30-day COVID-19 hospital admission rate

	Untreated but eligible group rate % (number/total)	Untreated but eligible group without contraindications to nirm/rit
Entire study period (Dec 16, 2021 to Oct 1, 2022)	2.41% (2343 / 97226)	1.37% (733 / 53357)
BA.2: (Feb 11, 2022 to May 31, 2022)	2.23% (868 / 38839)	1.25% (262 / 20908)
BA.5: (June 1, 2022 to Oct 1, 2022)	2.93% (650 / 22198)	1.84% (203 / 11010)
UKRR 2021 cohort (note: majority not eligible for nirm/rit): Dec 16, 2021 to Sep 1, 2022	4.15% (213 / 5137)	-

Source: OpenSAFELY authors provided hospitalisation data Nirm/rit, Nirmatrelvir plus ritonavir . 1. Comparative effectiveness of sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised patients on kidney replacement therapy: observational cohort study using the OpenSAFELY-UKRR linked platform and SRR database | medRxiv 2. https://www.bmj.com/content/379/bmj-2022-071932 3. https://www.medrxiv.org/content/10.1101/2023.01.20.23284849v1.full.pdf

Key issues

Issue	ICER impact
Consideration of *in vitro* evidence for neutralising monoclonal antibodies	Large / Unknown

Challenges with limited treatment options for the high-risk population:
• Should the hospitalisation rates be reconsidered based on newer evidence?
• Is nirm/rit cost effective in a broader high-risk group?
• Are any of the alternative treatments clinically effective and cost effective?
  • Molnupiravir evidence from PANORAMIC trial – Is the evidence generalisable to the high-risk population as defined by the McInnes report?
  • Should evidence from tix/cil treatment within 5 days of symptom onset be considered?
	Large

Challenges with treatment gaps in the hospital setting: • Consideration of remdesivir evidence - Should NMA include SOLIDARITY trial evidence? • Were the conclusions regarding role of antiviral biological plausibility in the hospital setting clinically relevant?	Large
No treatment options recommended in children: • Are any of the licensed treatments effective and cost effective for children?	Unknown

NMA, Network meta-analysis; Nirm/rit, Nirmatrelvir plus ritonavir, Tix/cil, tixagevimab plus cilgavimab

Key issue: Challenges with limited treatment options for the high-risk population

Background

- Committee defined high-risk using the McInnes report. One overall high-risk population was modelled.
- Hospitalisation rate was considered to be between 0.77% (PANORAMIC) and 2.79% (Discover now dataset)
- To consider age as an independent risk factor, committee requested evidence where the outcomes were adjusted by comorbidity. Supplementary evidence was provided by the companies.
- Committee was only able to recommend nirm/rit for the high-risk population which results in a treatment gap for people who are at increased risk of severe COVID-19 and contraindicated to nirm/rit.

Consultation comments

- Companies reported a range of recent hospitalisation rates
- Nirm/rit should be considered in a broader high-risk population.
- Requests for a separate highest risk group who are contraindicated to nirm/rit. Strong preference from most stakeholders for sotrovimab to be made available as the alternative treatment option for nirm/rit contraindicated population.
- Molnupiravir evidence for highest risk group excluding PANORAMIC

Nirm/rit, Nirmatrelvir and ritonavir; Tix/cil, Tixagevimab and cilgavimab

Hospitalisation rates:

Company	Hospitalisation rate suggestions
GSK (Targeted review) Mostly Omicron rates	Preferred: 4.51% (Krutikov 2022 – long term care residents) Other rates (population): 0% (Hemodialysis), 7.69% (chronic lymphocytic leukemia), 20.83% (Kidney transplant recipients), 26.42% (Hematological malignancy)
Pfizer	Patel 2022 (Discover dataset)
AstraZeneca	Lower bound: 5.48% Upper bound: 15.9% (Shields 2022)
MSD (Clinical feedback)	7%-8% (cannot mount immune response) 3%-5% (all other high-risk groups)

Patel 2022: Pre-print of interim DISCOVER-NOW database previously considered by committee. People with high-risk of disease progression receiving sotrovimab, oral antivirals or no treatment in England (North-West London), 1st December 2021 to 31st May 2022. Untreated rates:

- COVID-19 related hospitalisations: 2.8% 95% CI (2.3%-3.3%)
- Advanced renal diseases: 4.4% (3.0%-5.8%)
- BA.5: 1.8%, (0.8%-2.8%)
- BA.1: 3.2% (2.5%-3.9%)
- BA.2: 2.1% (1.3%-2.9%)

- DG 3.14: Significant uncertainty in estimating hospitalisation rate for the population who have high-risk of severe COVID-19.
- Based on strength of evidence rate was likely between the underestimate of PANORAMIC at 0.77% and 2.79% from the interim DISCOVER-NOW database analysis.

CI, Confidence interval

Example of risk group split
Patel 2022:

Highest-risk conditions	High-risk conditions
Down's syndrome	Age ≥70 years
Solid cancer	Long-term respiratory conditions
Haematological disease and stem cell transplant recipients	Chronic heart disease
Advanced renal disease	Chronic kidney disease
Liver disease	Chronic liver disease
IMID	Chronic neurological condition
Immune deficiencies	Diabetes
HIV/AIDS	Weakened immune system caused by medical condition or medication
Solid organ transplant	Obesity (class III)
Rare neurological conditions	Pregnancy
	Severe respiratory conditions
	Rare disease and inborn errors of metabolism

IMID, Immune-mediated inflammatory diseases;
Tix/cil, Tixagevimab and cilgavimab

CADTH tier system example specific to tix/cil:

Table 1: Prioritization of Patient Treatment With Mild to Moderate COVID-19 With Tixagevimab and Cilgavimab (Evusheld) Based on a Tiered Risk Group Approach

Tier	Risk group
1	Immunocompromised[a] individuals (≥ 12 years of age weighing at least 40 kg) who are not expected to mount an adequate immune response to SARS-CoV-2 infection.
2	Individuals who are at increased risk for progression to severe disease, which includes individuals with **all** the following risk factors: • age ≥ 70 years • presence of ≥ 2 comorbidities[b] • ≥ 12 weeks since the most recent of SARS-CoV-2 vaccine doses[c] or SARS-CoV-2 infection.
3	Individuals who are at increased risk for progression to severe disease, which includes individuals with **at least 1** of the following risk factors: • age ≥ 70 years • presence of ≥ 2 comorbidities[b] • ≥ 12 weeks since the most recent of SARS-CoV-2 vaccine doses[c] or SARS-CoV-2 infection.

DG 3.6: Committee recognised limitations of the model in characterising a group at high-risk but considered hospitalisation rate to be the most important variable for sensitivity to the clinical inputs. A wider definition of risk in PANORAMIC was included in the marketing authorisations for each of the treatments. The McInnes report's definition of high-risk included the most robust evidence of people who have a high-risk for progressing to severe COVID-19

High-risk population	PANORAMIC	McInnes report	JCVI[6]
Down's syndrome and other genetic disorders	✓	✓	✓
Solid cancer		✓	
Haematological diseases and recipients of haematological stem cell transplant (HSCT)	✓	✓	✓
Renal disease	✓	✓	✓
Liver diseases	✓	✓	✓
Solid organ transplant recipients	✓	✓	
Immune-mediated inflammatory disorders		✓	✓
Immune deficiencies	✓	✓	✓
HIV/AIDS		✓	✓
Rare neurological and severe complex life-limiting neuro-disability conditions	✓	✓	✓
Chronic respiratory disease	✓		✓
Chronic heart or vascular disease	✓		✓
Chronic neurological disease	✓		✓
Severe and profound learning disability	✓		✓
Diabetes mellitus (Type I or Type II)	✓		✓
Morbid obesity (BMI > 35)	✓		✓ (≥ 40)
Severe mental illness	✓		✓
Care home resident	✓		✓
Judged to be clinically vulnerable	✓		
Age ≥ 50 years	✓		✓
Pregnancy			✓
Carers*			✓
Household contacts of people with immunosuppression			✓
Frontline healthcare and social care workers			✓

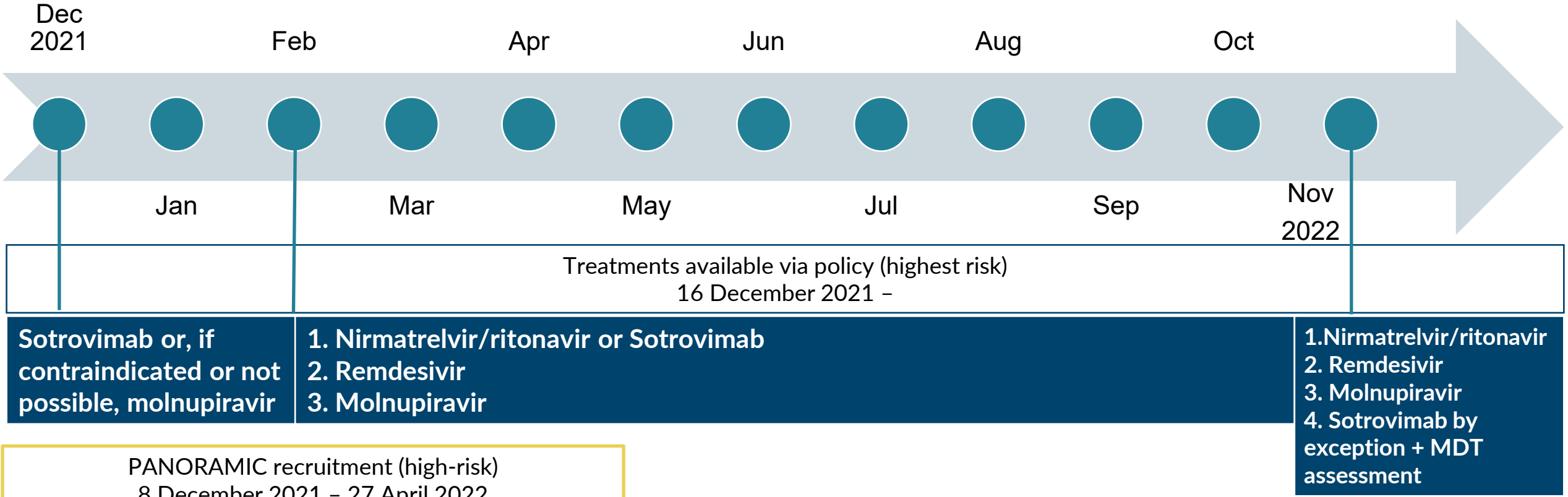
Pfizer Appendix 1: Comparison of 'high-risk' definitions

Table shows comparison between patient groups included in the PANORAMIC trial, McInnes report and JCVI 'high-risk' definitions

Committee will consider cost-effectiveness results with different hospitalisation rates as a proxy for the broader high-risk group

JCVI, The Joint Committee on Vaccination and Immunisation

Timeline of community treatment policies, PANORAMIC recruitment and OpenSAFELY data



PANORAMIC recruitment (high-risk)
8 December 2021 – 27 April 2022

OpenSAFELY 1 (highest-risk)
16 Dec 2021 – 10 Feb 2022

OpenSAFELY 2 (highest-risk)
16 December 2021 – 1 October 2022

MDT, Multidisciplinary team

Molnupiravir evidence from PANORAMIC trial

- COVID-NMA has included the PANORAMIC trial for molnupiravir. The AG have used this updated meta-analysis in their base case.
- Consultation comments suggest that based on non-randomised (real world) evidence higher risk groups were offered molnupiravir, while lower risk groups were offered nirmatrelvir plus ritonavir or standard care.
- The PANORAMIC trial does not reflect the higher risk groups who would have been offered treatment via COVID Medicines Delivery Units. Exclusion of PANORAMIC trial from molnupiravir's meta-analysis should be considered.

Table: Molnupiravir meta-analysis outcomes without and with the PANORAMIC trial

	Hospitalisation or death (RR [95% CI])	All cause mortality (RR [95% CI])
Without PANORAMIC	0.68 [0.50, 0.94]	0.19 [0.04,0.86]
With PANORAMIC	0.80 [0.56 – 1.15]	0.27 [0.09 – 0.82]

Source: 1. Final post-submissions AG report (Table 5) 2. Table 1 Post-DG consultation AG report

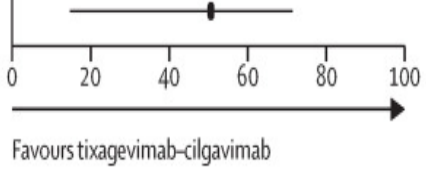
AG, Assessment group; CI, Confidence interval; RR, relative risk

Additional evidence for tixagevimab and cilgavimab

Tix/cil is more clinically effective when offered within 5 days of symptom onset compared with 7 days

Figure: Relative risk (RR) reduction of severe COVID-19 or death from any cause up to day 29

Time from symptom onset to random assignment	Number of participants with event: Tixagevimab–cilgavimab, n/N (%)	Number of participants with event: Placebo, n/N (%)	RR reduction (95% CI)
≤1 day	0/6	0/6	NE (NE)
≤2 days	0/29	3/34 (9%)	100% (NE)
≤3 days	1/90 (1%)	8/84 (10%)	88·0% (9·4–98·4)
≤4 days	4/172 (2%)	17/157 (11%)	78·4% (37·4–92·6)
≤5 days	9/253 (4%)	27/251 (11%)	66·9% (31·1–84·1)
≤6 days	11/329 (3%)	32/345 (9%)	64·1% (29·9–81·6)
≤7 days	18/407 (4%)	37/415 (9%)	50·5% (14·6–71·3)



Source: 1. Figure 2B - Montgomery 2022 (Lancet Respir Med. 2022 Oct; 10(10): 985–996.) 2. Post-DG consultation AG report (Section 3.2)

- Company would like tix/cil to be positioned as a treatment option offered within 5 days of symptom onset for people with contraindications for nirmatrelvir plus ritonavir.
- From the TACKLE trial, company provided unpublished outcomes for RR of hospitalisation or death 0.31 (95% CI 0.15 to 0.64), calculated mean value of 0.33, and RR of all-cause mortality at 28 days of 0.33 (95% CI 0.03 to 3.15), calculated mean value of 0.67.
- Committee will consider a scenario with the updated inputs

MA, Marketing authorisation; RR, Relative risk; Tix/cil, Tixagevimab and cilgavimab

Key issue: Challenges with limited treatment options for the high-risk population

AG response

- For the base case hospitalisation the preprint published for the Discover dataset was used (Patel 2022: 2.8%)
- Alternative scenarios were run using 0.77%, 1%, 1.5%, 5%, 10% and 20% hospitalisation rates. Provides an option to consider alternative high-risk population levels.
- Scenario run for tix/cil using clinical efficacy evidence of treatment within 5 days of symptom onset

In order to address this issue, the committee need to answer the following questions:

- ✓ Is there a case for splitting the high-risk group into 'highest-risk' and 'high-risk'?
- ✓ Revisiting hospitalisation rates with newer evidence – Should the rates be reconsidered split by these two groups?
- ✓ Broader high-risk population for nirm/rit – is it cost effective in a broader group?
- ✓ Are any of the alternatives clinically effective and cost effective?
  - ✓ Molnupiravir evidence from PANORAMIC trial – Is the evidence generalisable to the high-risk population as defined by the McInnes report?
  - ✓ Should evidence for tix/cil treatment within 5 days of symptom onset be considered?

Nirm/rit, Nirmatrelvir and ritonavir; Tix/cil, Tixagevimab and cilgavimab

Key issues

Issue	ICER impact
Consideration of *in vitro* evidence for neutralising monoclonal antibodies	Large / Unknown

Challenges with limited treatment options for the high-risk population:
• Should the hospitalisation rates be reconsidered based on newer evidence?
• Is nirm/rit cost effective in a broader high-risk group?
• Are any of the alternative treatments clinically effective and cost effective?
  • Molnupiravir evidence from PANORAMIC trial – Is the evidence generalisable to the high-risk population as defined by the McInnes report?
  • Should evidence from tix/cil treatment within 5 days of symptom onset be considered?
	Large

Challenges with treatment gaps in the hospital setting: • Consideration of remdesivir evidence - Should NMA include SOLIDARITY trial evidence? • Were the conclusions regarding role of antiviral biological plausibility in the hospital setting clinically relevant?	Large
No treatment options recommended in children: • Are any of the licensed treatments effective and cost effective for children?	Unknown

NICE

NMA, Network meta-analysis; Nirm/rit, Nirmatrelvir plus ritonavir, Tix/cil, tixagevimab plus cilgavimab

Key issue: Challenges with treatment gaps in the hospital setting

Background

- No treatments recommended for people in hospital without supplemental oxygen needs.
- Role of antivirals considered limited as mechanism of action blocks viral replication and cannot control inflammation. Expected to work more effectively before onset of hyperinflammatory stage associated with hospitalisation which could impact relative treatment effect. Low efficacy scenario considered for remdesivir.
- SOLIDARITY trial is an early study excluded from COVID-NMA, no clinical evidence available on remdesivir in vaccinated Omicron era. Committee stated all available evidence be considered if possible.

Consultation comments

- Statements on the role and reduced clinical efficacy of antivirals in hospital setting critiqued
- Antivirals may be important in immuno-suppressed/compromised
- Relevant in children who may not reach hyperinflammatory phases as older age groups
- Less severe, people with high comorbidity burden are presenting in hospitals in need of early treatment. Creates a role for antivirals in the hospital setting
- SOLIDARITY study should be included for the remdesivir NMA. Time to discharge data from ACTT-1 study for remdesivir should be included. Inconsistency in how remdesivir evidence was considered. Trial settings for remdesivir similar to other treatments (prior to vaccination/Omicron), yet final efficacy conclusions different.

NICE

NMA, Network meta-analysis

COVID-NMA WITHOUT AND WITH SOLIDARITY (total population)

Figure: NMA without SOLIDARITY (WHO 2022), hazard ratio of time to death

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Beigel 2020	-0.3147	0.1731	77.3%	0.73 [0.52, 1.02]	2020
Spinner 2020	-0.4463	0.5686	7.2%	0.64 [0.21, 1.95]	2020
Wang 2020	0.1044	0.3869	15.5%	1.11 [0.52, 2.37]	2020
WHO 2022	-0.1508	0.0631	0.0%	0.86 [0.76, 0.97]	2022
Total (95% CI)			**100.0%**	**0.77 [0.57, 1.04]**	

Heterogeneity: Chi² = 1.09, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)

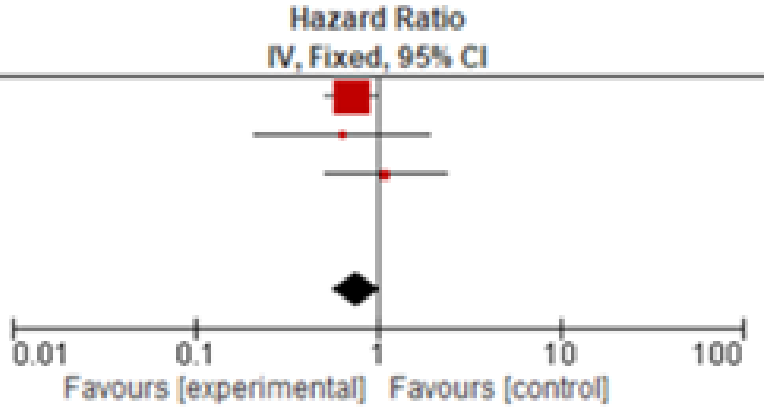
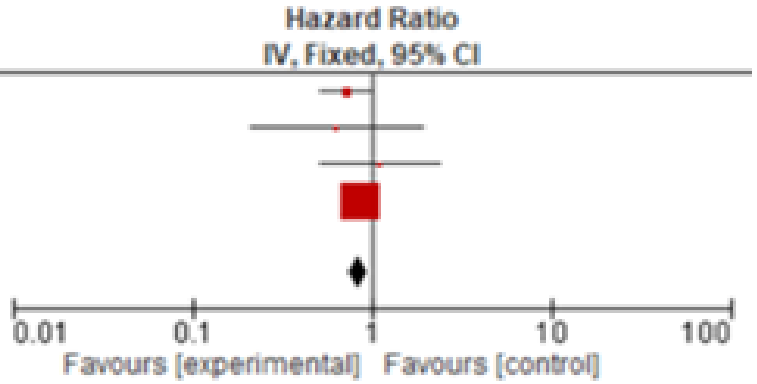


Figure: NMA with SOLIDARITY (WHO 2022), hazard ratio of time to death

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Beigel 2020	-0.3147	0.1731	11.3%	0.73 [0.52, 1.02]	2020
Spinner 2020	-0.4463	0.5686	1.1%	0.64 [0.21, 1.95]	2020
Wang 2020	0.1044	0.3869	2.3%	1.11 [0.52, 2.37]	2020
WHO 2022	-0.1508	0.0631	85.3%	0.86 [0.76, 0.97]	2022
Total (95% CI)			**100.0%**	**0.85 [0.76, 0.95]**	

Heterogeneity: Chi² = 1.53, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



- Inclusion of SOLIDARITY results in a smaller but a statistically significant mortality benefit for remdesivir compared with best supportive care
- Committee will consider a scenario with the updated NMA with SOLIDARITY

Source: Gilead amended meta-analysis (06.01.2023), https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00519-0/fulltext#figures

NMA, Network meta-analysis

SOLIDARITY trial

WHO Solidarity Trial Consortium – May 2022

Data collected from 454 hospitals across 35 countries between 22 March 2020 and 29 January 2021. Recruitment started before predominance of omicron variants (and widespread vaccination). Best supportive care differences across the countries.

- The hazard ratio (HR) of time to death from SOLIDARITY = 0.86 (95% CI 0.76 to 0.97)

The AG used the meta-analysis for the overall population (combining no oxygen at entry and needing oxygen and not ventilated) estimate supplied by the company: HR of 0.85 (95% CI 0.76 to 0.95).

- Mean efficacy value = 0.85
- High efficacy value = 0.76
- Low efficacy value = 0.95

Should the SOLIDARITY trial be included in the NMA?

Source: Gilead amended meta-analysis (06.01.2023), https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00519-0/fulltext#figures

Remdesivir clinical evidence summary from other sources

Evidence quality considered weak

NICE COVID-19 rapid guideline: Managing COVID-19 V27.7 (04 Jan 2023): Conditional recommendations

- High-risk of progression: PINETREE trial used for recommendations. Certainty of all outcomes from PINETREE was downgraded because of indirectness. Trial was prior to Delta, Omicron, unvaccinated era.
- In hospital with low-flow oxygen needs: Ten randomised controlled trials (includes WHO-SOLIDARITY) and 1 systematic review. For outcomes relevant to the benefit of remdesivir treatment (including all-cause mortality, need for mechanical ventilation, need for oxygen supplementation, clinical recovery, duration of hospital stay, discharge from hospital, oxygen-free days, ventilator-free days, time to improvement and time to recovery), certainty of evidence was very low to moderate.

A living WHO guideline on drugs for covid-19 | The BMJ

- People with non-severe COVID-19: Low to moderate - weak evidence quality - Recommended
- People with severe COVID-19: Low to moderate - weak evidence quality - Recommended
- People with critical COVID-19: Low to very low - no important difference in outcomes versus supportive care - Not recommended

Key issue: Challenges with treatment gaps in the hospital setting

AG response

- Additional evidence consideration for remdesivir:
  - A scenario where HR of time to death was included from the SOLIDARITY trial in the NMA
  - A scenario with time to discharge using data from ACTT-1

- ✓ Consideration of remdesivir evidence - Should the NMA include SOLIDARITY trial?
- ✓ Were the conclusions regarding role of antiviral biological plausibility in the hospital setting clinically relevant?
- ✓ Should alternative efficacy assumptions be considered for remdesivir for the hospital setting?

HR, Hazard ratio; NMA, Network meta-analysis

Key issues

Issue	ICER impact
Consideration of *in vitro* evidence for neutralising monoclonal antibodies	Large / Unknown

Challenges with limited treatment options for the high-risk population:
• Should the hospitalisation rates be reconsidered based on newer evidence?
• Is nirm/rit cost effective in a broader high-risk group?
• Are any of the alternative treatments clinically effective and cost effective?
  • Molnupiravir evidence from PANORAMIC trial – Is the evidence generalisable to the high-risk population as defined by the McInnes report?
  • Should evidence from tix/cil treatment within 5 days of symptom onset be considered?
	Large

Challenges with treatment gaps in the hospital setting: • Consideration of remdesivir evidence - Should NMA include SOLIDARITY trial evidence? • Were the conclusions regarding role of antiviral biological plausibility in the hospital setting clinically relevant?	Large
No treatment options recommended in children: • Are any of the licensed treatments effective and cost effective for children?	Unknown

NICE

NMA, Network meta-analysis; Nirm/rit, Nirmatrelvir plus ritonavir, Tix/cil, tixagevimab plus cilgavimab

Key issue: No treatment options recommended in children

Background

- Remdesivir licensed in children (at least 4 weeks of age and weighing at least 3 kg [severe COVID-19] or weighing at least 40 kg [high-risk of severe COVID-19])
- Sotrovimab licensed in younger people (aged 12 years and over and weighing at least 40 kg)
- Casirivimab plus imdevimab licensed in younger people (aged 12 years and over) – *MA is not clear
- The model considered a starting age of 55 years

Consultation comments

- Limited consideration of the needs of individuals under 18 years in this guidance
- The high-risk population definition excludes children
- Children present with less severe outcomes and are in more need of antivirals in the hospital setting

MA, Marketing authorisation

Key issue: No treatment options recommended in children

The DG recommendations for children are aligned with the McInnes report

Limited evidence availability from RCTs with small sample size and low event rates. Challenging to estimate the risk versus the benefits in this population.

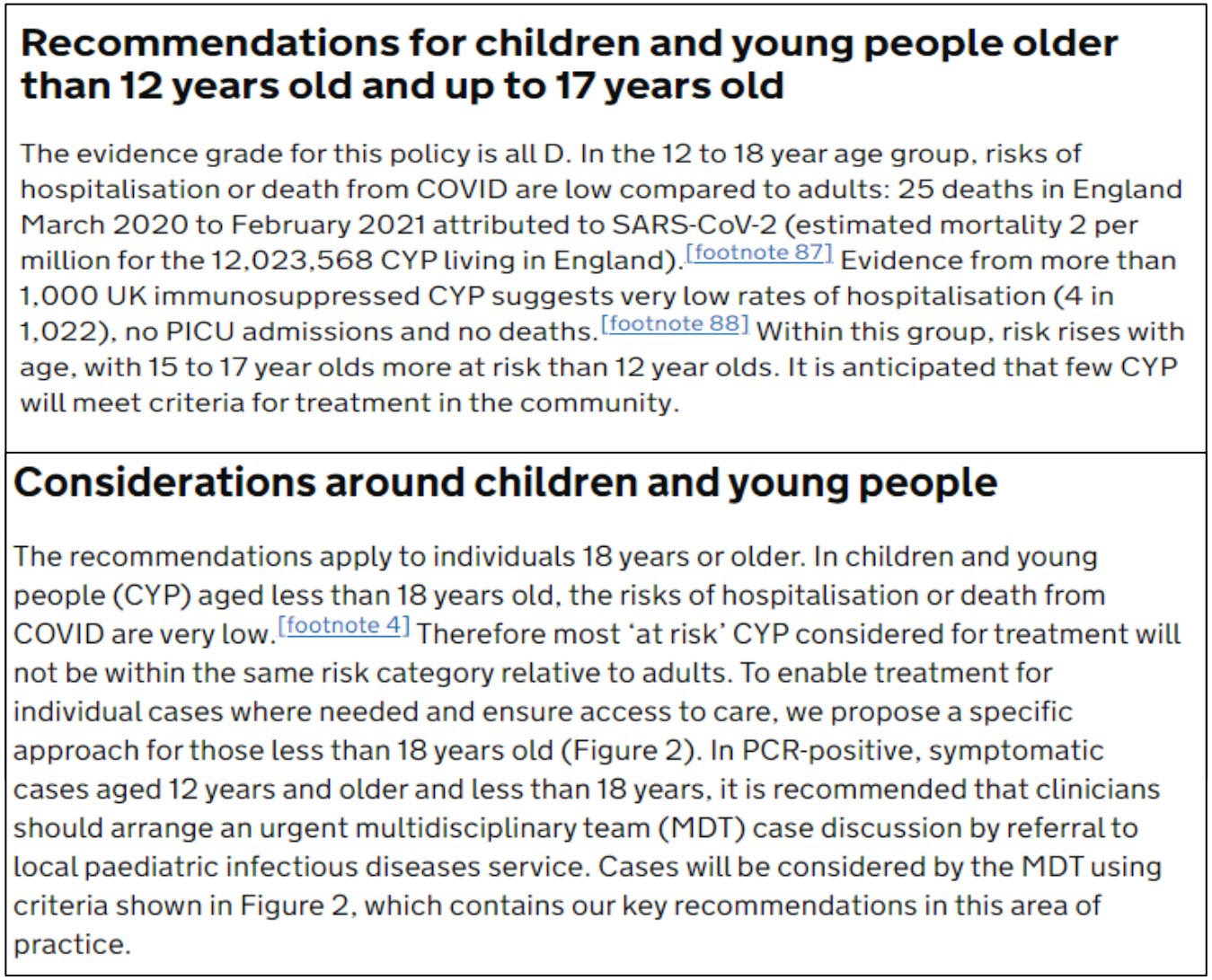
If a treatment is not cost effective for adults (18 and over), modelling children (4 weeks and over) and younger people (12 years and over) separately likely not to be cost effective:

- Baseline hospitalisation rates are very low
- Baseline risk of mortality will be lower

Are any of the licensed treatments clinically and cost-effective for children?

DG, Draft guidance, RCT, Randomised controlled trials

Figure: Additional considerations based on McInnes report overview



Recommendations for children and young people older than 12 years old and up to 17 years old

The evidence grade for this policy is all D. In the 12 to 18 year age group, risks of hospitalisation or death from COVID are low compared to adults: 25 deaths in England March 2020 to February 2021 attributed to SARS-CoV-2 (estimated mortality 2 per million for the 12,023,568 CYP living in England).[footnote 87] Evidence from more than 1,000 UK immunosuppressed CYP suggests very low rates of hospitalisation (4 in 1,022), no PICU admissions and no deaths.[footnote 88] Within this group, risk rises with age, with 15 to 17 year olds more at risk than 12 year olds. It is anticipated that few CYP will meet criteria for treatment in the community.

Considerations around children and young people

The recommendations apply to individuals 18 years or older. In children and young people (CYP) aged less than 18 years old, the risks of hospitalisation or death from COVID are very low.[footnote 4] Therefore most 'at risk' CYP considered for treatment will not be within the same risk category relative to adults. To enable treatment for individual cases where needed and ensure access to care, we propose a specific approach for those less than 18 years old (Figure 2). In PCR-positive, symptomatic cases aged 12 years and older and less than 18 years, it is recommended that clinicians should arrange an urgent multidisciplinary team (MDT) case discussion by referral to local paediatric infectious diseases service. Cases will be considered by the MDT using criteria shown in Figure 2, which contains our key recommendations in this area of practice.

Source: Higher-risk patients eligible for COVID-19 treatments: independent advisory group report

Key issues

Issue	ICER impact
Consideration of *in vitro* evidence for neutralising monoclonal antibodies	Large / Unknown

Challenges with limited treatment options for the high-risk population:
• Should the hospitalisation rates be reconsidered based on newer evidence?
• Is nirm/rit cost effective in a broader high-risk group?
• Are any of the alternative treatments clinically effective and cost effective?
  • Molnupiravir evidence from PANORAMIC trial – Is the evidence generalisable to the high-risk population as defined by the McInnes report?
  • Should evidence from tix/cil treatment within 5 days of symptom onset be considered?
	Large

Challenges with treatment gaps in the hospital setting: • Consideration of remdesivir evidence - Should NMA include SOLIDARITY trial evidence? • Were the conclusions regarding role of antiviral biological plausibility in the hospital setting clinically relevant?	Large
No treatment options recommended in children: • Are any of the licensed treatments effective and cost effective for children?	Unknown

NICE

NMA, Network meta-analysis; Nirm/rit, Nirmatrelvir plus ritonavir, Tix/cil, tixagevimab plus cilgavimab

Overview of changes to model and ACM1 assumptions

AG model update after DG consultation:

- ✓ Updated data from COVID-NMA
- ✓ Amendment to the code related to clinical improvement
- ✓ Capping efficacy values in the low efficacy scenario so that the treatments do not harm patients

Change	Updated values in bold
Increasing hospitalisation rates	2.79% vs **2.82%**
Increasing hospitalisation cost	ordinal scale 4 (£563 vs **£759**) ordinal scale 5 (£828 vs **£1,166**)
Increasing average duration of long Covid	Mean of lognormal distribution of 108.6 weeks to **113.6 weeks**). • 30% of people still have symptoms at 2 years, 10% at 5 years and 3% at 10 years
Increasing long Covid costs	(£1,013 vs **£2,267** per year)

Committee's ACM1 preferred assumptions:

- ❖ Community: Hospitalisation rate: ~1.5% (ranges 0.77% - 2.79%)
- ❖ Hospital: HR = 1 for time to discharge and clinical improvement at 28 days

Technology (efficacy assumption)
Nirmatrelvir plus ritonavir (mean to low/low)
Tocilizumab (mean)
Baricitinib (mean)
Casirivimab plus imdevimab (Limited/no efficacy)
Molnupiravir (low)
Sotrovimab (low)
Remdesivir (low) – Hospital setting
Tixagevimab plus cilgavimab (low)

NICE

ACM1, Appraisal committee meeting 1; AG, Assessment group; DG, Draft guidance; HR, Hazard ratio

Baricitinib

Withdrawal of application from European Medicines Agency (EMA)

On 7 December 2022 Eli Lilly withdrew its application for an extension to the marketing authorisation for baricitinib in the treatment of people in hospital with COVID-19. The application was withdrawn based on EMA's opinion on the clinical evidence of baricitinib.

- EMA considered that the evidence submitted by the company did not conclusively demonstrate that the medicine provides meaningful benefits to patients. At the time of the withdrawal, the Agency's opinion was that the benefit/risk balance of baricitinib was negative.
- Evidence submitted by company: 3 studies in people hospitalised with COVID-19.

Note: Committee considered the same studies for baricitinib:

- Kalil 2020 (ACTT-2 – 1033 patients)
- Marconi 2021 (COV-BARRIER – 1500 patients),
  - Ely 2022 (exploratory study of COV-BARRIER – 101 patients),
- Horby 2022 (RECOVERY – 8000 patients)

What did the company present to support its application?

The company presented the results from three studies in patients hospitalised with COVID-19.

In one study, around 1,000 patients were given Olumiant or placebo (a dummy treatment), in combination with remdesivir (an antiviral medicine used to treat COVID-19). The main measure of effectiveness was the time it took patients to recover. In another study, about 1,500 patients received Olumiant or placebo. This study investigated if the medicine prevented worsening of disease or death. A third study in over 8,000 patients compared treatment with Olumiant and placebo and looked at prevention of death.

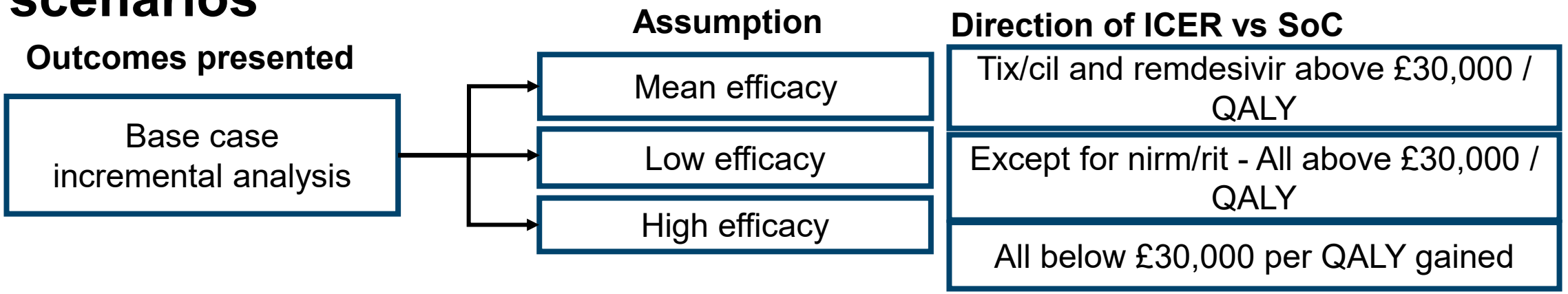
Source: 1. https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/olumiant 2. Final post-submissions AG report (Appendix 1, Table 24)

Cost-effectiveness results

All ICERs are reported in PART 2 slides
because they include:

- confidential list prices for casirivimab/imdevimab, molnupiravir, and tixagevimab/cilgavimab
- Patient Access Scheme prices for baricitinib, tocilizumab, sotrovimab and tixagevimab/cilgavimab

Community setting: Cost-effectiveness base case outcomes and scenarios

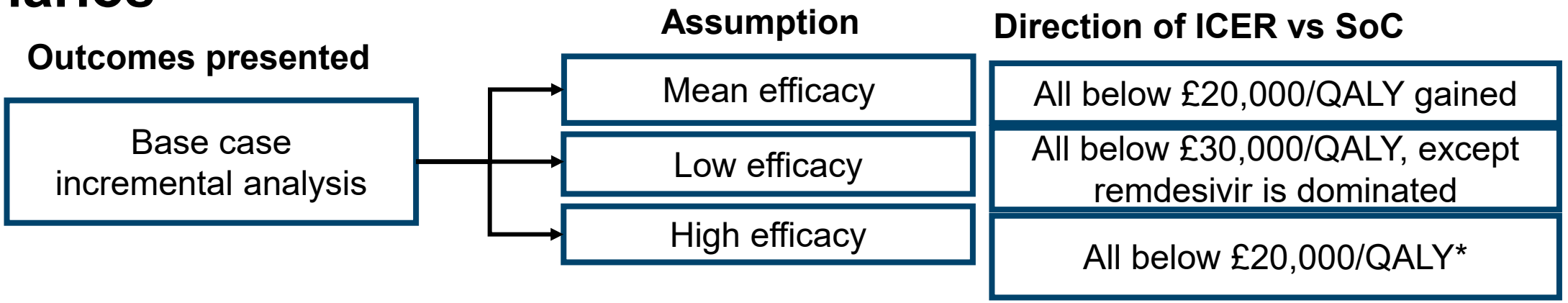


Scenarios applied to mean base case efficacy	Base case value	Direction of ICER vs SoC
0.77%, 1.5% hospitalisation rate	2.8%	Large ++ increase for all
5%, 10%, 15%, 20% hospitalisation rate	2.8%	Large ++ decrease for all
5 day symptom onset clinical efficacy (tix/cil)	7 day symptom onset	Large ++ decrease for tix/cil
Average age in community 50years	55 years	Small decrease for all
Average age in community 60 years	55 years	Small-medium increase for most
Duration of Long-COVID halved	113.6 weeks	Small increase for most
Duration of Long-COVID doubled	113.6 weeks	Small-medium decrease for most
Utility decrement for IV administration	No decrement	Minor (~0.2%) increase for two interventions

ICER, Incremental cost-effectiveness ratio; IV, Intravenous; Nirm/rit, Nirmatrelvir and ritonavir

PP, per person; QALY, Quality adjusted life year; SoC, Standard of care, Tix/cil, Tixagevimab and cilgavimab ++ indicates substantial change

Hospital setting: Cost-effectiveness base case outcomes and scenarios



Scenarios applied to mean base case efficacy	Base case values	Direction of ICER vs SoC
HR = 1 for TTD and clinical improvement	See AG report	No change for some interventions to large increase for some
SOLIDARITY included for remdesivir NMA	SOLIDARITY excluded	Small increase
ACTT-1 included for TTD for remdesivir	ACTT-1 excluded	Large ++ decrease
Long-COVID duration (doubled)	113.6 weeks	Small to medium increase
Long-COVID duration (halved)	113.6 weeks	Small to medium decrease
Changing SMR for people with Long-COVID to 5	7.7	Small decrease
Changing SMR for people with Long-COVID to 10	7.7	Small increase

HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; PP, per person; QALY, Quality adjusted life year; SMR, Standardised mortality ratio; SoC, Standard of care; TTD, Time to discharge *For cas/imd in no supplemental oxygen setting costs are lower and QALYs are higher compared with SoC

Revisiting the equality issues identified (DG 3.24)

- **Disability**: The committee evaluated alternative treatments for people who cannot take nirmatrelvir plus ritonavir. These alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources
- **Race**: The committee noted nirmatrelvir plus ritonavir was contraindicated in people with hepatic and renal impairments. Prevalence of certain comorbidities including renal impairment are known to be higher in people from Black, Asian and other minority ethnic family backgrounds. Issue of prevalence cannot be resolved within a technology appraisal. Alternative treatments had substantially higher ICERs and were not considered a cost-effective use of NHS resources
- **Age**: The committee was mindful of excluding age from its recommendations because it is a protected characteristic. The committee did not consider there was enough evidence to support a relationship between specific age cut-off points alone (for example, adjusted for comorbidities) and a high-risk of progression to severe COVID-19.
- **Pregnancy and or maternity**: By recommending tocilizumab there is a risk of indirectly discriminating against people who are pregnant. The committee considered that in the context of the acute hospital setting, no other alternative treatments for treating hyperinflammation were included in the scope of this appraisal.

Committee conclusions on the equality issues (DG 3.25)

- The committee acknowledged and considered the contraindications of nirmatrelvir plus ritonavir and tocilizumab.
- It noted that this could affect some people with protected characteristics disproportionately which would contribute to health inequality.
- The committee said that in theory it would be willing to accept an ICER slightly more than what is usually acceptable if it addressed such health inequalities.
    - However, it noted that departing from NICE's usual range needs to be done with caution, as it risks displacing funding from more cost-effective treatments in NHS, with an overall net loss of health.

WHO update (13 January 2023):
“The use of nirmatrelvir-ritonavir, now considered to be an option also for pregnant and breastfeeding women with non-severe COVID-19”
Based on data from WHO global database of reported potential side effects

ICER, Incremental cost-effectiveness ratio

Overview of the day

Section	Data relevant to both appraisals	
1.1	SARS-CoV-2: variant tracking	Public
1.2	*In vitro* data	Public
1.3	Position of various organisations	Public

ID 4038	MTA of COVID-19 treatments	ACM 2
2.1	Community setting (mild COVID-19) – Part 1	Public
3.1	Hospital setting (severe COVID-19) – Part 1	Public
2.2	Community setting – Part 2	Private
3.2	Hospital setting – Part 2	Private

ID 6136	STA of tixagevimab/cilgavimab (Evusheld)	ACM 1
4.1	Prophylaxis in highly vulnerable people – Part 1	Public
4.2	Prophylaxis – Part 2	Private

NICE National Institute for Health and Care Excellence

Thank you.