Molnupiravir for treating COVID-19 (ID6340)

For screen – REDACTED

Technology appraisal committee C [11 February 2025]

Chair: Stephen O'Brien

External assessment group: Southampton Health Technology Assessments Centre

Company: Merck Sharp & Dohme

Molnupiravir (Lagevrio, Merck Sharp & Dohme)

Marketing authorisation	MHRA conditional marketing authorisation granted on 4 November 2021: "for the treatment of mild to moderate COVID-19 in adults with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness."
Mechanism of action	Molnupiravir is an antiviral that acts via a viral error catastrophe mechanism.
Administration	Oral capsules • 800mg twice daily for 5 days
Price	The list price is currently confidential *
* A purchase price of molnupiravir of £513.00 per course was reported in the cost-utility analysis of molnupiravir for high-risk, community-based adults with COVID-19: an economic evaluation of the PANORAMIC trial	

Abbreviations: MHRA: Medicines and Healthcare products Regulatory Agency

Committee conclusions at ACM1 on positioning

- People included in the McInnes criteria who cannot have either nirmatrelvir plus ritonavir or sotrovimab remain at increased risk of poor outcomes and have the greatest unmet need
- This population - the ‘highest unmet need’ population - is the most appropriate for decision making and more closely aligns with current NHSE interim commissioing policy
- But uncertain exactly how the subpopulation who can not have either treatment is defined
- Need to see:
    - clearer definition of this population, including why these treatments would be contraindicated or clinically unsuitable
    - evidence on the clinical effectiveness of molnupiravir in this population

Company's revised positioning after ACM1

Company

- Agree most appropriate position is for the highest unmet need population, approximately in line with use under the interim commissioning policy. Revise population to those:
  - ≥1 risk factors for progression to severe COVID-19 (definition: McInnes or **Edmunds**), and
  - Who are contraindicated to nirmatrelvir plus ritonavir, and
  - For whom sotrovimab is contraindicated, unfeasible or undesirable (e.g. in cases of complex comorbidities, haematological disease, severe kidney or liver disease, or difficulties accessing sotrovimab due to geographical location)

- Population with highest unmet need expected to be small - Hospital Pharmacy Audit data shows [redacted] courses of molnupiravir were prescribed in 2023 despite being available via NHSE commissioning policy

Including Edmunds criteria is broader than the interim commissioning policy and committee's conclusion at ACM1

McInnes is a subset of Edmunds

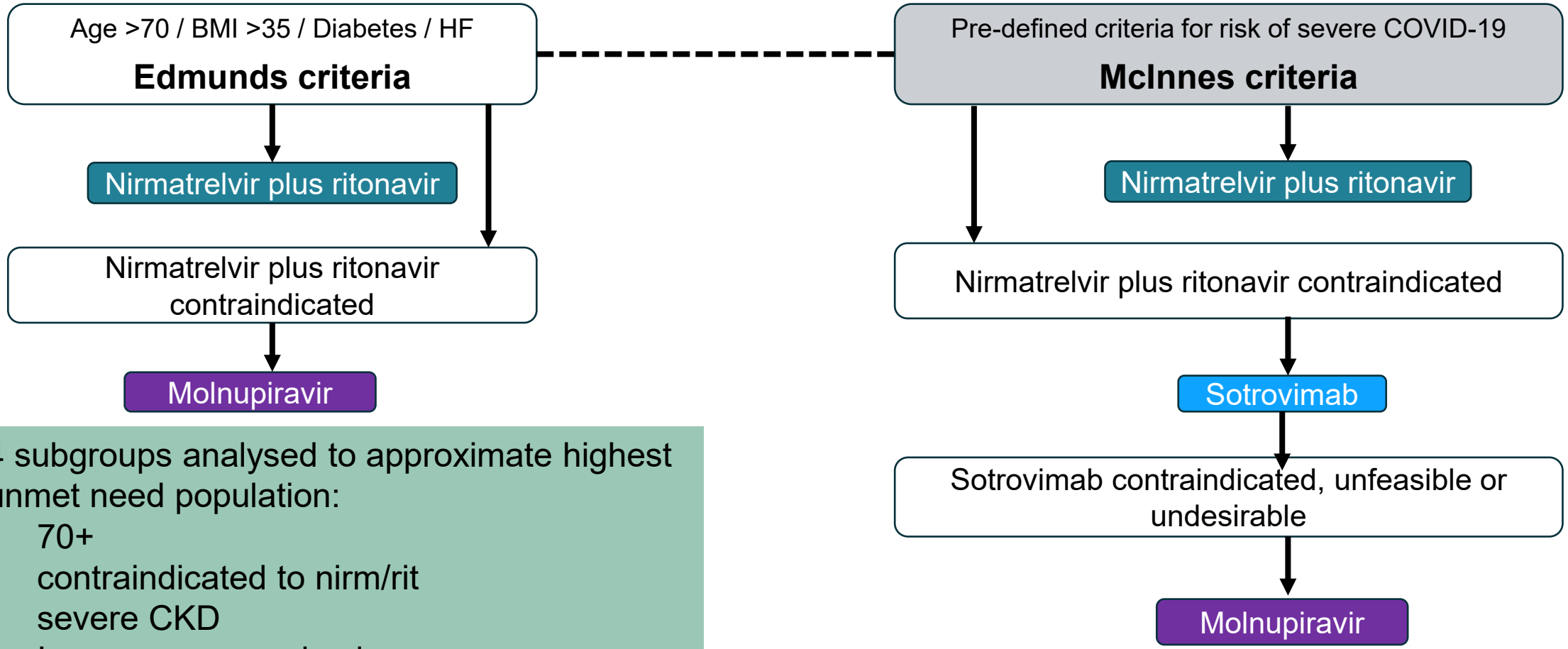
McInnes:

- Down's syndrome
- certain types of cancer including leukaemia
- certain conditions affecting the blood, such as sickle cell disease
- people who have had a stem cell transplant
- kidney disease
- liver disease
- people who have had an organ transplant
- conditions affecting the immune system, such as HIV or AIDS, inflammatory conditions or immunodeficiency
- respiratory disease
- conditions affecting the brain or nerves (MS, motor neurone disease, Huntington's disease etc).

* The full list of conditions is available in the independent advisory group report commissioned by the Department of Health and Social Care

Abbreviations: BMI: Body mass index; HF: Heart failure, MS; multiple sclerosis

Company's revised positioning after ACM1



4 subgroups analysed to approximate highest unmet need population:

- 70+
- contraindicated to nirm/rit
- severe CKD
- Immunocompromised

Comparator is no treatment in all subgroups

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Abbreviations: BMI: Body mass index; HF: Heart failure, CKD; chronic kidney disease

Responses from UKCPA and NHSE

UK Clinical Pharmacy Association

- Agrees there is an unmet need but also that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence
- Notes sotrovimab may be less effective than when it was recommended in TA878

NHSE

- Molnupiravir administration cost used in the cost effectiveness calculations are too low (£31.85)
- TA878 considered a range of administration costs for nirmatrelvir plus ritonavir from £117 to £410 and the same range should be considered in this evaluation.
- Data collection by NHSE from ICBs shows that the cost of the service delivery for oral COVID-19 antivirals so far in 2024/25 is [redacted]
- EAG has conducted scenario analyses using administration cost of £117 or £410 for molnupiravir

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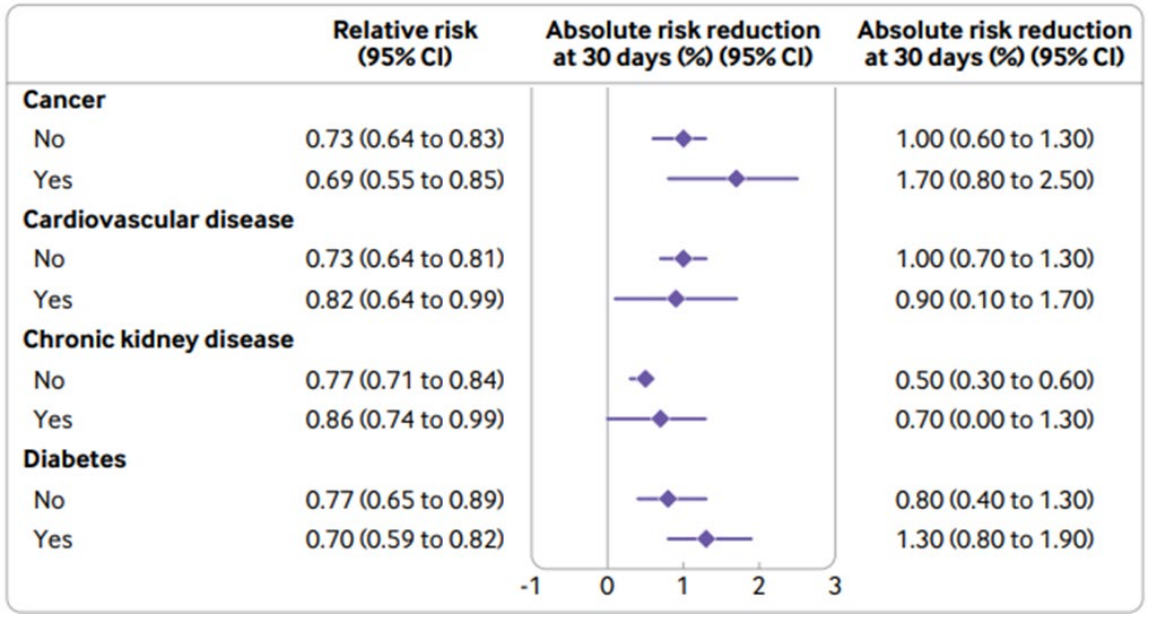
Effectiveness in revised population (1)
Company comments

- Current real-world use of molnupiravir is in patients at highest unmet need
- RWE NMA: molnupiravir clinically effective for patients who would otherwise remain untreated
    - statistically significant difference between molnupiravir and no treatment for:
        - all-cause hospitalisation - RR 0.79 [95% CrI: 0.66 to 0.92]
        - death - RR 0.31 [95% CrI: 0.21 to 0.46]
    - these relative effectiveness estimates can be used to inform cost-effectiveness
- Highlights Xie et al. (2023) - included in the RWE NMA and 1 new study Ahmad et al. (2024) an updated analysis of Arbel et al (2022), included in the RWE NMA

Abbreviations: RWE; real-world evidence, NMA; network meta-analysis; RR; relative risk, CrI; credible interval

Effectiveness in revised population (2)
Results of Xie and Ahmad

- **Xie** - 85,998 US COVID-19 patients (Jan-Sep 2022)
- 7,818 had molnupiravir, 78,180 had no treatment
- All patients had ≥1 risk factor for progression to severe COVID-19 (age >60, BMI>30, chronic lung disease, cancer, CVD, CKD and diabetes)



- **Ahmad** – 49,515 patients in Israel between 16 Jan 2022 - 16 Feb 2023
- 3,957 had molnupiravir, 19,785 were untreated
- All patients had ≥1 risk factor for progression to severe COVID-19 (age ≥60 years, BMI >30, chronic lung disease, cancer, CVD, CKD and diabetes) and were contraindicated to nirm/rit
- COVID-19-related hospitalisation or death:
  - 5.1 per 10,000 person/day for molnupiravir vs. 10.4 per 10,000 person/ day for no treatment - RR: 0.5; 95% CI: 0.39, 0.64
- All-cause mortality lower for molnupiravir:
  - 3.0 per 10,000 person/ day vs. no treatment: 6.1 per 10,000 person/ day - RR: 0.50; 95% CI: 0.36, 0.68

Abbreviations: BMI: Body mass index; CVD; cardiovascular disease, CKD; chronic kidney disease. RR; relative risk

Molnupiravir: COVID-19 evidence timeline

Randomised controlled trials (RCTs)

MOVe-OUT May-Oct 21

PANORAMIC Dec 21-Apr 22

WHO Public Health Emergency of International Concern – Jan 2020 to May 2023

2020 2021 2022 2023 2024

Real world evidence studies (RWE)[1, 2]

Tazare Dec 21-May 22*

Basoulis, Jan 22-Mar 23

Xie, Jan-Sep 22

Dryden-Peterson, Jan-Jul 22

Tiseo, Jan-Jul 22

Bajema, Jan-Jul 22

Arbel, Jan-Mar 22

Ahmed Jan 22- Feb 23

Manciulli, Jan-Mar 22

Schwartz, Apr-Aug 22

Cowman, Apr-Dec 22

Gentry, Jan-Feb 22

Kabore, Mar-Oct 22

Aggarwal, Mar-Aug 22

Zheng 2023, Feb-Nov 22

Paraskevis, Feb-Jul 22

Cegolon, Feb-May 22

Van Heer, Jul-Oct 22

Torti, Feb-Apr 22

[1] Only studies included in the RWE NMAs are shown here (see page 49 of EAR for more details)

[2] All studies included in the RWE NMAs were either retrospective or prospective cohort or case control design

* Tazare 2023, a UK study using OpenSAFELY data platform is not included in the company's RWE NMA

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EAR: External assessment report; NMAs: Network meta-analyses; WHO: World Health Organisation

Effectiveness in revised population (3)
EAG critique

- The company does not discuss whether the NMAs could be amended to focus on these high-risk subgroups to align with the company's definition of their highest unmet need and at-risk population.
- Both the Xie and Ahmad studies have uncertain relevance to the NHS and this limitation would also apply to any updated NMAs.
- Due to the lack of reporting of the company's methodology it is unclear whether further RWE studies with high-risk subgroups could be considered.
- Company's response broadly reiterates the existing clinical effectiveness evidence provided in their submission and does not specifically resolve the uncertainties relating to the RWE studies raised by the committee.

Abbreviations: RWE; real-world evidence, NMA; network meta-analysis

Hospitalisation rates in revised population
EAG critique

- COVID-19-related hospitalisation rates for patients aged over 70 years (12.84%) and for immunocompromised patients (22.47%) may be overestimates
    - estimates similar or higher than the hospitalisation rates reported in the MOVe-OUT trial which was conducted in the pandemic setting
- For immunocompromised patients, it is unclear whether the hospitalisation rates of untreated patients have changed significantly in the endemic setting, given the characteristics of these individuals (e.g., lower efficacy of the vaccines).
- Another issue with the estimates for immunocompromised patients is that the definition of immunocompromised patients is not consistent across the studies
- EAG tested the use of lower hospitalisation rates for these subgroups in scenario analyses:
    - 8% for the patients aged over 70 years and 15.9% for the immunocompromised patients, as reported by Shields et al. 2022
- Agree with the company's base case inputs for the other subgroups - around 4%

Hospitalisation rates in revised population

Difference in hospitalisation rate drives ICER difference

Highest-risk subgroup	COVID-19 related hospitalisation rate	RR All cause hospitalisation	Inc. QALYs	Inc. Costs	Company ICER
>70 years old	12.84% Kabore et al. 2023	0.71 RWE NMA	0.09	[redacted]	<£20K
Contraindicated to nirm/rit	4.0% Nirm/rit TA: 4% preferred as proxy for advanced renal disease		0.02	[redacted]	£20-30K
Immuno-compromised	22.47% Kabore et al. 2023 – severly immuno-compromised		0.19	[redacted]	Molnupiravir more effective, less costly
Severe CKD	4.4% Patel - DISCOVER NOW		0.02	[redacted]	£20-30K

In nirm/rit TA, committee concluded that the hospitalisation rate:

- for McInnes high-risk group is between 2.41% and 2.82% based on OpenSAFELY/DISCOVER-NOW.
- for people contraindicated to nirm/rit, 4% is an upper limit using advanced renal disease as a proxy

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Abbreviations: RWE; real-world evidence, NMA; network meta-analysis; RR; relative risk

Utility values
Company response

Utility values

- Accepts EAG value for general ward of 0.28 and a value of 0 for the ICU but used alternative utilities for the symptomatic outpatient health state and long COVID health state.
- Symptomatic outpatient - use UKHSA study (Sandmann et al 2021) - reports a utility of 0.57 for “worst day of COVID”.

Long COVID

- The impact of long COVID based on the patient representative testimony heard during the committee meeting demonstrates that the value suggested by the EAG (0.67) is too optimistic and lacks validity.
- Only 186 patients in the Soare et al study reported long COVID, and the study relied on patient self-report and may suffer from selection bias - those most severely impacted may have been less likely to engage.
- OpenPROMPT study is the most relevant - it is recent, large and uses OpenSAFELY database, data from which has been used in TA878 and TA971,
    - The study reported a long COVID utility of 0.49

Utility values

EAG

- Acknowledge that applying the utility for long COVID from Soare et al. might be an underestimate, particularly for the highest unmet need patients.
- Accept the company's revised estimate of 0.49 for this health state
- Continue to use 0.59 from Soare et al for symptomatic outpatient

	Company revised base case	EAG revised base case
Symptomatic outpatient	0.57	0.59
Hospitalised in general ward	0.28	0.28
Hospitalised in ICU with mechanical ventilation	0	0
Long-term sequelae	0.49	0.49

Cost-effectiveness results

Full results shown in part 2 due to confidential prices for subsequent treatments

Parameter	Company base case	EAG base case
Health state utility values	0.57 for symptomatic outpatient	0.59 for symptomatic outpatient
Immunocompromised hospitalisation rate	24.98% based on INFORM study	10.39% based on TA971

ICER vs no treatment	Age ≥ 70	Contraindicated to nirmatrelvir plus ritonavir	Immunocompromised	Severe chronic kidney disease
Company revised base case – revised utility values	<£20k	£20-30K	Molnupiravir, more effective, less costly	£20-30k
EAG revised base case	<£20k	£20-30K	Molnupiravir, more effective, less costly	£20-30k
Scenarios around EAG base case				
1) Hospitalisation rate of 0.77% for age ≥70 years	>£30k	N/A	N/A	N/A
2) Hospitalisation rate of 4% for immunocompromised	N/A	N/A	Molnupiravir, more effective, less costly	N/A
3) Molnupiravir administration cost of £117	<£20k	£20-30K	Molnupiravir, more effective, less costly	£20-30k
1) or 2) plus 3)	>£30k	N/A	Molnupiravir, more effective, less costly	N/A

Supplementary appendix

NICE National Institute for Health and Care Excellence

Summary of studies included in the RWE NMAs (1)

All studies included in the RWE NMAs were either retrospective or prospective cohort or case control design

Study	Population	Intervention	Age, years
Aggarwal (USA) (N=21,493)	Non-hospitalised adults with confirmed SARS-CoV-2	Nirmatrelvir plus ritonavir versus no treatment	≥18
Arbel (Israel) (N=19,868)	Non-hospitalised patients (≥ 40 years of age), infected with Omicron and at high risk for progression to severe disease and who were ineligible for nirmatrelvir plus ritonavir	Molnupiravir versus no treatment	Mean 69-73
Bajema (USA) (N=191,057)	Non-hospitalised veterans in VHA care who are at risk for severe COVID-19 and tested positive for SARS-CoV-2	Molnupiravir versus nirmatrelvir plus ritonavir versus no treatment	Median 59-70
Basoulis (Greece) (N=521)	High-risk adults with COVID-19, without requirements for supplemental oxygen on presentation	Nirmatrelvir plus ritonavir versus remdesivir	Mean 60-65
Cegolon (Italy) (N=386)	High-risk COVID-19 outpatients	Molnupiravir versus nirmatrelvir plus ritonavir versus sotrovimab versus no treatment	Median 66-71
Cowman (USA) (N=3,207)	High-risk, non-hospitalised adults with COVID-19	Molnupiravir versus nirmatrelvir plus ritonavir	Median 58-64
Dryden-Peterson (USA) (N= 44,551)	Non-hospitalised adults aged ≥50 years with early COVID-19	Nirmatrelvir plus ritonavir versus no treatment	≥50
Gentry (USA) (N=43,416)	US Veterans ≥ 65 years of age with mild to moderate COVID-19 considered to be at high risk of progression	Molnupiravir versus nirmatrelvir plus ritonavir	≥65 (mean 74)

Summary of studies included in the RWE NMAs (2)

All studies included in the RWE NMAs were either retrospective or prospective cohort or case control design

Study	Population	Intervention	Age, years
Kaboré (Canada) (N=259,542)	Non-hospitalised adults with confirmed SARS-CoV-2 with at least one risk factor for progression to severe disease	Nirmatrelvir plus ritonavir versus no nirmatrelvir plus ritonavir or no molnupiravir	Mostly >17 to <90
Manciulli (Italy) (N=781)	Mild or moderate COVID-19 treated with sotrovimab, remdesivir, nirmatrelvir plus ritonavir or molnupiravir as outpatients, who had ≥ 1 risk factor for severe disease	Molnupiravir versus nirmatrelvir plus ritonavir versus sotrovimab versus remdesivir	Median 65-69
Paraskevis (Greece) (N=18,101)	Non-hospitalised patients with COVID-19 ≥ 65 years	Molnupiravir versus nirmatrelvir plus ritonavir versus no treatment	≥65
Schwartz (Canada) (N=177,545)	Adults with confirmed SARS-CoV-2 infection	Nirmatrelvir plus ritonavir versus no nirmatrelvir plus ritonavir or no molnupiravir	>17; mean 52-74
Tiseo (Italy) (N=562)	Outpatients with documented COVID-19 who were at high risk of progression to severe disease	Molnupiravir versus nirmatrelvir plus ritonavir versus remdesivir	Median 65-72
Torti (Italy) (N=29,553)	Non-hospitalised patients aged ≥18 years with confirmed SARS-CoV-2 infection	Molnupiravir versus nirmatrelvir plus ritonavir	Mean 66-74
Van Heer (Australia) (N=38,933)	Individuals ≥ 70 years of age diagnosed with COVID-19 and reported to the Victorian Department of Health	Molnupiravir versus nirmatrelvir plus ritonavir versus no treatment	≥70
Xie (USA) (N=85,998)	Non-hospitalised adults with confirmed SARS-CoV-2 with at least one risk factor for progression to severe disease	Molnupiravir versus no treatment	Mean 67-69
Zheng (UK, OpenSAFELY) (N=9,026)	Non-hospitalised high-risk COVID-19 patients across England	Molnupiravir versus nirmatrelvir plus ritonavir versus sotrovimab	≥18 Mean 52-56

NICE Only studies included in the RWE NMAs are shown here (see page 49 of EAR for more details)

NMAs of RWE – Results

Table: Results of the NMAs of RWE, including UK OpenSAFELY cohort study

Outcome	Results for molnupiravir versus each comparator			
	Nirmatrelvir plus ritonavir	Sotrovimab	Remdesivir	Placebo
All-cause hospitalisation or death	**NMA: 1.22 (0.50 to 2.99)** No significant difference **OpenSAFELY study** (Zheng et al. 2023)**: 1.64 (1.09 to 2.47)** Comparator favoured	**NMA: 1.07 (0.33 to 3.55)** No significant difference	No data	**NMA: 0.61 (0.43 to 0.86)** Molnupiravir favoured
COVID-19 related hospitalisation or death	**NMA: 1.79 (0.61 to 4.49)** No significant difference **OpenSAFELY study** (Zheng et al. 2023)**: 2.22 (1.08 to 4.59)** Comparator favoured	**NMA: 2.40 (0.88 to 7.32)** No significant difference	**NMA: 0.94 (0.26 to 3.46)** No significant difference	**NMA: 0.75 (0.22 to 2.60)** No significant difference **OpenSAFELY study** (Tazare et al. 2023)**:** no significant difference
All-cause hospitalisation	**NMA: 1.01 (0.53 to 1.81)** No significant difference	No data	**NMA: 1.40 (0.21 to 9.45)** No significant difference	**NMA: 0.79 (0.66 to 0.92)** Molnupiravir favoured
COVID-19 related hospitalisation (fixed-effect analysis)	**NMA: 0.50 (0.11 to 2.26)** No significant difference	**NMA: 0.43 (0.03 to 5.29)** No significant difference	No data	**NMA: 0.85 (0.49 to 1.53)** No significant difference
All-cause death	**NMA: 1.48 (1.22 to 1.79)** Comparator favoured	No data	No data	**NMA: 0.31 (0.21 to 0.46)** Molnupiravir favoured

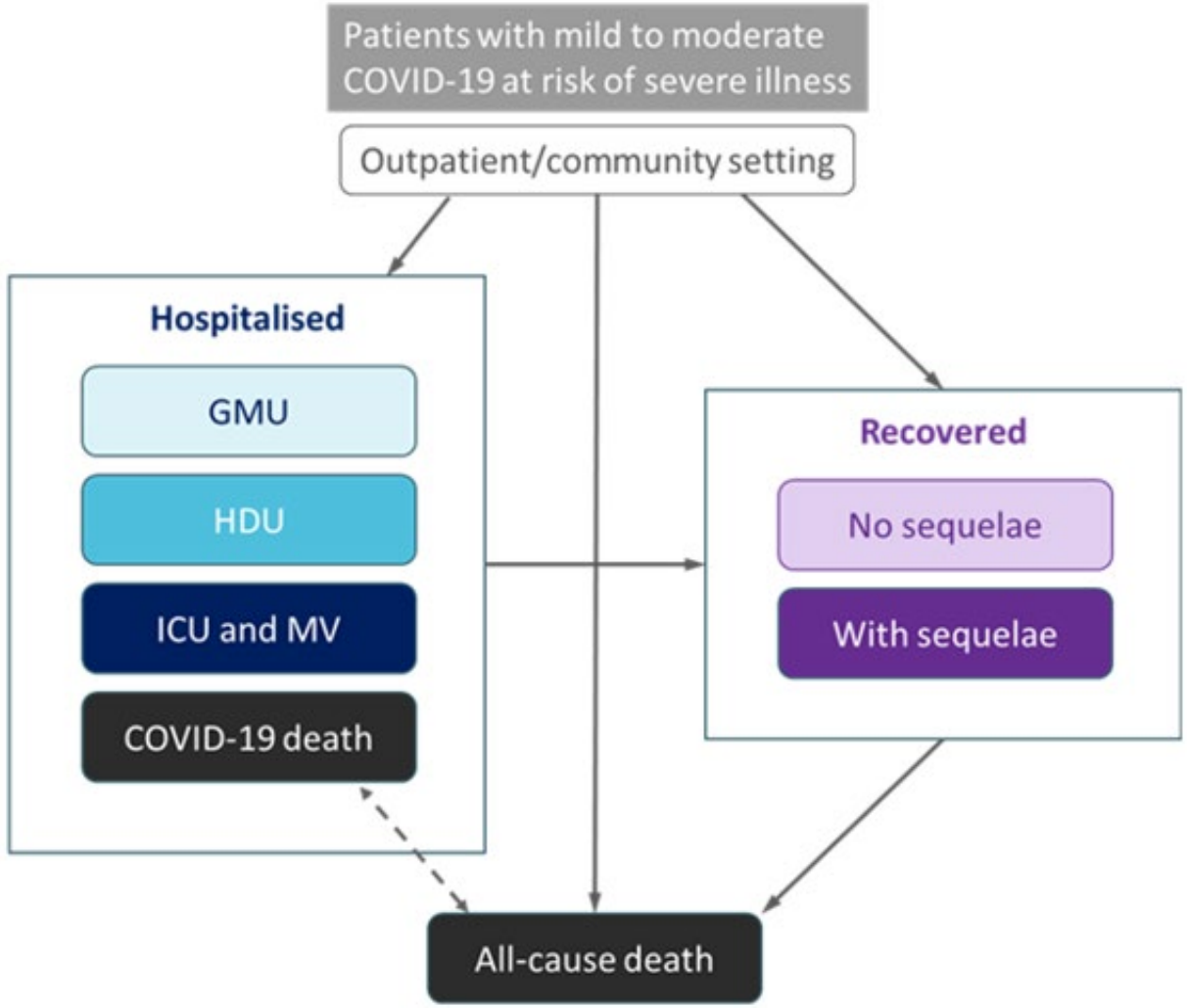
Source: EAR Appendix 6

See appendix: NMAs of RWE – relevant studies and comparisons

NMAs: Network meta-analyses; RWE: Real world evidence

Company's model overview

Model structure



Model structure	• Hybrid decision tree (acute phase) and Markov model (following acute phase through to lifetime horizon) • NHS PSS perspective • 3.5% discount rate
Assumptions with large impact on cost effectiveness results	
Hospitalisation rates for untreated patients	
Treatment effect on hospitalisation	
Proportion of patients with long-term sequelae	
Health state utilities	

Source: EAR, Figure 2

GMU: General medical ward; HDU: High-dependency unit; ICU: Intensive care unit; MV: Mechanical ventilation; NHS PSS: NHS and personal social services